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NDA 20-677

1 OF 8

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Clin. Pharm Co. Corres
+ Bio
Pharm/Tox
Stat

A p L+r



DEC 19 1995

NDA 20-677

Rhone-Poulenc Rorer
Attention: Jack J. Savarese, M.D., Ph.D.
Director Regulatory Affairs Liaison
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Dr. Savarese: .

Please refer to your December 27, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zagam® (sparfloxacin) 200- mg Tablets.

We acknowledge receipt of your amendments dated March 21, 1996; April 30, 1996; June 6, and 27, 1996; August 15, 1996; October 15, 1996; and November 6, 1996.

This new drug application provides for the indications of Community-acquired pneumonia, Acute bacterial exacerbations of chronic bronchitis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the following indications:

1. **Community-acquired pneumonia** caused by *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*
2. **Acute bacterial exacerbations of chronic bronchitis** caused by *Chlamydia pneumoniae*, *Enterobacter cloacae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Streptococcus pneumoniae*.

Although there were adequate data to support the efficacy of sparfloxacin for the treatment of _____, the safety profile of sparfloxacin precludes us from granting this indication.

Accordingly, the application is approved for the above mentioned indications effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling dated November 26, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-677. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 20-677
Page 3

If you have any questions, please contact Ms. Frances LeSane, Project Manager, at (301) 827-2125.

Sincerely yours,

A handwritten signature in black ink, appearing to read "David W. Feigal, Jr.", followed by the date "12-19-96". The signature is fluid and cursive.

David W. Feigal, Jr., M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:

Original NDA 20-677

HFD-520/Div. files

HFD-2/M.Lumpkin

HFD-104/TNearing

HFD-101/L.Carter (with labeling)

HFD-830/E.Sheinin

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling)

HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.

HFD-021/J.Treacy (with labeling)

HFD-520/MO/NMoledina *nm 11/26/96*

HFD-520/CHEM/BShetty

HFD-520/PHARM/Aellis *Ad Ellis 12/19/96*

HFD-520/BIOPHARM/HSun *HS 12/19/96*

HFD-520/MICRO/PDionne

HFD-520/STAT/JJiang

HFD-520/STAT/SBell

HFD-520/labeling File/CDeBellas

HFD-520/PMS/FVLeSane/11-19-96/11-26-96 *FA 11-26-96*

TEAM LEADERS

HFD-520/TLMO/MAlbuerne

HFD-520/Act.TLCHEM/JTimper *JK 12/20/96*

HFD-520/TLPHARM/ROsterberg *RO 12/18/96*

HFD-520/TLBIOPHARM/FPelsor

HFD-520/TLMICRO/ASheldon *HVS for ATS*

HFD-520/TLSTAT/DLin *DL 12/20/96*

Concurrence Only:

HFD-520/TLMO/MAlbuerne *MAl 11/26/96*

HFD-520/CPMS/JBona *JB 12/20/96*

APPROVAL

mor

NDA 20-677
Safety Update

**MEDICAL OFFICER'S REVIEW OF SAFETY UPDATE
NDA 20-677 - SPARFLOXACIN**

Date Submitted: April 30, 1996.
Date Reviewed: November 25, 1996.

The Safety Update Report of the Integrated Summary of Safety was submitted in April 1996. The reports in this update include safety results from studies performed in patients with AIDS with *Mycobacterium Avium* complex or MAI bacteremia. The report also included safety data from studies that are ongoing in Europe for the treatment of patients with

The duration of therapy with sparfloxacin in these studies ranged from 5-10 days. There were no reports of any additional studies being conducted in the United States.

Medical Officer's Comments:

The Safety Update Report did not contain any additional safety data from studies conducted in the U.S.A.



Nasim Moledina, M.D.
Medical Officer, DAIDP.

cc: Orig NDA 20-677
HFD-340
HFD-520
HFD-520/MO/NMoledina
HFD-520/Pharm/AEllis
HFD-520/Micro/PDionne
HFD-520/Chem/VShetty
HFD-520/PMS/FLeSane
nm/safety update/11-25-96.

Concurrence Only:

HFD-520/Acting DivDir/DFeigal
HFD-520/TL/MSAlbuerne

[Handwritten initials] 12.19.96
11/24/96

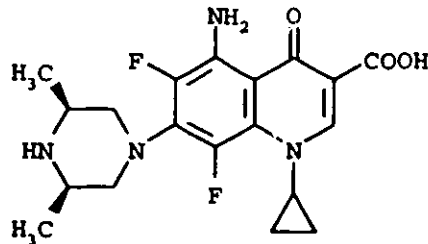
MEDICAL OFFICER'S REVIEW OF NDA 20-677

Date Submitted: December 27, 1996.
Date Received: December 28, 1996.
MOR Initiated: March 1, 1996.

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107.

DRUG: Generic: Sparfloxacin
 Trade: Zagam
 Chemical
 Name: 5-amino-1-cyclopropyl-7-(cis-3,5-dimethylpiperazinyl)-6,8-difloro-
 1,4-dihydro-4-oxo-quinolinecarboxylic acid

Chemical Structure:



Molecular Formula: C₁₉H₂₂F₂N₄O₃
Molecular Weight: 392.41.

Pharmacologic Category: Fluoroquinolone antimicrobial

Dosage Form: 200 mg tablets

PROPOSED INDICATIONS:

Treatment of patients with Community Acquired Pneumonia, Acute Bacterial Exacerbation of Chronic Bronchitis,

The **INDICATIONS AND USAGE** Section of the package insert has the following proposed labeling:

RELATED MATERIAL:

IND

SUBMISSIONS REVIEWED:

Double-blind Controlled Clinical Studies conducted in the United States of America, and Safety data from studies conducted in the U.S.A. and Foreign Countries. Total number of volumes submitted - 610. Number of volumes containing Clinical Data - 387.

MANUFACTURING CONTROLS:

Refer to the Chemistry Review by Dr. Vittal Shetty.

MICROBIOLOGY REVIEW:

Refer to the review by Mr. Peter Dionne.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY:

Refer to the pharmacology and toxicology review by Dr. Amy Ellis.

HUMAN PHARMACOKINETIC/BIOAVAILABILITY:

Refer to the review by Dr. He Sun.

REVIEW OF CLINICAL STUDIES:

Each study conducted for a particular indication will be reviewed separately. The clinical and bacteriologic data will be pooled, the final results summarized and the recommendations for the approval/non-approval of the reference antimicrobial for that particular indication will be made. Studies conducted for indications which the applicant is not seeking approval for will only be reviewed for their safety data.

COMMUNITY-ACQUIRED PNEUMONIA

Overview of U. S. Pivotal Studies:

1. **Study 301:** Double-Blind, Double-Dummy, Randomized, Comparative, Multi-center trial conducted with erythromycin as the comparator drug. Total days of therapy was 10 days.
2. **Study 352:** Double-Blind, Double-Dummy, Randomized, Comparative, Multi-center trial conducted with cefaclor as the comparator drug. Total days of therapy was 10 days.

The Applicant is proposing the following indication and dosage recommendations for the package insert:

INDICATIONS AND USAGE

DOSAGE AND ADMINISTRATION

INTRODUCTION

RP 64206 (sparfloxacin) is a synthetic, broad-spectrum, fluoroquinolone antibacterial agent for oral administration. Improvements over currently available quinolones include better Gram-positive activity and an increased half-life which will allow for once daily administration.

The bactericidal activity of sparfloxacin is typical of the quinolone class of antibacterial agents. Sparfloxacin is a potent inhibitor of bacterial DNA gyrase, the enzyme which regulates supercoiling, uncoiling and spatial geometry of bacterial DNA, functions that are necessary for controlling DNA replication and repair, transcription and recombination. Sparfloxacin is bactericidal at or near the minimum inhibitory concentration (MIC). A summary of its *in vitro* MIC activity against some important pathogens is listed in Table 1.

Table 1. Summary of *In Vitro* Activity (Median MIC₉₀ µg/mL)^a

ORGANISM	NUMBER	MIC ₉₀
<i>Streptococcus pneumoniae</i>	476	0.5
<i>Streptococcus pyogenes</i> (Grp A)	483	0.5
<i>Staphylococcus aureus</i> MS ^b	734	0.1
<i>Staphylococcus aureus</i> MR ^c	700	0.1
<i>Haemophilus influenzae</i>	274	0.015
<i>Legionella pneumophila</i>	34	0.025
<i>Moraxella catarrhalis</i>	253	0.03
<i>Mycoplasma pneumoniae</i>	65	≤0.008
<i>Chlamydia pneumoniae</i>	4	0.125
<i>Klebsiella pneumoniae</i>	805	0.12
<i>Escherichia coli</i>	1845	0.06

a. Data from combined studies as noted in the sparfloxacin Investigators Brochure.

b. MS = methicillin sensitive

c. MR = methicillin resistant

Community Acquired Pneumonia

In phase I pharmacokinetic studies in Europe and Japan with sparfloxacin, mean steady-state maximum plasma concentrations (Mean C_{max}) were 1.4 to 2.9 $\mu\text{g/mL}$ after repeated doses of 200 to 400 mg QD. Maximum plasma concentration (C_{max}) occurred between 4 to 5 hours following administration. The terminal half-life ($t_{1/2}$) was 16 to 20 hours. Mean C_{max} and area under the curve (AUC) values were dose-proportional over the dose range of 100 to 400 mg. Based upon single-dose data, the extent of absorption may be reduced at higher doses. Table 2 lists the C_{max} values after a single and repeated administration of sparfloxacin between 100 to 800 mg doses.

Table 2. Sparfloxacin (plasma) C_{max} values at 100 to 800 mg doses
 C_{max} ($\mu\text{g/mL}$)

DOSE	SINGLE DOSE	STEADY STATE
100 mg	-	0.7
200 mg	0.7	1.4
300 mg	-	2.1
400 mg	1.2	2.9
600 mg	1.7	-
800 mg	2.0	-

Distribution of sparfloxacin into body fluids and tissues was rapid and extensive. Following administration, the majority of sparfloxacin was recovered unchanged in the feces (~55%) and urine (10%) with a smaller amount excreted in the urine as a glucuronide conjugate (20%).

Sparfloxacin pharmacokinetics were not altered by the ingestion of food or by concurrent probenecid administration. Volunteers with moderate or severe renal impairment (mean creatinine clearance of 22 mL/min and 7 mL/min, respectively) had an increase in sparfloxacin $t_{1/2}$ and AUC after a single 400 mg oral dose. Theophylline pharmacokinetics were not altered by sparfloxacin administration. When a single 400 mg oral dose of sparfloxacin was given to healthy subjects dosed to steady state with digoxin 0.25 mg orally QD, digoxin C_{max} and AUC increased by approximately 20% and 9%, respectively. Sparfloxacin C_{max} and AUC were reduced 45% with concurrent Maalox[®] administration.

Sparfloxacin was generally well-tolerated in studies completed in Europe and

Community Acquired Pneumonia

Japan. In a European Phase 1 study of fair-skinned Caucasian subjects, sparfloxacin produced dose-dependent phototoxicity with UVA radiation and with natural sunlight that was mild at daily doses of 100 mg (2 of 8 subjects) and 200 mg (5 of 9 subjects) and more severe at 300 mg (8 of 8 subjects) and 400 mg (7 of 8 subjects). In a United States Phase 1 study, subjects who received 100 or 200 mg daily had no phototoxicity, whereas at 300 mg QD, 7 of 7 subjects had mild to moderate signs of phototoxicity after 12 days of treatment. In recently completed European Phase 3 trials, sparfloxacin was associated with phototoxicity in 1.9% of patients.

REVIEW OF PIVOTAL STUDIES

These studies were conducted in the United States of America and Canada.

I. Study 301 Synopsis:

Objective: To compare the safety and efficacy of orally administered sparfloxacin and erythromycin in the treatment of community-acquired pneumonia.

Patient Population: Male or female patients >18 years of age.

Structure: Parallel group.

Study Dates: May 1, 1992 to February 2, 1995.

Dosage: Sparfloxacin 400 mg loading dose followed by 200 mg once a day for 10 days.
Erythromycin 500 mg every 6 hours for 10 days.

Multicenter: Yes.

No. of centers: 65 in the U.S.A. and 6 in Canada.

Blinding: Double-blind, Double-dummy.

Method of Randomization: Randomization in a 1:1 ratio at each investigational site to receive either sparfloxacin or erythromycin.

Efficacy Variables: The primary efficacy parameter was clinical response in the clinically evaluable patient population. Secondary efficacy parameters included clinical response (all-treated and bacteriologically evaluable patient populations); clinical recurrence (all-treated, clinically evaluable, and bacteriologically evaluable patient populations); and by-patient bacteriologic response, by-pathogen bacteriologic response, bacteriologic relapse/reinfection; and overall response (all-treated with a baseline pathogen and bacteriologically evaluable patient populations).

Community Acquired Pneumonia

Study Evaluations:

Study visits were scheduled for baseline (Visit 1), Day 4 + 1 of treatment (Visit 2), Day 20 + 3 (10 days post-treatment (Visit 3 [Test-of-Cure]), and Day 38 + 7 (28 days post-treatment (Visit 4). The investigator was to assess the patient's signs and symptoms of pneumonia at Visits 1, 2, 3, and 4. An assessment of the patient's response to study drug treatment was to be made at Visit 3 (or Premature Discontinuation before Visit 3); recurrence of infection was to be determined at Visit 4 (or Premature Discontinuation after Visit 3).

Safety measurements:

Adverse clinical and laboratory events and changes in electrocardiogram (ECG), vital sign and physical examination findings.

Statistical methods:

The two-sided 95% confidence interval method of statistical analysis was used to demonstrate equivalence between sparfloxacin and erythromycin for efficacy variables.

A. Inclusion Criteria

Patients must have met ALL of the following conditions:

1. Either a male or a nonpregnant, non-lactating female, who was postmenopausal or surgically sterilized, or was using birth control pills, Norplant[®] or an IUD for at least two months for contraception;
2. For all women of child-bearing potential (i.e., those not postmenopausal or surgically sterilized), including those using birth control, a negative serum pregnancy test by _____ at baseline; a screening (serum or urine) pregnancy test performed on site must have been reported as negative before study medication was administered;
3. ≥ 18 years of age;
4. Presenting with presumed community-acquired bacterial pneumonia, as confirmed by a) chest X-ray (CXR) (PA and lateral views) showing pulmonary findings consistent with pneumonia AND b) new (or worsened from premonitory state) cough and sputum production. Patients may have been enrolled based on the investigator's interpretation of the CXR. However, a formal radiologist's interpretation must have been obtained; if this reading did not confirm the presence of pulmonary findings consistent with pneumonia, then the patient must have been discontinued from the study, with dropout procedures completed, and appropriate therapy must have been prescribed. In addition to the above-noted inclusion criteria, patients may also have had fever (temperature $> 100.4^{\circ}\text{F}$ [38.0°C] by the oral route), abnormal pulmonary examination (evidence of pulmonary consolidation), shortness of breath, rigors and/or pleuritic chest pain; these were not inclusion criteria per se.
5. Had produced a sputum specimen for laboratory evaluation within 48 hours prior to starting study medication.
6. Capable of providing written informed consent.

B. Exclusion Criteria

1. Female with childbearing potential (i.e. not postmenopausal or not surgically sterilized), unless using contraception;
2. Hypersensitivity to quinolones or erythromycin;
3. Nosocomial pneumonia (acute-care hospital or nursing home setting). Patients from self-care, ambulatory, long-term convalescent facilities presenting with pneumonia were allowed to participate in the study;
4. Pneumonia suspected on clinical or epidemiologic grounds of being due to Gram-negative enteric bacilli, *Pseudomonas aeruginosa* or methicillin-resistant

Community Acquired Pneumonia

Staphylococcus, since erythromycin has no significant activity against these organisms;

5. Pulmonary disease(s) that preclude evaluation of the therapeutic response, including cystic fibrosis, pleural empyema, bronchiectasis, obstructing lung cancer, or other significant focal pulmonary structural defects;
6. Known HIV infection or current use of immunosuppressive or chemotherapeutic agents for hematologic, oncologic or organ transplantation purposes;
7. Systemic antimicrobial treatment within three days prior to study drug administration;
8. Baseline pathogen(s) known to be resistant to either study drug prior to randomization;
9. Concomitant infections requiring systemic antibacterial therapy;
10. Use of other antibiotics or any other concomitant medication (including specifically antacids, sucralfate, or antacid-containing compounds such as Ascriptin[®]) that may interfere with the interpretation of the data or the patient's participation in the study;
11. Use of any other investigational compound within 28 days of starting study medication (Day 1 of study) or during study (i.e. prior to Visit 4 or Dropout);
12. Prior participation in this study;
13. A rapidly fatal illness;
14. A life expectancy of one month or less;
15. Shock, respiratory failure, or other clinical findings which, in the investigator's opinion, warrant parenteral antibiotic therapy;
16. Significant hepatic disease or obstruction of the biliary tract. This includes patients with baseline bilirubin or hepatic enzyme levels (AST, ALT) that are greater than two times the upper limit of normal.
17. Baseline known or estimated creatinine clearance of less than 30 mL/min; when a known creatinine clearance based on a 24-hour urine collection was not available, creatinine clearance was to be estimated using the following formula:
 Men: creatinine clearance (mL/min) =
$$\frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

 Women: 0.85 x value calculated for men
18. Congenital prolonged QT Syndrome;
19. Concurrent use of antiarrhythmic agents or other medications known to cause QT prolongation including terfenadine (Seldane[®]) and astemizole (Hismanal[®]); probucol (Lorelco[®]); Class Ia antiarrhythmic agents (quinidine, procainamide, disopyramide); Class III antiarrhythmic agents (amiodarone [Cordarone[®]] bretylium); tricyclic antidepressants; and phenothiazines;
20. Baseline (Visit 1) QT_c interval of 500 msec;
21. Epilepsy, history of convulsive disorders or underlying conditions which could

Community Acquired Pneumonia

- predispose to seizures;
22. Inability to minimize exposure to sunlight as a result of unprotected exposure;
 23. Gastrointestinal tract abnormalities which would prevent absorption of oral medication (e.g., persistent nausea and vomiting or malabsorption);
 24. Unwillingness to cooperate with the investigator and to participate in all required portions of the study;
 25. History of non-compliance, likely to be unreliable, or mentally or legally incapacitated.
 26. A prior phototoxicity reaction with a quinolone.

PLAN OF THE STUDY

Each patient screened by the investigator for this study was to be given a unique screening number until either study entry or exclusion from participation. Demographic information was to be collected for screened patients and the reason(s) for exclusion were to be documented for those who did not qualify. Patients who met the inclusion/exclusion criteria were asked to give written informed consent for the study. (NOTE: Patients must have given informed consent before any procedure performed solely for study purposes.) The schedule of visits for the study and the procedures performed are discussed below:

A. Visit 1: (Baseline), Including Microbiological Considerations

The baseline visit was to be conducted within 48 hours prior to initiation of therapy. (NOTE: there was not to be clinically inappropriate delay in initiating treatment once the diagnosis of pneumonia was established). The following procedures were to be done during this visit(s):

1. Completion of inclusion, exclusion, and patient consent forms;
2. Chest X-ray (PA and lateral views), to be read by a radiologist with the interpretation formally recorded in a signed report; comparison was to be made with premorbid chest X-rays, if any; this information must have been recorded on the "CXR₁" Case Report Form;

3. Collection of laboratory samples for SciCor:

a. BLOOD

b. SPUTUM

(i) Hematology	(i) Unstained slide for
(ii) Chemistry	Gram stain
(iii) Serology	(ii) routine culture & susceptibility
(iv) Serum pregnancy test (if applicable)	(iii) <i>Mycoplasma</i> & <i>Legionella</i> culture
(v) Theophylline level (if applicable)	(iv) <i>Legionella</i> DNA probe (if applicable)
(vi) Digoxin level (if applicable)	
c. URINE	
d. THROAT SWAB	
(i) Urinalysis	(i) <i>Chlamydia</i> culture
(ii) <i>Legionella</i> urine antigen	

4. Blood was to be obtained for culture from patients with an oral temperature 101.5°F (38.6°C), or if otherwise indicated in the investigator's judgment. Blood cultures were to be sent to an accredited laboratory other than SciCor. If the blood culture revealed a pathogen (not a contaminant), the "BCX" CRF (blood culture Case Report Form) was to be completed.
5. "Stat" urine pregnancy test (women of child-bearing potential), was to be performed on site with result available before study medication administered.
6. Medical history;
7. Physical examination, vital signs measurements (including route of temperature measurement and whether an antipyretic had been taken within the preceding four hours);
8. 12-lead ECG; Note: The QT_c interval was to be determined at this visit and the patient excluded if the QT_c was >500 msec;
9. Clinical evaluation of premorbid and current symptoms and signs by the investigator;
10. List of concurrent illness(es);
11. List of all antibiotics taken within the previous 14 days;
12. List of other concurrent medications;
13. Initiate therapy: Administer first dose of study medication at site. Patients were to be given the first five days of their study medication in a "Blister

Community Acquired Pneumonia

- Pack Card" along with instructions.
14. Schedule appointment for patient to return on Day 4±1 of treatment (Visit 2).
 15. Microbiological Considerations at Baseline

A variety of methods were employed to identify etiologic pathogens. An unstained slide of sputum for Gram-staining was to be sent to SciCor. Those samples which met screening criteria (> 25 neutrophils and < 10 squamous epithelial cells per low power field [10 X objective, 100 X total magnification]) were to be submitted for routine culture. Those samples meeting Gram-staining criteria which showed 2+ pleomorphic Gram-negative coccobacilli (possibly consistent with a *Haemophilus species*) were to be reported to the investigator as a telephone alert. Those samples not meeting Gram-stain screening criteria were to be cultured for *Legionella sp.* and *Mycoplasma pneumoniae*, as was that fraction of sputum samples meeting screening criteria but having rare or no bacteria on Gram-stain. In addition, if the routine culture showed "no growth" of pathogen(s) at 24 hours, then isolation of *Legionella sp.* and *M. pneumoniae* was to be attempted. A throat swab was to be obtained for isolation of *Chlamydia sp.* and processed if screening criteria were not met. Non-bacteriologic (i.e. non-culture) methods for identification of "atypical" organisms (i.e., serology, DNA probe, urinary antigen) were also to be employed.

Culture and identification of the etiologic routine bacterial pathogen(s) and susceptibility to both sparfloxacin and erythromycin was to be performed by _____, and the results were to be reported by telephone to the clinical site. Organisms resistant to either or both study drugs were to be automatically tested to a backup panel of antibiotics. _____ was subsequently to send follow-up confirmatory written reports to the study sites.

B. Visit 2: (Study Day 4±1)

During this visit the following was to be performed:

1. Clinical evaluation and physical examination with vital signs by the investigator (including route of temperature measurement and whether an antipyretic had been taken within the preceding four hours);
2. 12-lead ECG; Note: The QT_c was to be determined at this visit; patients discontinued due to QT_c criteria were to return one and five days after dropout for repeat physical examination and ECG.
3. Collection of laboratory specimens for SciCor:
 - a. BLOOD
 - (i) Hematology
 - (ii) Chemistry
 - (iii) Serology (if not obtained at Visit 1)
 - (iv) Theophylline level (if applicable)
 - (v) Digoxin level (if applicable)
 - b. SPUTUM
 - (i) Unstained slide for Gram stain
 - (ii) routine culture & susceptibility
 - c. URINE
 - (i) Urinalysis
4. Collection of the used study medication "Blister Pack Cards", verification of compliance, and, if appropriate, dispensing of remaining study medication.
5. **If the isolated routine bacterial pathogen(s) were "Resistant" (i.e., not "Susceptible" or "Intermediate") to one or both of the drugs, and the patient was not clinically improving by Visit 2, the patient was to be immediately discontinued from the study medication and appropriate therapy was to be started. Details were to be recorded on the CRF and dropout procedures were to be completed. If the isolated pathogen(s) were Resistant to one or both of the drugs, and the patient showed clinical improvement by Visit 2, the patient was to remain on study treatment as long as clinical improvement continued.**

Patients with negative (i.e. no pathogen identified) culture results at

baseline remained in the study as long as they continued to show an improved clinical response.

6. For patients who did not drop out, scheduling of an appointment for return on Day 20 $\pm$ 3 (Day 10 $\pm$ 3 post treatment) (Visit 3).

C. Visit 3: Study Day 20 $\pm$ 3 (Day 10 $\pm$ 3 post-treatment)

During this visit to the site the following was to be performed:

1. Clinical evaluation of symptoms and signs by the investigator;
2. Physical examination with vital signs (including route of temperature measurement and whether an antipyretic had been taken within the preceding four hours);
3. Collection of laboratory samples for

a. BLOOD

- (i) Hematology
- (ii) Chemistry
- (iii) Serology
- (iv) Theophylline level
(if applicable)
- (v) Digoxin level
(if applicable)

b. SPUTUM

- (i) Unstained slide for Gram stain
- (ii) routine culture & susceptibility
- (iii) *Mycoplasma* and *Legionella* culture
(if prior positive)
- (iv) *Legionella* DNA probe
(if prior positive)

c. URINE

- (I) Urinalysis
- (ii) *Legionella* urine antigen (if prior positive)

d. THROAT SWAB

- (I) *Chlamydia* culture
(if prior positive)

4. Chest X-ray (PA and lateral views) read by a radiologist with a formal report and including comparison to Visit 1 CXR;
5. 12-lead ECG, including determination of QT_c;
6. Blood culture was to be performed if Visit 1 blood culture revealed a pathogen (not a contaminant); complete "BCX" CRF.
7. Collection of the used study medication "Blister Pack cards" and verification of compliance;

Community Acquired Pneumonia

8. Completion of "Investigator Assessment of Clinical Response" CRF;
9. Completion of "CXR," CRF (CFR pertaining to Chest X-Rays at Visit 3).
10. Scheduling of an appointment for patient to return on Day 38 ± 7 (Day 28 ± 7 post treatment) (Visit 4).

D. Visit 4: Study Day 38 ± 7 (Day 28 ± 7 post-treatment)

The following tests were to be completed:

1. Clinical evaluation by the investigator;
2. Physical examination and vital signs (including route of temperature measurement and whether an antipyretic had been taken within the preceding four hours);
3. Repeat chest X-ray (PA and lateral views), read by a radiologist with a formal report, if Visit 3 chest X-ray was not done, abnormal, not returned to premorbid status or patient's condition warrants it;

4. If not done at Visit 3, if the patient's clinical condition warranted it, or if so indicated below (by *), there was to be collection of laboratory samples for

a. BLOOD

- (i) Hematology
- (ii) Chemistry
- (iii) Serology*

b. SPUTUM

- (i) Unstained slide for Gram stain*
- (ii) routine culture & susceptibility *
- (iii) *Mycoplasma* & *Legionella* culture (if prior positive & no negative follow-up)
- (iv) *Legionella* DNA probe (if prior positive & no negative follow-up)

c. URINE

- (i) Urinalysis
- (ii) *Legionella* urine (if prior positive & no negative follow-up)

d. THROAT SWAB

- (i) *Chlamydia* culture

(if prior positive follow-up) & no negative follow-up)

5. 12-lead ECG, if not done at Visit 3 or patient's clinical condition warrants, to include determination of QT_c.

6. Completion of "CXR₄" CRF, if Visit 4 CXR performed.

7. Completion of "BCX" CRF, if Visit 4 blood culture performed.

8. Completion of "Recurrence" CRF.

9. If a patient could not return for Visit 4 and prior authorization had been obtained from the sponsor, telephone contact was to suffice and data were to be recorded on the CRF. However, whenever possible, the patient was to return so that blood could be obtained for serologic studies.

The following are the breakpoints for erythromycin susceptibility for *

routine bacterial pathogens (does not include atypical organisms).

Erythromycin

MIC

Susceptible	< 0.5 mcg/mL
Intermediate	1-4 mcg/mL
Resistant	> 8 mcg/mL

Reference: NCCLS Guidelines, January, 1991

The following are the tentative breakpoints for sparfloxacin:

Sparfloxacin

	MIC	DISK (Kirby-Bauer) 5 mcgs
Susceptible	1 mcg/mL	18 mm
Intermediate	2 mcg/mL	15-17 mm
Resistant	4 mcg/mL	14 mm

Reference: Data on file.

10. Beta -lactamase production was to be performed on appropriate microorganisms, such as *Haemophilus sp.*, *Moraxella catarrhalis*, and *Staphylococcus sp.*

11. Identification of "atypical" etiologic pathogen(s) (*Mycoplasma*, *Chlamydia*, and *Legionella spp*) was to be established by culture and could also be made by non-microbiologic methods (e.g., DNA-probe, serology).

SA ANALYSIS

A. Safety Parameters

The following safety parameters were to be evaluated:

1. subjective reports of adverse experiences
2. changes in laboratory measurements;
3. changes in physical examination findings;
4. changes in ECG findings.

B. Efficacy Parameters

The primary efficacy parameter was to be the Clinical Response as defined below and determined at Visit 3 (post-treatment Day 10 + 3 days), or when patients dropout before Visit 3. Secondary efficacy parameters defined below include the Bacteriologic Response, Overall Response, and Clinical Recurrence.

1. **Clinical Response:** Clinical Response was to be assessed by the investigator at Visit 3 or when patients dropout before Visit 3 as follows:

Cure: Resolution of ALL symptoms and signs of pneumonia, with no new symptoms or signs associated with the original infection. ["Resolution" will by definition include return of the given finding to the premorbid state]. In addition, the Visit 3 CXR (or CXR done at dropout prior to Visit 3) must be stable, improved, or resolved in comparison with the Visit 1 CXR.

Improvement: In patients not cured, resolution or reduction of the majority of symptoms and signs of pneumonia with no new or worsened symptoms or signs associated with original infection. In addition, the Visit 3 CXR (or CXR done at dropout prior to Visit 3) must be stable, improved, or resolved in comparison with the Visit 1 CXR.

Failure: Either (a) no resolution and no reduction of a majority of symptoms and signs of pneumonia or (b) worsening of one or more symptoms and signs or (c) new symptoms or signs associated with the original infection or a new infection, or (d) worsened pulmonary findings on CXR compared to Visit 1 or (e) patient required other antimicrobial therapy for this episode of pneumonia prior to or at Visit 3.

Indeterminate: Inability to assess the patient's symptoms and signs due to "lost to follow-up" or no information.

2. **Patient Bacteriologic Response:** Patient Bacteriologic Response was to be based on the sputum or throat culture results performed at Visit 3 or at dropout prior to Visit 3. (Relapse and reinfection was to be assessed at Visit 4). For pathogens identified by non-bacteriologic methods, bacteriologic efficacy (eradication/presumed eradication vs. other) was to be assessed using the patient Clinical Response.

The following definitions were to be used:

Eradication: Complete eradication of baseline pathogen(s).

Presumed Eradication: "No material available for culture" (due to lack of sputum to produce), or, if non-bacteriologic methods were used for identification, a clinical cure or improvement was noted.

Persistence: Persistence of baseline pathogen(s), or, if non-bacteriologic methods were used for identification, a clinical failure was noted.

Superinfection: Emergence of a new or resistant pathogen which was not identified as the original causative pathogen, and associated with signs and symptoms of pneumonia during treatment or up to Visit 3.

Multiple pathogens with partial eradication (MPPE): Identification of more than one etiologic pathogen at baseline and eradication of one or more of those pathogens with the persistence of one or more of those pathogens at Visit 3.

Relapse: Eradication of baseline pathogen(s) at Visit 3 and reappearance of the same pathogen(s) after Visit 3, accompanied by symptoms and signs of pneumonia.

Reinfection: Eradication of the baseline pathogen(s) at Visit 3 but with emergence of new pathogen(s) thereafter, accompanied by symptoms and signs of pneumonia.

Each pathogen(s) present at baseline was assessed as ERADICATED, PRESUMED ERADICATED, PERSISTENT, or RELAPSE. New pathogen(s) was (were) assessed as causing SUPERINFECTION or REINFECTION. For each patient, the investigator determined which, if any, of the organism(s) isolated from the Visit 1 culture represent(s) the pathogen(s) responsible for this episode of community-acquired pneumonia.

Colonization: Appearance of new organism(s), during or after therapy, not accompanied by clinical symptoms and signs of pneumonia. Colonization will not be included in assessment of the Patient Bacteriologic Response.

Indeterminate: No information.

3 **Overall Response:** The Overall Response was to be derived from the

Community Acquired Pneumonia

Clinical Response and the Patient Bacteriologic Response and defined as either Success, Failure or Indeterminate, as follows:

- (i) **Success:** Clinical Response of either "Cure" or "Improvement," and Patient Bacteriologic Response of "Eradication" or "Presumed Eradication".
- (ii) **Failure:** Clinical Response of "Failure" or Patient Bacteriologic Response of "Persistence", "Superinfection", or "MPPE".
- (iii) **Indeterminate:** All other outcomes.

4. **Clinical Assessment of Recurrence (Visit 4):** A clinical assessment of "Recurrence" of symptoms and signs of pneumonia was to be performed by the investigator at Visit 4 (or if patient drops out after Visit 3). Recurrence is defined as the development of new or worsened symptoms and signs of pneumonia in those patients who had a Clinical Response of "Cure" or "Improvement" at Visit 3. In addition, to identify a "Recurrence", a Visit 4 CXR (or CXR done at dropout after Visit 3) must have been obtained and must have been stable or worsened compared to the Visit 3 CXR.

The information obtained from this assessment was to be analyzed with the Visit 4 (or post Visit 3 dropout) microbiologic data to determine if there has been a Relapse or Reinfection.

C. Evaluability Criteria

1. Clinically Evaluable

To be clinically evaluable, patients MUST HAVE HAD:

- a. cough, sputum production, and radiographically documented pulmonary findings consistent with pneumonia; and
- b. completion of all Visit 3 or dropout procedures such that an assessment of Clinical Response could be made.

Patients MUST NOT HAVE:

- a. received systemic antimicrobial therapy within three days prior to study drug administration;
- b. a baseline (Visit 1) sputum sample taken more than 48 hours prior to start of the study medication or taken after the study medication had started;
- c. insufficient treatment period (less than 48 hours therapy);
- d. missed more than 20% of doses of (active) drug, unless patient discontinued due to failure;

Community Acquired Pneumonia

- e. taken non-study-drug antimicrobial therapy prior to or at Visit 3 (does not apply to failures);
- f. concurrent medical condition preventing evaluation of Clinical Response;
- g. incorrect diagnosis of community-acquired pneumonia (e.g. pulmonary embolus).

2. Bacteriologically Evaluable

To be bacteriologically evaluable, patients MUST HAVE HAD:

- a. a lower respiratory tract pathogen identified at Visit 1 by bacteriologic and/or non-bacteriologic methods (excluding serology, which is not visit-specific);
- b. Visit 3 (or dropout) culture or non-bacteriologic test of cure performed between seven and thirteen days after therapy was stopped (does not apply to early failures, provided supporting cultures were performed at time of study dropout, or patients who had no sputum to produce for culture);
- c. baseline susceptibility testing performed for both study medications, except for *Chlamydia sp.*, *M. pneumoniae* or *Legionella sp.* diagnosed by bacteriologic or non-bacteriologic methods;

In addition, patients MUST NOT HAVE:

- a. any Visit 1 (baseline) pathogen(s) resistant to either sparfloxacin or erythromycin;

3. Identification of Etiologic Agents

A specific microbiologic etiology for the pneumonia will be determined by the following criteria (adapted from Fine M.J., et al. Am. J. Med. 1990;88: 5-1N-8N and SciCor interpretative criteria):

- a. Routine bacterial pathogens
 - (i) blood culture positive for a pulmonary pathogen, or
 - (ii) light (2+), moderate (3+), or heavy (4+) growth of a pulmonary pathogen from sputum culture, or
 - (iii) rare (1+) growth of a pulmonary pathogen from sputum when neither (i) nor (ii) was present and the sputum gram stain revealed an organism (quantity: 1+ (rare) or greater) compatible with the culture result.

Community Acquired Pneumonia

- b. *Legionella sp.*
 - (i) positive sputum culture, or
 - (ii) positive urine antigen, or
 - (iii) positive DNA-probe of sputum, or
 - (iv) single serum IgG titer > 1:256 or
 - (v) > 4 x rise in serum IgG titer to > 1:128 (Zeus IFA),

- c. *Mycoplasma pneumoniae*
 - (i) positive sputum culture, or
 - (ii) positive DNA-probe of sputum, or
 - (iii) single serum IgM > 1:16 (Zeus IFA), or
 - (iv) single serum IgG > 1:128 (Zeus IFA), or
 - (v) > 4 x rise in serum IgG

- d. *Chlamydia pneumoniae* (TWAR) or *C. psittaci*
 - (i)* positive sputum and/or throat swab culture, or
 - (ii) single serum IgM > 1:20 (Micro-IF), or
 - (iii) single serum IgG > 1:128 (Micro-IF) (> 1:64 for *C psittaci*),
or
 - (iv) > 4 x rise in serum IgG

D. Patient Populations

1. Randomized Patients

The randomized patient population consisted of all patients randomized to study medication.

2. Clinically Evaluable Patients

The clinically evaluable patient population consisted of all patients who met the clinically evaluable criteria.

3. Clinically Evaluable Patients with LRT Pathogen

The "clinically evaluable patients with LRT pathogen" population consisted of all clinically evaluable patients who had a lower respiratory tract pathogen identified by bacteriologic and/or non-bacteriologic methods.

4. Clinically and Bacteriologically evaluable patients

The clinically and bacteriologically evaluable patient population consisted of all clinically evaluable patients who also met the bacteriologically evaluable criteria.

E. Statistical Methods

1. Sample Size Considerations

Sample size calculations were based on a two-sided 95% confidence interval method of establishing equivalence of two proportions with an assumed Clinical Response success rate of 90% in the erythromycin treatment group. To have an 80% probability of showing that sparfloxacin does not differ by more than 10 percentage points in either direction, 190 patients per treatment group are needed for the analysis of the Clinical Response based on the clinically evaluable patients. Note that this is equivalent to having a probability of 90% that the lower end of the 95% confidence interval is above -10%. That is, there is a 90% chance of concluding that sparfloxacin is not 10% worse than erythromycin. Given that only about 90% of enrolled patients can be expected to be clinically evaluable and an attrition rate of about 10%, total study enrollment is estimated at 470 patients.

2. Efficacy Analyses

The two-sided 95% confidence interval method was to be used to establish equivalence between sparfloxacin and erythromycin for all efficacy analyses.

The following primary efficacy analyses were to be carried out:

- a. For the clinically evaluable patients, the Clinical Response was to be analyzed as the primary endpoint with the cured and improved categories pooled together as a positive response (i.e., cured/improved categories vs. other).

b. In addition, the Clinical Response was to be analyzed for all randomized patients.

3. Formal Statistical Analysis Plan

The detailed formal plan for the statistical analysis was to be written and filed with Records and Information prior to unblinding of the study and opening of the data file for the statistical analysis. This plan was to provide the framework for statistical inferences drawn from the protocol and will specify in detail both primary and secondary analyses.

ADVERSE EVENTS

Patients were to be instructed by the investigator to report the occurrence of any adverse event. An adverse event is any undesirable event associated with the use of a drug, whether or not considered drug related, and includes any side effect, injury, toxicity, or sensitivity reaction. It also includes any undesirable clinical or laboratory event which is not normally observed in the patient.

A serious adverse event includes any event, including lack of efficacy, that is fatal or life-threatening, is permanently or severely disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

"Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death. "Requires inpatient hospitalization" should be defined as hospital admission required for treatment of the adverse event. Hospital admission for scheduled elective surgery would not be a serious adverse event.

All adverse events, regardless of severity, were to be followed up by the investigator until satisfactory resolution. The following guidelines will pertain to adverse events:

1. SIGNS/SYMPTOMS OF INFECTION WHICH ARE ASSESSED AS PRIMARY CLINICAL PARAMETERS: Worsening or appearance during the study should have been reported as adverse events if the investigator judged the change to be **UNUSUAL** for a treatment failure. [NOTE: (1) if worsening/appearance was not considered an adverse event, source documents should reflect this; e.g., "worsening cough manifests treatment failure, not an

adverse event"; (2) changes in primary clinical parameters were to be tabulated in study reports.]

2. ALL OTHER UNDESIRABLE EVENTS: Appearance or worsening during study, irrespective of severity, were to be reported as adverse events.

3. ADVERSE EVENTS SHOULD BE REPORTED UP TO 14 DAYS POST DRUG

TREATMENT.

CONCOMITANT MEDICATION

All medications required by the patient to manage underlying illnesses unrelated to the present episode of pneumonia were permitted, with the exception of antacids (including sucralfate and antacid-containing compounds such as Ascriptin™) and medications with any antimicrobial action, which may interfere with the interpretation of study data. All medications taken, including over-the-counter drugs (e.g., ferrous sulfate, multivitamins with zinc, zinc supplements, antipyretics, and non-steroidal anti-inflammatory drugs), must have been recorded on the CRF.

APPLICANT'S EFFICACY ANALYSIS

Investigators:

A total of 428 patients were enrolled by 71 investigators.

Community Acquired Pneumonia

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group	Treatment Group	Treatment Group	Treatment Group		

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Spar	Eryc	Spar	Eryc	Spar	Eryc
Al-Ibrahim	Baltimore, MD	9	11	4	7	2	2
Angelo	New Orleans, LA	1	1	1	0	0	0
Behiels	Edmonton, Alberta	2	1	2	0	1	0
Bensch	Stockton, CA	11	10	8	9	2	2
Black	Cuyahoga Falls, OH	0	1	0	1	0	0
Blumberg	Charleston, SC	0	1	0	1	0	0
Bowman	Clearwater, FL	0	1	0	1	0	0
Boyajian	Elk Gove Village, IL	2	1	2	1	1	1
Caralis	Miami, FL	1	1	1	1	0	0
Chick	Albuquerque, NM	1	0	1	0	0	0
Clecner	St. Jerome, Quebec	9	9	8	8	3	4
Corser	Cincinnati, OH	0	1	0	1	0	0
Cuellar	Lake St. Louis, MO	1	1	1	0	0	0
Daniel	Wenatchee, WA	3	2	3	0	0	0
Dark	Kansas City, MO	0	2	0	1	0	0
DeAbate	Metairie, LA	2	1	2	1	1	0
DeGraff	Hartford, CT	3	1	3	1	1	0
Drehobl	San Diego, CA	2	0	1	0	1	0
Farber	Indianapolis, IN	5	4	4	2	1	0
Fidelholtz	Cincinnati, OH	2	1	2	1	1	0
Gooch	Salt Lake City, UT	4	3	3	2	0	0
Grimard	Chicoutimi, Quebec	11	9	7	7	1	1
Hanna	Spartanburg, NC	7	8	5	4	2	0
Harris	Lake Oswego, OR	7	5	6	4	2	1

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	

		Treatment Group		Treatment Group		Treatment Group	
		Spar	Ery	Spar	Ery	Spar	Ery
Henry	Salt Lake City, UT	23	21	21	18	9	5
Irwin	Birmingham, AL	2	1	2	1	0	1
Jackson	Bellevue, WA	2	2	1	2	0	1
Jacobson	Eugene, OR	2	2	2	2	1	1
Jubran	Hines, IL	4	4	3	2	0	1
Khairi	Indianapolis, IN	2	0	2	0	1	0
Kimmerling	Dallas, TX	0	1	0	1	0	0
LaFata	Oceanside, CA	2	2	2	1	0	0
LaForge	Quebec, Quebec	6	7	5	5	2	1
Lipsky	Seattle, WA	2	3	2	2	0	0
Maggiacomo	Providence, RI	3	4	2	3	0	0
Mahoney	Voorhees, NJ	1	0	1	0	0	0
Makinen	Edmonton, Alberta	1	0	1	0	0	0
Markel	Broomfield, MI	2	3	2	2	1	0
McCluskey	Mogadore, OH	5	5	3	2	0	0
McElvaine	El Paso, TX	4	4	4	2	1	0
Miller	Morrisville, PA	2	1	1	1	0	0
Morales	Santurce, Puerto Rico	1	1	1	1	0	0
Moyer	Hibbing, MN	5	6	5	6	2	1
Nelson	Kansas City, MO	0	1	0	1	0	1
Padgett	Bamberg, SC	2	2	2	2	2	0
Paster	Oregon, WI	0	1	0	1	0	0
Patel	Dayton, OH	4	4	1	2	1	1
Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	

Community Acquired Pneumonia

		Treatment Group		Treatment Group		Treatment Group	
		Spar	Eryc	Spar	Eryc	Spar	Eryc
Platt	Akron, OH	2	3	1	2	0	0
Ranniger	Denver, CO	4	3	3	3	0	0
Redington	Denver, CO	3	2	3	2	0	1
Rogers	Tucson, AZ	1	0	1	0	0	0
Schwartz	Fort Meyers, FL	0	1	0	0	0	0
Segreti	Chicago, IL	0	1	0	0	0	0
Solomon	Denver, CO	5	3	5	3	1	1
Spangenthal	Charlotte, NC	1	2	1	2	1	1
Springmeyer	Seattle, WA	1	1	1	1	1	1
Stein	Rochester, NY	13	12	12	10	3	2
Stewart	Orange, CA	2	4	2	4	0	1
Stone	Cumberland, MD	5	5	4	5	2	2
Tan	Akron, OH	0	1	0	1	0	0
Taylor	Tacoma, WA	2	1	2	1	0	0
Tidman	Smyrna, GA	1	2	0	2	0	1
Trop	Scottsdale, AZ	3	3	1	3	0	0
Tucker	Birmingham, AL	6	5	5	4	1	0
Tung	Dover, NH	2	1	1	1	0	0
Victor	Ottawa, Ontario	3	3	2	2	1	2
Weaver	Pensacola, FL	2	2	2	2	0	1
Williams	Redwood City, CA	1	0	1	0	0	0
Willsie	Kansas City, CA	1	1	1	1	0	0
Wolfe	Denver, CO	2	3	1	2	0	1
Yee	San Diego, CA	1	0	1	0	0	0

DRUG ADMINISTRATION:

The average duration of study drug therapy was 9.3 days (range 1 -12 days) for sparfloxacin and 9.3 days (range 1- 12 days) for erythromycin. The mean daily dosage was 225.3 mg for the sparfloxacin group and 1718 mg for the erythromycin group. The sparfloxacin and erythromycin groups were generally comparable in the number of days of study drug treatment..

SUMMARY OF DAYS OF STUDY DRUG TREATMENT BY TREATMENT GROUP

SPARFLOXACIN VS. ERYTHROMYCIN N=428

DAYS OF STUDY DRUG TREATMENT	TREATMENT GROUP: SPARFLOXACIN		TREATMENT GROUP: ERYTHROMYCIN	
	N	%	N	%
TOTAL PATIENTS:	219		209	
*****	*****	*****	*****	*****
0 - 1	2	(0.9%)	8	(3.8%)
2 - 3	10	(4.6%)	19	(9.1%)
4 - 5	15	(6.8%)	9	(4.3%)
6 - 7	3	(1.4%)	5	(2.4%)
8 - 9	1	(0.5%)	4	(1.9%)
10 - 11	183	(83.6%)	158	(75.6%)
12+	5	(2.3%)	6	(2.9%)

Summary of Patient Disposition

Population	Number (%) of Patients	
	Sparfloxacin 400*/200 mg OD	Erythromycin 500 mg q 6h
All Enrolled (All Randomized)	219 (100)	209 (100)
Completed	172 (78.5)	145 (69.4)
Discontinued	47 (21.5)	64 (30.6)
Clinically Evaluable	177 (80.8)	161 (77.0)
All-Treated With Baseline Pathogen	173 (79.0)	156 (74.6)
Bacteriologically Evaluable	49 (22.4)	38 (18.2)

* Loading Dose .

Demographics:

Summary of Demographic Characteristics (All-Treated Population)*

Characteristic	Sparfloxacin 400*/200 mg QD (n=219)	Erythromycin 500 mg q 6h (n=209)	Treatment Group Comparison p-value
Age, years Mean Range	47.4	47.7	0.889 ^a
Gender, n (%) Male Female	139 (63.5) 80 (36.5)	139 (66.5) 70 (33.5)	0.475 ^b
Race, n (%) Caucasian Black Oriental Other Hispanic	184 (84.0) 21 (9.6) 1 (0.5) 2 (0.9) 11 (5.0)	172 (82.3) 25 (12.0) 1 (0.5) 0 11 (5.3)	0.710 ^b
Body weight, lbs. Mean Range	169.4	177.3	0.017 ^a

* Loading Dose

a Two-way analysis of variance on ranks.

b Generalized Cochran-Mantel-Haenszel test.

Summary of Demographic Characteristics (Clinically Evaluable Population)*

TREATMENT GROUP:

VARIABLE	STATISTIC	SPARFLOXACIN 400/200 MG	ERYTHROMYCIN

AGE (YEARS):	N	177	161
	MEAN	47.9	48.4
	MEDIAN	46	45
	STD	17.5	15.5
	MIN	18	19
	MAX	84	85
GENDER:			
MALE	N	110 (62.1%)	112 (69.6%)
FEMALE	N	67 (37.9%)	49 (30.4%)
			-
HEIGHT (INCH):			
	N	177	161
	MEAN	67.7	68.5
	MEDIAN	68	69
	STD	4.2	4.3
	MIN	52	58
	MAX	78	83
RACE:			
CAUCASIAN	N	150 (84.7%)	138 (85.7%)
BLACK	N	15 (8.5%)	14 (8.7%)
ORIENTAL	N	1 (0.6%)	1 (0.6%)
OTHER	N	2 (1.1%)	
HISPANIC	N	9 (5.1%)	8 (5.0%)

Applicant's Summary of Primary Efficacy Results*

Efficacy Parameter (Population, Time Point)	Number (%) of Patients		95% CI
	Sparfloxacin 400*/200 mg QD	Erythromycin 500 mg q 6h	
Clinical Response Rate - Cured + Improved**	153/177 (86.4)	130/161 (80.7)	-2.2, 13.6
Clinical Cure Rate (clinically evaluable, at TOC)	85/177 (48.0)	65/161 (40.4)	-2.9, 18.2
Clinical Recurrence Rate (clinically evaluable, at late follow-up)	2/134 (1.5)	2/109 (1.8)	ND
By-Pathogen Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	61/65 (93.8)	48/52 (92.3)	ND
By-Patient Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	46/49 (93.9)	35/38 (92.1)	-9.1, 12.7
Bacteriologic Relapse Rate	0/29 (0.0)	1/19 (5.3)	ND
Reinfection Rate	0/29 (0.0)	0/19 (0.0)	ND
Relapse + Reinfection Rate (bacteriologically evaluable, at late follow-up)	0/29 (0.0)	0/19 (0.0)	ND
Overall Response Rate - Cured or Improved and Eradicated or Presumed Eradicated (bacteriologically evaluable, at TOC)	43/49 (87.8)	35/38 (92.1)	-16.9, 8.2

CI = confidence interval; TOC = Test-of-Cure; ND = not done.

* Loading Dose

** Primary efficacy parameter

Clinical Response at Test of Cure

Clinically Evaluable with Baseline Pathogen

Protocol 301

Sparfloxacin (S)

Erythromycin (E)

	S	%	E	%	S	%	E	%
Cure	71	49.0%	72	48.3%	53	43.4%	55	42.3%
Failure	18	12.4%	20	13.4%	20	16.4%	23	17.7%
Improvement	56	38.6%	57	38.3%	49	40.2%	52	40.0%
Indeterminate	0		0		0		0	

Percent = Group Total / Total Number of Patients
(Total Number of Patients does not include Indeterminate totals)

	Sparfloxacin		Erythromycin		Difference (S)		95% Confidence Interval (CI)	
	N	%	N	%	Diff	%	Diff	%
Total Number of Patients:	145	149	122	130				
Cured:	71	72	53	55	5.5%	6.0%	(-6.5% , 17.5%)	(-5.7% , 17.7%)
Cured + Improved:	127	129	102	107	4.0%	4.3%	(-4.5% , 12.5%)	(-4.3% , 12.8%)

Medical Officer's Comments:

The overall clinical response (cure+improvement) at test-of-cure was 129/149 (86.6%) for the sparfloxacin group compared to 107/130 (82.3%) for the erythromycin group.

Clinical Response By All Baseline Pathogens

Clinically Evaluable with Baseline Pathogen

Protocol 301

Evaluated by: RPR

Sparfloxacin (S)

Erythromycin (E)

Pathogen	S	E	Both	None	%	S	E	Both	None	%
C. PNEU AB	8	11	2	0	90.5%	6	5	5	0	68.8%
C. PSITTACI	3	1	1	0	80.0%	2	2	1	0	80.0%
C. SPECIES	6	2	0	0	100.0%	1	2	2	0	60.0%
ENTEROBACTER AEROGENES	0	2	0	0	100.0%	0	1	0	0	100.0%
ENTEROBACTER CLOACAE	1	0	1	0	50.0%	1	0	1	0	50.0%
HAEMOPHILUS INFLUENZAE	15	15	5	0	85.7%	11	14	11	0	69.4%
HAEMOPHILUS PARAINFLUENZAE	30	27	8	0	87.7%	20	22	6	0	87.5%
KLEBSIELLA OXYTOCA	0	1	0	0	100.0%	0	0	0	0	0.0%
KLEBSIELLA PNEUMONIAE	1	2	0	0	100.0%	1	0	2	0	33.3%
L. PNEUMOPHILA GROUP	0	0	0	0	0.0%	1	0	1	0	50.0%
LEGIONELLA URIN. ANT	0	0	0	0	0.0%	0	0	1	0	0.0%
OXELLA CATARRHALIS	2	1	2	0	60.0%	5	2	0	0	100.0%
PLASMA PNEUMONIA	15	13	1	0	96.6%	10	14	4	0	85.7%
NEISSERIA MENINGITIDIS	1	1	0	0	100.0%	0	0	1	0	0.0%
PSEUDOMONAS AERUGINOSA	0	0	0	0	0.0%	1	0	1	0	50.0%
SERRATIA MARCESCENS	0	0	0	0	0.0%	1	0	0	0	100.0%
STAPHYLOCOCCUS AUREUS	3	5	3	0	72.7%	5	2	3	0	70.0%
STREPTOCOCCUS AGALACTIAE	1	0	1	0	50.0%	2	0	2	0	50.0%
STREPTOCOCCUS EQUISIMILIS	1	0	0	0	100.0%	1	1	1	0	66.7%
STREPTOCOCCUS MITIS	1	0	0	0	100.0%	0	0	0	0	0.0%
STREPTOCOCCUS PNEUMONIAE	23	14	2	0	94.9%	15	5	4	0	83.3%
STREPTOCOCCUS PYOGENES	0	1	0	0	100.0%	0	1	0	0	100.0%

Clinical Response By All Baseline Pathogens

Clinically Evaluable with Baseline Pathogen

Protocol 301

Evaluated by: FDA

Sparfloxacin (S)

Erythromycin (E)

Baseline Pathogen	S. Counts	S. Improv.	S. Fail.	S. No Resp.	S. Percent	E. Counts	E. Improv.	E. Fail.	E. No Resp.	E. Percent
C. PNEU AB	8	12	2	0	90.8%	6	5	5	0	68.8%
C. PSITTACI	3	1	1	0	80.0%	2	2	1	0	80.0%
C. SPECIES	6	2	0	0	100.0%	2	2	2	0	66.7%
ENTEROBACTER AEROGENES	0	2	0	0	100.0%	0	1	0	0	100.0%
ENTEROBACTER CLOACAE	1	0	1	0	50.0%	1	0	1	0	50.0%
HAEMOPHILUS INFLUENZAE	15	16	5	0	86.1%	12	14	13	0	66.7%
HAEMOPHILUS PARAINFLUENZAE	31	26	9	0	86.4%	20	23	7	0	86.0%
EBSEIELLA OXYTOCA	0	1	0	0	100.0%	0	0	0	0	0.0%
EBSEIELLA PNEUMONIAE	1	2	0	0	100.0%	1	0	2	0	33.3%
L. PNEUMOPHILA GROUP	0	0	0	0	0.0%	1	0	1	0	50.0%
LEGIONELLA URIN. ANT	0	0	0	0	0.0%	0	0	1	0	0.0%
MORAXELLA CATARRHALIS	2	1	2	0	60.0%	5	2	0	0	100.0%
MYCOPLASMA PNEUMONIA	15	13	1	0	96.6%	10	14	4	0	85.7%
NEISSERIA MENINGITIDIS	1	1	0	0	100.0%	0	0	1	0	0.0%
PSEUDOMONAS AERUGINOSA	0	0	0	0	0.0%	1	0	1	0	50.0%
SERRATIA MARCESCENS	0	0	0	0	0.0%	1	0	0	0	100.0%
STAPHYLOCOCCUS AUREUS	3	5	3	0	72.7%	5	2	3	0	70.0%
STREPTOCOCCUS AGALACTIAE	1	0	1	0	50.0%	2	0	2	0	50.0%
STREPTOCOCCUS EQUISIMILIS	1	0	0	0	100.0%	1	1	1	0	66.7%
STREPTOCOCCUS MITIS	1	0	0	0	100.0%	0	0	0	0	0.0%
STREPTOCOCCUS PNEUMONIAE	23	15	3	0	92.7%	16	6	4	0	84.6%
STREPTOCOCCUS PYOGENES	0	1	0	0	100.0%	0	1	0	0	100.0%

**Clinical Response at Test of Cure
Sustained/Delayed Response (by Patient)**

Clinically Evaluable with Baseline Pathogen

Protocol 301

Sparfloxacin (S)

Erythromycin (E)

	S, n/N	S, %	E, n/N	E, %	S, n/N	S, %	E, n/N	E, %
Delayed Cure	19	14.5%	20	14.7%	15	14.0%	16	14.0%
Early Failure	18	13.7%	19	14.0%	20	18.7%	21	18.4%
Indeterminate	14		13		15		16	
Recurrence	1	0.8%	1	0.7%	2	1.9%	2	1.8%
Sustained Cure	64	48.9%	65	47.8%	46	43.0%	48	42.1%
Sustained Imp.	29	22.1%	31	22.8%	24	22.4%	27	23.7%

Percent = Group Total / Total Number of Patients
(Total Number of Patients does not include indeterminate totals)

	Sparfloxacin		Erythromycin		Difference 95%		95% CI (Upper/Lower)	
	n/N	%	n/N	%	n/N	%	n/N	%
Number of Patients:	131	136	107	114				
Delayed Cure:	64	65	46	48	5.9%	5.7%	(-6.8% , 18.6%)	(-6.7% , 18.0%)
Sustained Cure + Delayed Cure:	83	85	61	64	6.3%	6.4%	(-6.1% , 18.8%)	(-5.9% , 18.6%)
Sust. Cure + Del. Cure + Sust. Impr.:	112	116	85	91	6.1%	5.5%	(-3.7% , 15.8%)	(-4.0% , 14.9%)

Medical Officer's Comments:

The failure rate was 14% in the sparfloxacin group compared to 18.4% in the erythromycin group. The recurrence rate was also higher in the erythromycin group (1.8% compared to 0.7% in the sparfloxacin group).

Community Acquired Pneumonia

Bacteriologic Response - By Baseline Pathogen at Test of Cure**Bacteriologically evaluable patients****SPARFLOXACIN (S)****ERYTHROMYCIN (E)**

Organism	S - Erad	S- PE	S- Pers	S- PPers	S-%	E- Erad	E- PE	E-Pers	E- PPers	E-%
<i>C. pneumoniae</i>	0	9	0	0	100%	0	3	0	1	75%
<i>H. parainfluenzae</i>	0	8	0	0	100%	0	4	0	0	100%
<i>M. catarrhalis</i>	1	2	0	1	75%	1	3	0	0	100%
<i>M. pneumoniae</i>	0	15	0	1	93.8%	0	15	0	0	100%
<i>S. pneumoniae</i>	3	13	1	0	94.1%	2	8	1	0	90.0%

Key: Erad -eradicated; PE - presumed eradicated; Pers - persisted; PPers - presumed persisted

Medical Officer's Comments:

The Medical Officer concurs with the Applicant's analysis of the bacteriologic response at test-of-cure. In this study, patients who had *H. influenzae* isolated at baseline were clinically evaluable but not bacteriologically evaluable. None of the *Streptococcus pneumoniae* isolated in this study were penicillin-resistant.

**Bacteriologic Response at Test of Cure
Sustained/Delayed Response**

Bacteriologically Evaluable

Protocol 301

Sparfloxacin (S)

Erythromycin (E)

	S, n (%)	S, n (%)	E, n (%)	E, n (%)
Early Persistence	3 9.7%	3 9.1%	3 14.3%	3 13.6%
Indeterminate	18	16	17	16
Relapse	0 0.0%	0 0.0%	1 4.8%	1 4.5%
Sustained Eradicated	28 90.3%	30 90.9%	17 81.0%	18 81.8%

Percent = Group Total / Total Number of Patients
(Total Number of Patients does not include Indeterminate totals)

	Sparfloxacin		Erythromycin		95% CI	
	n	%	n	%	Lower	Upper
Total Number of Patients:	31	33	21	22		
Sustained Eradicated:	28	30	17	18	(-10.4% , 29.1%)	(-9.8% , 28.0%)

Medical Officer's Comments:

The eradication rate at the follow-up period was 90.9% for the sparfloxacin group compared to 81.8% for the erythromycin group.

SAFETY

Safety Summary

Safety Parameter	Number (%) Patients		
	Sparfloxacin (N=219)	Erythromycin (N=209)	p-value
Adverse Event ^a	136 (62.1)	140 (67.0)	ND
Most Common ^b			
Nausea	13 (5.9)	43 (20.6)	ND
Diarrhea	15 (6.8)	38 (18.2)	ND
Vomiting	12 (5.5)	25 (12.0)	ND
Abdominal Pain	9 (4.1)	24 (11.5)	ND
Headache	16 (7.3)	14 (6.7)	ND
Photosensitivity Reaction	14 (6.4)	1 (0.5)	<0.001
Digestive System	48 (21.9)	93 (44.5)	<0.001
Musculoskeletal System	6 (2.7)	7 (3.3)	ND
Nervous System	28 (12.8)	24 (11.5)	0.494
Cardiovascular System	19 (8.7)	16 (7.7)	0.661
Adverse Events Related to Study Drug	85 (38.8)	108 (51.7)	ND
Most Common ^b			
Diarrhea	14 (6.4)	36 (17.2)	ND
Nausea	9 (4.1)	35 (16.7)	ND
Abdominal Pain	4 (1.8)	22 (10.5)	ND
Vomiting	8 (3.7)	17 (8.1)	ND
Photosensitivity Reaction	13 (5.9)	1 (0.5)	ND
Adverse Events Leading to Discontinuation	21 (10.0)	31 (14.8)	ND
Most Common ^c			
Nausea	2 (1.0)	9 (4.3)	ND
Vomiting	1 (0.5)	9 (4.3)	ND
Pneumonia	2 (1.0)	5 (2.4)	ND
Abdominal Pain	0	6 (2.8)	ND
Adverse Laboratory Events	30 (13.7)	28 (13.4)	ND
Most Common ^c			
↑SGPT	12 (5.5)	9 (4.3)	ND
↑SGOT	9 (4.1)	6 (2.9)	ND
↑Neutrophils	5 (2.3)	5 (2.4)	ND
↑White Blood Cell Count	7 (3.2)	5 (2.4)	ND
↓Platelets	5 (2.3)	2 (1.0)	ND
ND = not done			
a The majority of adverse events were of mild or moderate severity.			
b Reported by 5% of patients in either treatment group.			
c Reported by 2% of patients in either treatment group.			

CONCLUSIONS

The overall clinical response rates for both drug groups are comparable but the photosensitivity reactions in the sparfloxacin group are worrisome. These are patients who while on therapy were told to stay indoors and away from the UV light, and the amount of photosensitivity reactions in that group is approximately 6% compared to <1% in patients on erythromycin.

RECOMMENDATIONS:

The results of this study will be combined with those of other pivotal study to make the final recommendations.

II. Study 352 Synopsis:

Objective: To compare the safety and efficacy of orally administered sparfloxacin and cefaclor in the treatment of community-acquired pneumonia.

Patient Population: Male or female patients >18 years of age.

Structure: Parallel group.

Study Dates: June 1, 1992 to March 4, 1995.

Dosage: Sparfloxacin 400 mg loading dose followed by 200 mg once a day for 10 days.
Cefaclor 500 mg every 8 hours for 10 days.

Multicenter: Yes.

No. of centers: 74 in the U.S.A.

Blinding: Double-blind, Double-dummy.

Method of Randomization: Randomization in a 1:1 ratio at each investigational site to receive either sparfloxacin or cefaclor.

Efficacy Variables:

The primary efficacy parameter was clinical response in the clinically evaluable patient population. Secondary efficacy parameters included clinical response (all-treated and bacteriologically evaluable patient populations); clinical recurrence (all-treated, clinically evaluable, and bacteriologically evaluable patient populations); and by-patient bacteriologic response, by-pathogen bacteriologic response, bacteriologic relapse/reinfection and overall response (all-treated with a baseline pathogen and bacteriologically evaluable patient populations).

Study Evaluations:

Study visits were scheduled for baseline (Visit 1), Day 4 + 1 of treatment (Visit 2), Day 20 + 3 (10 days post-treatment; Visit 3 [Test-of-Cure]) and Day 38 + 7 (28 days post-treatment; Visit 4). An assessment of the patient's response to study drug treatment was to be made at Visit 3 (or Premature Discontinuation before Visit 3); recurrence of infection was to be determined at Visit 4 (or Premature Discontinuation after Visit 3).

Safety measurements:

Adverse clinical and laboratory events and changes in electrocardiogram (ECG), vital sign and physical examination findings.

Statistical methods:

The two-sided 95% confidence interval method of statistical analysis was used to demonstrate equivalence between sparfloxacin and cefaclor for efficacy variables.

Medical Officer's Comments:

This study design was identical to study 301 with the exception of the comparator drug. The comparator drug used in this study was cefaclor instead of erythromycin.

APPLICANT'S EFFICACY ANALYSIS

Investigators:

A total of 330 patients were enrolled by 74 investigators.

Community Acquired Pneumonia

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group		Treatment Group		Treatment Group	
		Spar	Cef	Spar	Cef	Spar	Cef
Al-Ibrahim	Baltimore, MD	2	3	2	1	2	1
Alwine	Downingtown, PA	2	1	1	1	0	1
Avsar	Birmingham, AL	0	1	0	0	0	0
Beauford	High Point, NC	3	4	3	4	3	2
Bensch	Stockton, CA	0	1	0	1	0	1
Bloom	Houston, TX	2	2	2	2	2	1
Branditz	Zanesville, OH	13	11	10	9	7	6
Brandon	San Diego, CA	5	8	3	7	2	4
Bush	Eclectic, AL	0	1	0	1	0	1
Campbell	Tucson, AZ	8	4	7	4	6	3
Cernea	Berkley, NJ	0	1	0	1	0	1
Chausow	Sunnyvale, CA	2	1	2	1	1	1
Cohen	Trumbull, CT	0	1	0	1	0	1
Cole	Fayetteville, GA	2	2	2	2	1	1
Collins, D	Winston-Salem, NC	4	4	4	4	4	4
Collins, G	Charlotte, NC	0	2	0	1	0	0
D'Amico	Nashville, TN	0	1	0	1	0	1
David	Johnson City, TN	3	3	2	3	1	3
Donowitz	Charlottesville, NC	4	2	0	2	0	1
Douglas	Ruston, LA	2	2	0	0	0	0
Erlandson	Monroe, WI	0	1	0	1	0	0
Ervin	Kansas City, MO	1	1	1	1	1	1
Fellers	Greeley, CO	0	1	0	1	0	0
Fleegler	Sarasota, FL	3	2	3	1	3	1
Flenniken	Shreveport, LA	4	2	3	0	3	0

Community Acquired Pneumonia

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group		Treatment Group		Treatment Group	
		Spar	Cef	Spar	Cef	Spar	Cef
Garamy	Crescent Springs, KY	1	1	1	0	1	0
Ginsberg	Harleysville, PA	2	4	1	2	1	2
Greene	Salem, VA	0	2	0	2	0	1
Henry, W.	Greer, SC	8	5	5	4	3	4
Henry, D.	Salt Lake City, UT	1	2	1	2	1	2
Hilmi	Rosendale, NY	4	6	4	5	2	5
Holloway	Atlanta, GA	1	1	1	1	1	1
Hu	St. Peters, MO	1	1	0	1	0	1
Karetzky	Newark, NJ	1	1	1	1	1	1
Kirby	Ruston, LA	2	2	2	2	2	2
Kirstein	Salt Lake City, UT	0	2	0	2	0	2
Kulback	Birmingham, AL	0	1	0	1	0	1
LaLonde	Greensboro, NC	6	5	6	3	5	3
Matlock	San Antonio, TX	0	1	0	1	0	0
McCollum	Chanhassen, MN	1	1	1	0	1	0
McInroy	Camp Hill, PA	4	0	4	0	2	0
Memon	Absecon, NJ	1	0	1	0	1	0
Morell	Winston-Salem, NC	3	1	2	1	2	1
Murphree	Jacksonville, FL	5	5	2	2	2	2
Nolen	Columbiana, AL	1	1	0	1	0	1
Pape	Wilmington, NC	2	1	2	1	2	0
Parman	Middletown, NJ	3	2	2	2	1	2
Pierone	Vero Beach, FL	2	1	2	0	2	0
Riley	Dubuque, IA	4	3	4	3	4	3
Rosen, J	Coral Gables, FL	3	4	2	4	2	4

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group		Treatment Group		Treatment Group	
		Spar	Cef	Spar	Cef	Spar	Cef
Rosen, R	Winston-Salem, NC	2	1	1	1	1	1
Ruoff	Kalamazoo, MI	4	3	3 *	1	3	1
Salisbury	Red Bank, NJ	12	11	11	9	10	7
Santiago	Los Angeles, CA	1	3	1	2	1	1
Schultz	Dubuque, IA	5	4	5	4	4	2
Scott	South Euclid, OH	1	0	1	0	1	0
Simpson	Albuquerque, NM	2	0	2	0	2	0
Sklar	Alameda, CA	0	2	0	2	0	1
Smith, W	New Orleans, LA	1	3	1	2	1	2
Smith, D	Atlanta, GA	1	0	0	0	0	0
Snow	Birmingham, AL	1	2	1	2	1	2
Spira	Cherry Hill, NJ	2	2	2	2	1	2
Steinberg	New Hyde Park, NY	2	0	2	0	0	0
Sterman	Lawrenceville, NJ	3	0	2	0	2	0
Stringer	Manilus, NY	2	2	2	1	1	0
Tolle	Indianapolis, IN	0	1	0	0	0	0
Trop	Scottsdale, AZ	3	2	2	2	2	1
Vandewalker	Rolla, MO	1	0	1	0	0	0
Van Hook	Winter Haven, FL	1	0	1	0	0	0
Weisman	Warminster, PA	1	2	1	1	1	0
Wilhelm	Birmingham, AL	5	5	4	4	4	3
Zaremba	Birmingham, AL	1	1	1	1	1	1
Zdunek	Calcutta, OH	1	0	1	0	1	0
Zuschke	Mobile, AL	0	3	0	3	0	3

DRUG ADMINISTRATION:

The average duration of study drug therapy was 9.6 days (range 1 -12 days) for sparfloxacin and 9.9 days (range 1- 12 days) for cefaclor. The mean daily dosage was 223.7 mg for the sparfloxacin group and 1381 mg for the cefaclor group. The sparfloxacin and cefaclor groups were generally comparable in the number of days of study drug treatment..

SUMMARY OF DAYS OF STUDY DRUG TREATMENT BY TREATMENT GROUP

PROTOCOL : RP64206X_352 - SPARFLOXACIN VS. CEPACLOR IN CAP, N=330
 INVESTIGATOR : 74 INVESTIGATORS COMBINED
 TREATMENT GROUP : 2 TREATMENT GROUPS COMBINED

DAYS OF STUDY DRUG TREATMENT	TREATMENT GROUP: SPARFLOXACIN		TREATMENT GROUP: CEPACLOR	
	N	%	N	%
TOTAL PATIENTS:	168		162	
*****	*****		*****	
0 - 1	1	(0.6%)	2	(1.2%)
2 - 3	7	(4.2%)	7	(4.3%)
4 - 5	9	(5.4%)	9	(5.6%)
6 - 7	3	(1.8%)	3	(1.9%)
8 - 9	5	(3.0%)	2	(1.2%)
10 - 11	135	(80.4%)	129	(79.6%)
12+	8	(4.8%)	10	(6.2%)

Summary of Patient Disposition*

Population	Number (%) of Patients		
	Sparfloxacin 400*/200 mg QD	Cefaclor 500 mg q 8h	Total
All Enrolled (All Randomized)	168 (100)	162 (100)	330 (100)
Completed	111 (66.1)	113 (69.8)	224 (67.9)
Discontinued	57 (33.9)	49 (30.2)	106 (32.1)
Clinically Evaluable	134 (79.8)	128 (79.0)	262 (79.4)
All-Treated With Baseline Pathogen	151 (89.9)	145 (89.5)	296 (89.7)
Bacteriologically Evaluable	109 (64.9)	100 (61.7)	209 (63.3)

* Loading Dose

Summary of Demographic Characteristics (All-Treated Population)

Characteristic	Sparfloxacin 400*/200 mg QD (n=168)	Cefaclor 500 mg q 8h (n=162)	Treatment Group Comparison p-value
Age, years			
Mean	48.0	50.9	0.224 ^a
Range			
Gender, n (%)			0.239}b}
Male	93 (55.4)	101 (62.3)	
Female	75 (44.6)	61 (37.7)	
Race, n (%)			0.509}b}
Caucasian	136 (81.0)	128 (79.0)	
Black	28 (16.7)	26 (16.0)	
Oriental	0	2 (1.2)	
Hispanic	4 (2.4)	6 (3.7)	
Body weight, lbs			0.517}a}
Mean	173.5	176.0}c	
Range			

* Loading Dose

a Two-way analysis of variance on ranks

b Generalized Cochran-Mantel-Haenszel test

c For one patient a baseline weight was not available (N = 151)

Summary of Primary Efficacy Results*

Efficacy Parameter (Population, Time Point)	Number (%) of Patients		
	Sparfloxacin 400*/200 mg QD	Cefaclor 500 mg q 8h	95% CI
Clinical Response Rate - Cured + Improved**	116/134 (86.6)	108/128 (84.4)	-6.3, 10.7
Clinical Cure Rate (clinically evaluable, at TOC)	59/134 (44.0)	50/128 (39.1)	-7, 16.9
Clinical Recurrence Rate (clinically evaluable, at late follow-up)	3/99 (3.0)	1/99 (1.0)	ND
By-Pathogen Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	159/173 (91.9)	119/142 (83.8)	ND
By-Patient Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	97/109 (89.0)	79/100 (79.0)	0.1, 19.9
Bacteriologic Relapse Rate	0/81 (0.0)	1/72 (1.4)	ND
Reinfection Rate	0/81 (0.0)	0/72 (0.0)	ND
Relapse + Reinfection Rate (bacteriologically evaluable, at late follow-up)	0/81 (0.0)	0/72 (0.0)	ND
Overall Response Rate - Cured or Improved and Eradicated or Presumed Eradicated (bacteriologically evaluable, at TOC)	95/109 (87.2)	79/100 (79.0)	-2, 18.3

CI=confidence interval; TOC=Test-of-Cure; ND=not done.

* Loading Dose

** Primary efficacy parameter

CLINICAL RESPONSE AT TEST-OF-CURE- Pts with Baseline Pathogens

Cure	54	44.26%	55	44.35%	47	39.83%	48	40.34%
Failure	15	12.30%	16	12.90%	18	15.25%	18	15.13%
Improvement	53	43.44%	53	42.74%	53	44.92%	53	44.54%
Indeterminate	0		0		0		0	

KEY:

S - sparfloxacin; C - cefaclor

RPR - Applicant; MO - Medical Officer

Medical Officer's Comments:

The clinical response (cure + improvement) at test-of-cure for the sparfloxacin group was 108/124 (87.1%) compared to cefaclor group 101/119 (84.9%). There were two additional patients in the sparfloxacin group and one additional patient in the cefaclor group that the Medical Officer considered evaluable and the applicant did not. These 3 patients were evaluated one day outside the study test-of-cure window period. The Medical Officer considered that as a minor violation of protocol and included them in the evaluable patient population.

APPLICANT'S ANALYSIS - CLINICAL RESPONSE

Organism	S	Imp	F	% S	S/S	CEP	SEP	Other	% S
ACINETOBACTER ANITRATUS	2	0	0	100.0%	1	1*	0	0	100.0%
ACINETOBACTER LWOFFI	0	0	0	0.0%	0	1	1	0	50.0%
C. PSITTACI	0	1	0	100.0%	1	0	0	0	100.0%
C. SPECIES	1	1	0	100.0%	0	2	0	0	100.0%
CHLAMYDIA AB.	7	3	3	76.9%	3	4	0	0	100.0%
ENTEROBACTER AEROGENES	0	1	0	100.0%	0	1	0	0	100.0%
ENTEROBACTER CLOACAE	2	0	1	66.7%	2	1	2	0	60.0%
HAEMOPHILUS INFLUENZAE	10	10	5	80.0%	10	18	5	0	84.8%
HAEMOPHILUS PARAINFLUENZAE	27	27	6	90.0%	22	19	8	0	83.7%
KLEBSIELLA OXYTOCA	2	1	0	100.0%	0	0	0	0	0.0%
KLEBSIELLA PNEUMONIAE	1	1	2	50.0%	1	4	0	0	100.0%
L. PNEUMOPHILA GROUP	2	0	0	100.0%	0	0	0	0	0.0%
MORAXELLA CATARRHALIS	2	2	0	100.0%	2	4	1	0	85.7%
MYCOPLASMA PNEUMONIA	9	17	3	89.7%	13	10	4	0	85.2%
NEISSERIA MENINGITIDIS	3	1	0	100.0%	2	1	0	0	100.0%
PSEUDOMONAS AERUGINOSA	0	2	2	50.0%	1	4	1	0	83.3%
SERRATIA MARCESCENS	1	2	0	100.0%	1	1	0	0	100.0%
STAPHYLOCOCCUS AUREUS	3	3	1	85.7%	2	2	1	0	80.0%
STREPTOCOCCUS AGALACTIAE	1	3	0	100.0%	0	0	0	0	0.0%
STREPTOCOCCUS EQUISIMILIS	0	1	0	100.0%	0	0	0	0	0.0%
STREPTOCOCCUS PNEUMONIAE	15	11	1	96.3%	11	8	1	0	95.0%
STREPTOCOCCUS PYOGENES	1	1	1	66.7%	1	1	0	0	100.0%

KEY:

S- sparfloxacin; CEP - cefactor

C - cure; Imp - improved; F - failure

MEDICAL OFFICER'S ANALYSIS

Pathogen	Number of Patients	Number of Patients with Baseline Pathogen	Percentage of Patients with Baseline Pathogen	Number of Patients with Baseline Pathogen and Requested Pathogen	Percentage of Patients with Baseline Pathogen and Requested Pathogen
CHLAMYDIA PNEUMONIA	7	3	100.0%	3	100.0%
HAEMOPHILUS INFLUENZAE	10	10	100.0%	10	96.2%
H. PARAINFLUENZAE	26	26	98.1%	22	100.0%
MORAXELLA CATARRHALIS	2	2	100.0%	2	100.0%
MYCOPLASMA PNEUMONIA	9	17	100.0%	13	100.0%
STREPTOCOCCUS PNEUMONIAE	15	10	100.0%	10	94.7%

Medical Officer's Comments:

The Medical Officer analysis table has included patients who had a baseline pathogen and only those pathogens that the applicant is requesting for the Community-Acquired Pneumonia Indication in the package insert.

Bacteriologic Evaluation by Applicant - Test-of-Cure

Organism	S	C	E	PE	P	PP	COL	%	Eradicated	Presumed Eradicated	Persisted	Presumed Persisted	Colonization	%	
ACINETOBACTER	0	1	0	0	0	0	0	100	0	0*	0	0	0	0	0.0
ACINETOBACTER	0	0	0	0	0	0	0	0.0	0	1	0	0	0	0	100
C. PSITTACI	0	1	0	0	0	0	0	100	0	0	0	0	0	0	0.0
C. SPECIES	0	2	0	0	0	0	0	100	0	2	0	0	0	0	100
CHLAMYDIA AB	0	10	0	3	0	0	0	76.9	0	5	0	0	0	0	100
ENTEROBACTER	0	1	0	0	0	0	0	100	0	0	1	0	0	0	0.0
ENTEROBACTER	0	2	0	0	0	0	0	100	1	1	0	0	0	0	100
HAEMOPHILUS	4	18	0	4	0	0	0	83.3	5	20	3	3	0	0	80.6
HAEMOPHILUS	9	44	1	1	0	0	0	96.4	2	29	6	4	0	0	75.6
KLEBSIELLA	0	1	0	0	0	0	0	100	0	0	0	0	0	0	0.0
KLEBSIELLA	2	0	1	0	0	0	0	86.7	2	2	0	0	0	0	100
L. PNEUMOPHILA	0	2	0	0	0	0	0	100	0	2	0	0	0	0	0.0
MORAXELLA	1	3	0	0	0	0	0	100	0	5	0	1	0	0	83.3
MYCOPLASMA	0	21	0	2	0	0	0	91.3	0	20	0	4	0	0	83.3
NEISSERIA	1	2	0	0	0	0	0	100	1	2	0	0	0	0	100
STAPHYLOCOCC	0	6	0	1	0	0	0	85.7	0	3	0	0	0	0	100
STREPTOCOCCU	0	3	0	0	0	0	0	100	0	0	0	0	0	0	0.0
STREPTOCOCCU	3	20	1	0	0	0	0	95.8	3	13	1	0	0	0	94.1
STREPTOCOCCU	2	1	0	0	0	0	0	100	0	2	0	0	0	0	100

Key:

S - sparfloracin; C - cefaclor

E - eradicated; PE - presumed eradicated; P - persisted; PP - presumed persisted; COL - colonization

Community Acquired Pneumonia

FDA'S BACTERIOLOGIC RESPONSE - TEST OF CURE

C. PNEUMONIA	0	10	0	3	0	75.9	0	5	0	0	0	100
H. INFLUENZAE	4	16	0	4	0	83.3	5	20	2	3	0	80.6
H. PARAINFLUENZA	9	44	1	1	0	96.4	2	29	1	4	0	75.6
M. CATARRHALIS	1	3	0	0	0	100	0	5	0	1	0	83.3
M. PNEUMONIA	0	21	0	2	0	91.3	0	20	0	4	0	83.3
S. PNEUMONIAE	3	20	1	0	0	95.8	3	13	1	0	0	94.1

Key:

S - sparfloxacin; C - cefaclor

E - eradicated; PE - presumed eradicated; P - persisted; PP - presumed persisted; COL - colonization

MEDICAL OFFICER'S COMMENTS:

The above analysis includes all those patients who had a baseline pathogen isolated, and had a post-treatment culture and/or serology performed.

None of the *S. pneumoniae* isolated were penicillin-resistant.

Community Acquired Pneumonia

Clinical Response at Follow-up - FDA and Applicant's Analyses

	RPR	RPR %	MO	S, MO %	C, RPR	C, RPR %	C, MO	C, MO %
Delayed Cure	26	24.30%	26	23.85%	36	33.03%	36	32.73%
Early Failure	15	14.02%	16	14.68%	10	16.51%	10	16.36%
Indeterminate	15		15		9		9	
Recurrence	3	2.80%	3	2.75%	1	0.92%	1	0.91%
Sustained Cure	46	42.98%	47	43.12%	43	39.45%	44	40.00%
Sustained Imp.	17	15.89%	17	15.80%	11	10.09%	11	10.00%

Key:

S - sparfloxacin; C - cefaclor

RPR - Applicant; MO - Medical Officer

MEDICAL OFFICER'S COMMENTS:

The failure rate was 14.68% in the sparfloxacin group compared to 16.36% in the cefaclor group, but the recurrence rate was slightly higher in the sparfloxacin group (2.8% compared to 0.91%).

Bacteriologic Response at Follow-up

	RPR	MO	RPR %	MO %	RPR	MO	RPR %	MO %
Early Persistence	14	15	13.73%	14.42%	26	26	24.30%	24.07%
Indeterminate	20	20			11	11		
Release	0	0	0.00%	0.00%	1	1	0.93%	0.93%
Sustained Eradicated	88	89	86.27%	85.58%	80	81	74.77%	75.0

Key: S - sparfloxacin; C - cefaclor

RPR - Applicant; MO - Medical Officer

Medical Officer's Comments:

The eradication rate at the follow-up period was 85.58% in the sparfloxacin group compared to 75% in the cefaclor group.

Safety Summary

Safety Parameter	Number (%) Patients		
	Sparfloxacin (n= 168)	Cefaclor (n= 162)	p-value
Adverse Event ^a	84 (50.0)	80 (49.4)	ND
Most Common ^b			
Headache	18 (10.7)	14 (8.6)	ND
Rhinitis	10 (6.0)	11 (6.8)	ND
Diarrhea	7 (4.2)	10 (6.2)	ND
Digestive System	24(14.3)	21 (13.0)	0.846
Musculoskeletal System	3 (1.8)	3 (1.9)	ND
Nervous System	16 (9.5)	14(8.6)	0.924
Cardiovascular System	12 (7.1)	8 (4.9)	0.446
Photosensitivity Reaction	4(2.4)	1 (0.6)	0.177
Adverse Events Related to Study Drug	37 (22.0)	41 (25.3)	ND
Adverse Events Leading to Discontinuation ^c	11 (6.5)	9 (5.6)	ND
Most Common ^d			
Pneumonia	1 (0.6)	4 (2.5)	ND
Adverse Laboratory Events	18 (10.7)	14 (8.6)	ND
Most Common ^d			
↑SGPT	9 (5.4)	6 (3.7)	ND
↑SGOT	8 (4.8)	5 (3.1)	ND
↑Blood Glucose	4 (2.4)	1 (0.6)	ND

ND=not done

- a The majority of adverse events were of mild or moderate severity.
- b Reported by 5% of patients in either treatment group.
- c One additional patient in the cefaclor group experienced an adverse event that led to discontinuation from the study by the investigator; however, the investigator classified the reason for discontinuation for this patient as test drug ineffective in the disposition section of the case report form.
- d Reported by 2% of patients in either treatment group.

Medical Officer's Comments and Recommendations:

Based upon the data submitted, it is recommended that sparfloxacin be approved for the indication of community-acquired pneumonia caused by *Chlamydia pneumoniae*, *Hemophilus influenzae*, *Hemophilus parainfluenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*. Although the eradication rates for *Chlamydia pneumoniae* and *Hemophilus influenzae* are lower than expected, the clinical response rate in those patients infected with these organisms was 100%, thus, these patients did very well clinically. Community-acquired pneumonia caused by *Moraxella catarrhalis* can not be recommended at this time because the number of organisms studied is small.

The final recommendations will be made after results from both the studies are combined.

Medical Officer's combined analysis of bacteriological outcome for studies 301 and 352:

Bacteriologic Response - By Baseline Pathogen at Test of Cure
Bacteriologically evaluable patients

SPARFLOXACIN

Organism	Eradicated	Presumed eradicated	Persisted	Presumed persisted	Total -%
<i>C. pneumoniae</i>	0	19	0	3	19/22 -86.4%
<i>H. influenzae</i>	4	16	0	4	20/24 -83.3%
<i>H. parainfluenzae</i>	9	52	1	1	61/63 -96.8%
<i>M. catarrhalis</i>	2	5	0	1	7/8 -87.5%
<i>M. pneumoniae</i>	0	36	0	3	36/39 - 92.3%
<i>S. pneumoniae</i>	6	33	2	0	39/41 - 95.1%

Medical Officer's Comments:

When the results of the bacteriological outcome from two studies are combined, sparfloxacin appears to be effective in eradicating the common pathogens that are responsible for causing community acquired pneumonia.

In these two studies, the number of evaluable patients where *M. catarrhalis* was isolated is small, but in study 356 (Acute Exacerbation of Chronic Bronchitis), there were 38 isolates in the sparfloxacin group, and the eradication/presumed eradication rate was 94.7%.

Community Acquired Pneumonia

OVERALL RECOMMENDATIONS:

Based upon the data submitted, sparfloxacin is recommended for approval for community acquired pneumonia caused by *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*. Although the eradication rates for *Chlamydia pneumoniae* and *Haemophilus influenzae* are lower than expected, the clinical response rate in those patients infected with these organisms was 100%, thus, these patients did very well clinically. None of the *Streptococcus pneumoniae* isolated were penicillin-resistant.

INDICATION - ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Overview of U. S. Pivotal Study:

1. **Study 356:** Double-Blind, Double- Dummy, Randomized, Comparative, Multi-center trial conducted with ofloxacin as the comparator drug.

The Applicant is proposing the following indication and dosage recommendations for the package insert:

INDICATIONS AND USAGE SECTION

DOSAGE AND ADMINISTRATION

REVIEW OF PIVOTAL STUDY

This study was conducted in the United States of America and Canada.

I. Study 356 Synopsis:

Objective: To compare the safety and efficacy of orally administered sparfloxacin and ofloxacin in the treatment of patients with acute exacerbation of chronic bronchitis.

Patient Population: Male or female patients ≥ 18 years of age.

Structure: Parallel group.

Study Dates: November 12, 1992 to October 18, 1994.

Dosage: Sparfloxacin 400 mg loading dose followed by 200 mg once a day for 10 days.
Ofloxacin 400 mg every 12 hours for 10 days.

Multicenter: Yes.

No. of centers: 68 in the U.S.A. and Canada.

Blinding: Double-blind, Double-dummy.

Method of Randomization: Randomization in a 1:1 ratio at each investigational site to receive either sparfloxacin or ofloxacin.

Efficacy Variables:

The primary efficacy parameter was clinical response in the clinically evaluable patient population. Secondary efficacy parameters included clinical response (all-treated and bacteriologically evaluable patient populations); clinical recurrence (all-treated, clinically evaluable, and bacteriologically evaluable patient populations); and by-patient bacteriologic response, by-pathogen bacteriologic response, bacteriologic relapse/reinfection and overall response (all-treated with a baseline pathogen and bacteriologically evaluable patient populations).

Study Evaluations:

Study visits were scheduled for baseline (Visit 1), Day 4 + 1 of treatment (Visit 2), Day 20 + 3 (10 days post-treatment; Visit 3 [Test-of-Cure]) and Day 38 + 7 (28 days post-treatment; Visit 4). The investigator was to assess the patient's signs and symptoms of pneumonia at Visits 1, 2, 3, and 4. An assessment of the patient's response to study drug treatment was to be made at Visit 3 (or Premature Discontinuation before Visit 3); recurrence of infection was to be determined at Visit 4 (or Premature Discontinuation after Visit 3).

Safety measurements:

Adverse clinical and laboratory events and changes in electrocardiogram (ECG), vital sign and physical examination findings.

Statistical methods:

The two-sided 95% confidence interval method of statistical analysis was used to demonstrate equivalence between sparfloxacin and ofloxacin for efficacy variables.

Inclusion Criteria

Patients must have met **ALL** of the following conditions:

1. either a male or a nonpregnant, non-lactating female, who was postmenopausal or surgically sterilized, or was using birth control pills, Norplant[®], or an IUD for at least two months for contraception;
2. for all women of child-bearing potential (i.e., those not postmenopausal or surgically sterilized), including those using birth control, a negative serum pregnancy test by at baseline; a screening (serum or urine) pregnancy test performed on site was reported as negative before study medication is administered;
3. ≥ 18 years of age;
4. presenting with:
 - a) a diagnosis of chronic bronchitis (i.e., history of cough with production of sputum occurring on most days for at least 3 months of the year for at least two successive years) and
 - b) an acute bacterial exacerbation of chronic bronchitis, as confirmed by the acute (within 14 days) onset of new (or worsened from the immediate premorbid state) cough and sputum production. If the immediate premorbid state includes sputum production, the patient must have had both an increased volume and an increased purulence of the sputum produced. (Note: The term "immediate premorbid state" refers to the patient's stable baseline condition in the 60 days prior to the onset of the current exacerbation of symptoms).

Acute Exacerbation of Chronic Bronchitis

In addition to the above-noted inclusion criteria, patients may also have had fever (temperature > 100.4°F [38.0°C] by the oral route), wheezing, and shortness of breath; these are not inclusion criteria per se.

5. a chest x-ray (CXR) must confirm the absence of pulmonary findings consistent with pneumonia. Patients were to be enrolled based on the investigator's interpretation of the CXR. However, a formal radiologist's interpretation must have been obtained; if this reading identified the presence of pulmonary findings consistent with pneumonia, then the patient must be discontinued from the study, with dropout procedures completed, and appropriate therapy must have been prescribed.

6. have to produce a purulent, mucopurulent sputum specimen for laboratory evaluation within 48 hours prior to starting study medication; for enrollment to occur, the Gram stain of this specimen must have shown > 25 neutrophils and < 10 squamous epithelial cells per low power field (10x objective, 100x total magnification). A Gram stain must have been performed at the site by the investigator (or another person qualified by training and/or experience) before a patient could be enrolled. The stained slide and an unstained slide for Gram-staining was to be sent to [redacted] was to make a determination of patient eligibility based on review of both Gram stains.

7. capable of providing written informed consent.

Exclusion Criteria

Patients may not have met ANY of the following conditions:

1. female with childbearing potential (i.e. not postmenopausal or not surgically sterilized), unless using contraception;
2. hypersensitivity to quinolones;
3. pneumonia, as confirmed by CXR;
4. pulmonary disease(s) that preclude evaluation of the therapeutic response, including cystic fibrosis, bronchiectasis, obstructing lung cancer, or other significant focal pulmonary structural defects;
5. known HIV infection, or neutropenia (white blood cell count < 3000/mm³), or current use of immunosuppressive or chemotherapeutic agents for hematologic, oncologic or organ transplantation purposes;
6. systemic antimicrobial treatment within three days prior to study drug administration;
7. baseline pathogen(s) known to be resistant to either study drug prior to randomization;
8. concomitant infections requiring systemic antibacterial therapy;
9. use of other antibiotics or any other concomitant medication (including specifically antacids, sucralfate, or antacid-containing products such as Ascriptin[®]) that may interfere with the interpretation of the data or the patient's participation in this study;
10. use of any other investigational compound within 28 days of starting study

medication (Day 1 of study) or during study (i.e. prior to Visit 4 or Dropout);

11. prior participation in this study;
12. a rapidly fatal illness;
13. a life expectancy of one month or less;
14. clinical findings which, in the investigator's opinion, warranted parenteral antibiotic therapy;
15. significant hepatic disease or obstruction of the biliary tract. This included patients with baseline bilirubin or hepatic enzyme levels (AST, ALT) that were greater than two times the upper limit of normal.
16. baseline known or estimated creatinine clearance of ≥ 50 mL/min; when a known creatinine clearance based on a 24-hour urine collection is not available, creatinine clearance was to be estimated using the following formula:

$$\text{Men: creatinine clearance (mL/min)} = \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x value calculated for men

17. congenital prolonged QT Syndrome;
18. concurrent use of antiarrhythmic agents or other medications known to cause QT prolongation including terfenadine (Seldane®) and astemizole (Hismanal®); probucol (Lorelco®); Class Ia antiarrhythmic agents (quinidine, procainamide, disopyramide); Class III antiarrhythmic agents (amiodarone [Cordarone®], bretylium); tricyclic antidepressants; and phenothiazines;
19. baseline (Visit 1) QTc interval > 500 msec;
20. epilepsy, history of convulsive disorders (other than febrile seizures of childhood) or underlying conditions which could predispose to seizures;
21. inability to minimize unprotected exposure to sunlight;
22. gastrointestinal tract abnormalities which would prevent absorption of oral medication (e.g., persistent nausea and vomiting or malabsorption);
23. unwillingness to cooperate with the investigator and to participate in all required portions of the study;
24. history of non-compliance, likely to be unreliable, or mentally or legally incapacitated.
25. history of prior phototoxicity reaction with a quinolone.

PLAN OF THE STUDY

Each patient screened by the investigator for this study was given a unique screening number until either study entry or exclusion from participation. Demographic information was to be collected for screened patients and the reason(s) for exclusion was to be documented for those who did not qualify.

Patients who met the inclusion/exclusion criteria were to be asked to give written informed consent for the study.

The study plan for protocol 356 was identical to the study plan for the protocols for pneumonia (301 and 352) with the exception of susceptibility criteria. The following susceptibility criteria were used:

Identification of the etiologic routine bacterial pathogen(s) and susceptibility patterns were to be completed by at Visits 1, 2, 3, 4, and dropout. All bacteria considered to be pathogenic were to be identified to genus and species and tested for susceptibility to both sparfloxacin and ofloxacin according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Susceptibility was to be done by the broth dilution (MIC) method for ofloxacin and by MIC and disk (Kirby-Bauer) for sparfloxacin.

The following are the breakpoints for ofloxacin susceptibility for routine bacterial pathogens (does not include atypical organisms):

Category	ofloxacin	
	MIC	DISK (Kirby-Bauer) 5 mcgs
Susceptible	≤ 2 mcg/mL	≥ 16 mm
Intermediate	4 mcg/mL	13-15 mm
Resistant	≥ 8 mcg/mL	≤ 14 mm

Reference: Floxin[®] package insert*

The following are the tentative breakpoints for sparfloxacin:

Category	sparfloxacin	
	MIC	DISK (Kirby-Bauer) 5 mcgs
Susceptible	≤ 1 mcg/mL	≥ 18 mm
Intermediate	2 mcg/mL	15-17 mm
Resistant	≥ 4 mcg/mL	≤ 14 mm

Reference: Data on file,

Chlamydia pneumoniae was to be isolated and identified by accepted laboratory methods (Visit 1, 3, 4, and dropout). Isolates were to be batched for susceptibility testing.

Beta-lactamase production was to be performed on appropriate microorganisms, such as *Haemophilus* spp. *Moraxella catarrhalis*, and *Staphylococcus* spp.

DATA ANALYSIS

Safety Parameters

The following safety parameters were to be evaluated:

1. subjective reports of adverse experiences;
2. changes in laboratory measurements;
3. changes in physical examination findings;
4. Changes in ECG findings.

Efficacy Parameters

The primary efficacy parameter was to be the *Overall Response* as defined below and determined at Visit 3 (study day 20 + 3; post-treatment Day 10 + 3 days), or when patients drop out before Visit 3. The Overall Response was to be determined by consideration of two separate parameters, the *Clinical Response* and the *Patient Bacteriologic Response*.

1. **Clinical Response:** Clinical Response was to be assessed by the investigator at Visit 3 or when patients drop out before Visit 3 as follows:

Cure: Resolution of ALL symptoms and signs of the acute bacterial exacerbation of chronic bronchitis, with no new symptoms or signs associated with the original infection. As an exception, wheezing was not to be evaluated as part of the clinical response.

["Resolution" was by definition to include return of the given finding to the premorbid state].

Improvement: In patients not cured, resolution or reduction of the majority of symptoms and signs of the acute bacterial exacerbation of chronic bronchitis, with no new or worsened symptoms or signs associated with the original infection. As an exception, wheezing was not be evaluated as part of the clinical response.

Failure: Either (a) no resolution and no reduction of a majority of symptoms and signs of the acute bacterial exacerbation of chronic bronchitis or (b) worsening of one or more symptoms and signs or © new symptoms or signs associated with the original infection or a new infection, or (d) patient required other antimicrobial therapy for this episode of acute bacterial exacerbation of chronic bronchitis prior to or at Visit 3. As an exception, wheezing was not be evaluated as part of the clinical response.

Indeterminate: Inability to assess the patient's symptoms and signs due to "lost to follow-up" or no information.

2. Patient Bacteriologic Response:

Patient Bacteriologic Response was to be based on the sputum or throat culture results performed at Visit 3 or at dropout prior to Visit 3. (Relapse and reinfection was to be assessed at Visit 4 or at dropout after Visit 3). The following definitions were to be used:

Eradication: Complete eradication of baseline pathogen(s).

Presumed Eradication: "No material available for culture" (due to lack of sputum production), or if *Chlamydia pneumoniae* serology was diagnostic, a Clinical Response of "Cure" or "Improvement" was to be noted

Persistence: Persistence of baseline pathogen(s); or if Chlamydia pneumoniae serology was diagnostic, a Clinical Response of "Failure" was to be noted.

Superinfection: Emergence of a new or resistant pathogen which was not identified as the original causative pathogen, and associated with signs and symptoms of pulmonary infection during treatment or up to Visit 3.

Multiple pathogens with partial eradication (MPPE):

Identification of more than one etiologic pathogen at baseline and eradication of one or more of those pathogens with the persistence of one or more of those pathogens at Visit 3.

Relapse: Eradication of baseline pathogen(s) at Visit 3 and reappearance of the same pathogen(s) after Visit 4, accompanied by symptoms and signs of pulmonary infection.

Reinfection: Eradication of the baseline pathogen(s) at Visit 3 but with emergence of new pathogen(s) thereafter, accompanied by symptoms and signs of pulmonary infection.

Each pathogen(s) present at baseline was to be assessed as ERADICATED, PRESUMED ERADICATED, PERSISTENT, or RELAPSE. New pathogen(s) were to be assessed as causing SUPERINFECTION or REINFECTION.

Colonization: Appearance of new organism(s), during or after therapy, not accompanied by clinical symptoms and signs of pulmonary infection. Colonization was not to be included in assessment of the Patient Bacteriologic Response.

Indeterminate: No information.

3. Overall Response: The Overall Response was to be derived from the Clinical Response and the Patient Bacteriologic Response and defined as either Success, Failure or Indeterminate, as follows:

Success: Clinical Response of either "Cure" or "Improvement," and Patient Bacteriologic Response of "Eradication", or "Presumed Eradication".

Failure: Clinical Response of "Failure" or Patient Bacteriologic Response of "Persistence", "Superinfection", or "MPPE".

Indeterminate: All other outcomes.

4. Clinical Assessment of Recurrence (Visit 4):

A clinical assessment of "Recurrence" of symptoms and signs of pulmonary infection was to be performed by the investigator at Visit 4 (or if patient drops out after Visit 3). Recurrence is defined as the development of new or worsened symptoms and signs of pulmonary infection in those patients who had a Clinical Response of "Cure" or "Improvement" at Visit 3. A CXR was to be performed if there was concern that pneumonia could be present.

The information obtained from this assessment was to be analyzed with the Visit 4 (or post Visit 3 dropout) microbiologic data to determine if there had been a Relapse or Reinfection.

Evaluability Criteria

Clinically Evaluable

To be clinically evaluable, patients **MUST HAVE HAD:**

- a. a diagnosis of chronic bronchitis, as defined in the Inclusion Criteria.
- b. new (or worsened from the immediate premorbid state) cough and sputum production. If the immediate premorbid condition included sputum production, the patient must have had both an increased volume and increased purulence of the sputum produced;
- c. a baseline sputum Gram stain showing > 25 neutrophils and < 10 squamous epithelial cells per low power field;
- d. completion of all Visit 3 or dropout procedures such that an assessment of Clinical Response could be made.

Patients MUST NOT HAVE HAD:

- a. received systemic antimicrobial therapy within three days prior to study drug administration;
- b. a baseline (Visit 1) sputum sample taken more than 48 hours prior to start of the study medication or taken after the study medication had started;
- c. insufficient treatment period (less than 48 hours therapy);

- d. missed more than 20% of doses of (active) drug, unless patient discontinued due to failure;
- e. taken non-study-drug antimicrobial therapy prior to or at Visit 3 (does not apply to failures);
- f. concurrent medical condition preventing evaluation of Clinical Response;
- g. incorrect diagnosis of an acute bacterial exacerbation of chronic bronchitis (e.g. CXR showing pulmonary findings consistent with pneumonia).

Bacteriologically Evaluable

To be bacteriologically evaluable, patients **MUST HAVE HAD**:

- a. a lower respiratory tract pathogen identified at Visit 1;
- b. Visit 3 (or dropout) test-of-cure culture performed between seven and thirteen days after therapy was stopped (did not apply to early failures, provided supporting cultures were performed at time of study dropout, or to patients who had had no sputum to produce for culture);
- c. baseline susceptibility testing performed for both study medications, except for *Chlamydia pneumoniae*.

In addition, patients **MUST NOT HAVE HAD**:

Any Visit 1 (baseline) pathogen(s) resistant to either sparfloxacin or ofloxacin.

Identification of Etiologic Agents

Only those sputum specimens meeting Gram stain screening criteria were to be submitted for routine culture. A specific microbiologic etiology for the acute bacterial exacerbation of chronic bronchitis was to be determined by the following criteria:

- a. Routine bacterial pathogens
 - i. light (2+), moderate (3+) or heavy (4+) growth of a pulmonary pathogen from sputum culture, or
 - ii. rare (1+) growth of a pulmonary pathogen from sputum and the sputum Gram stain revealed an organism (quantity: rare (1+) or greater) compatible with the culture result.
- b. *Chlamydia pneumoniae* (TWAR)

- i. positive throat swab culture, or
- ii. single serum IgM $\geq$ 1:20 (micro-IF), or
- iii. single serum IgG $\geq$ 1:128 (micro-IF), or
- iv. $\geq$ 4 x rise in serum IgG.

For each patient, the investigator was to determine which, if any, of the organisms isolated from the Visit 1 culture represent(s) the pathogen(s) responsible for this episode of acute bacterial exacerbation of chronic bronchitis.

Patient Populations

1. Randomized Patients

The randomized patient population were to consist of all patients randomized to study medication.

2. Clinically Evaluable Patients

The clinically evaluable patient population was to consist of all patients who met the clinically evaluable criteria.

3. Clinically Evaluable Patients with LRT Pathogen

The "clinically evaluable patients with LRT pathogen" population were to consist of all clinically evaluable patients who had a lower respiratory tract pathogen.

4. Clinically and Bacteriologically evaluable patients

The clinically and bacteriologically evaluable patient population was to consist of all clinically evaluable patients who also met the bacteriologically evaluable criteria

Statistical Methods

1. Sample Size Considerations

Sample size calculations were to be based on a two-sided 95% confidence interval method of establishing equivalence of two proportions with an assumed Overall Response success rate of 90% in the ofloxacin treatment group. To have an 80% probability of showing that sparfloxacin did not differ by more than 10 percentage points in either direction, 190 patients per treatment group were needed for the analysis of the Overall Response based on the clinically and bacteriologically evaluable patients. Note that this was equivalent to having a probability of 90% that the lower end of the 95% confidence interval is above -10%. That is, there was a 90% chance of concluding that sparfloxacin was not 10% worse than ofloxacin.

Given that about 50% of enrolled patients could be expected to have an identified respiratory tract pathogen, and an attrition rate of about 10%, the total study enrollment needed was 846 patients.

2. Efficacy Analyses

The two-sided 95% confidence interval method was to be used to establish equivalence between sparflloxacin and ofloxacin for all efficacy analyses.

The following primary efficacy analyses were to be carried out:

- a. For the clinically evaluable patients, the Clinical Response was to be analyzed with the cured and improved categories pooled together as a positive response (i.e., cured/improved categories vs. other).
- b. For the clinically evaluable patients with LRT pathogen, three analyses were to be carried out:
 - i. the Overall Response was to be the primary endpoint (success vs. other)
 - ii. the Clinical Response (cured/improved vs. other)
 - iii. the Patient Bacteriological Response (eradication/presumed eradication vs. persistence/superinfection/MPPE).
- c. For the clinically and bacteriologically evaluable patients, the same three analyses specified in item b were also to be carried out. In addition, the Clinical Response was to be analyzed for all randomized patients.

3. Formal Plan for Statistical Analysis

The detailed formal plan for the statistical analysis was to be written and filed with Records and Information prior to unblinding of the study and opening of the data file for the statistical analysis. This plan was to provide the framework for statistical inferences drawn from the protocol and was to specify in detail both primary and secondary analyses.

ADVERSE EVENTS (EXPERIENCES)

Patients were to be instructed by the investigator to report the occurrence of any adverse event. An adverse event was any undesirable event associated with the use of a drug, whether or not considered drug related, and included any side effect, injury, toxicity, or sensitivity reaction. It also included any undesirable clinical or laboratory event which was not normally observed in the patient.

A serious adverse event included any event, including lack of efficacy, that was fatal or life-threatening, was permanently or severely disabling, required or prolonged inpatient hospitalization, or was a congenital anomaly, cancer, or overdose.

"Life-threatening" meant that the patient was at **immediate** risk of death from the event as it occurred. It did not include an event that, had it occurred in a more serious form, might have caused death. "Required inpatient hospitalization" was to be defined as hospital admission required for treatment of the adverse event. Hospital admission for scheduled elective surgery would not be a serious adverse event. All adverse events, regardless of severity, were to be followed up by the investigator until satisfactory resolution. The following guidelines were to pertain to adverse events:

1. SIGNS/SYMPTOMS OF INFECTION WHICH WERE ASSESSED AS PRIMARY CLINICAL PARAMETERS (specifically those found on the CE CRF): Worsening or appearance during the study were to be reported as adverse events if the investigator judged the change to be **UNUSUAL** for a treatment failure. [Note: (1) if worsening/appearance was not to be considered an adverse event, source documents were to reflect this; e.g., "worsening cough manifests treatment failure, not an adverse event"; (2) changes in primary clinical parameters were to be tabulated in study reports.]

2. ALL OTHER UNDESIRABLE EVENTS: Appearance or worsening during the study, irrespective of severity, were to be reported as adverse events.

3. ADVERSE EVENTS WERE TO BE REPORTED UP TO 14 DAYS POST DRUG TREATMENT.

DROPOUT INFORMATION

The reason and date of discharge for all study patients who were discharged from the study was to be documented on the case report form (e.g. adverse event, lost to follow-up, completed study, etc.). The investigator was to attempt to complete all discharge procedures at the time a patient was discontinued from treatment. Patients were to be dropped from the study immediately if they met **ANY** of the following conditions:

1. a positive serum pregnancy test (specify "protocol deviation" on CRF D);

Acute Exacerbation of Chronic Bronchitis

2. formal interpretation of a Visit 1 CXR by radiologist which identified pulmonary findings consistent with pneumonia, Visit 1 Gram stain which did not meet screening criteria, or other information defining an incorrect diagnosis of acute bacterial exacerbation of chronic bronchitis ("protocol deviation");
3. < 18 years old ("protocol deviation");
4. could not complete the obligations of this study ("protocol deviation");
5. asked to be withdrawn ("consent withdrawn");
6. the sponsor or IRB stopped the study ("other");
7. treatment-limiting adverse event ("adverse clinical experience" or "adverse laboratory experience");
8. the isolated etiologic routine bacterial pathogen was "Resistant" to one or both study drugs and the symptoms and signs of the acute bacterial exacerbation of chronic bronchitis did not improve by Visit 2 ("test drug ineffective");
9. the symptoms and signs of the acute bacterial exacerbation of chronic bronchitis worsened during study drug treatment or recurred after study drug treatment such that alternative antimicrobial therapy was warranted ("test drug ineffective").
10. the baseline (Visit 1) QTc interval was determined to have been > 500 msec ("protocol deviation").
11. the Visit 2 QTc interval was > 550 msec ("adverse clinical experience").

CONCOMITANT MEDICATION

All medications required by the patient to manage underlying illnesses unrelated to the present episode of acute bacterial exacerbations of chronic bronchitis were permitted, with the exception of antacids (including sucralfate and antacid-containing compounds such as Ascriptin®) and medications with any antimicrobial action, which may have interfered with the interpretation of study data. All medications taken, including over-the-counter drugs (e.g., ferrous sulfate, multivitamins with zinc, zinc supplements, antipyretics, non-steroidal anti-inflammatory drugs), must have to be recorded on the CRF.

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group	Treatment Group	Treatment Group	Treatment Group	Treatment Group	Treatment Group
		Spar	Oflx	Spar	Oflx	Spar	Oflx
Al-Ibrahim	Baltimore, MD	1	1	1	1	0	1
Bach	Sacramento, CA	2	2	1	2	0	1
Banov	Charleston, SC	8	9	5	9	2	7
Beauford	High Point, NC	1	2	1	2	1	2
Bensch	Stockton, NC	25	25	21	19	18	14
Black	Cuyahoga Falls, OH	2	0	2	0	2	0
Bowman	Clearwater, FL	8	9	8	9	4	5
Broker	Simpsonville, SC	12	14	11	13	7	10
Brzezinski	Charleson, NC	9	8	8	7	6	5
Chappel	Kissimmee, FL	4	3	4	2	2	2
Chick	Albuquerque, NM	2	1	1	1	0	1
Chodosh	Boston, MA	15	14	15	14	12	13
Clecner	St. Jerome, Quebec	1	0	1	0	0	0
Coalson	Dayton, OH	2	2	2	1	2	1
Daniel	Wenatchee, WA	4	5	3	4	3	4
Dark	Kansas City, MO	0	2	0	2	0	2
DeAbate	Metairie, LA	46	45	40	42	37	35
Drehobl	San Diego, CA	3	3	3	3	2	1
Drelichman	Southfield, MI	0	1	0	0	0	0
Fellers	Greely, CO	1	0	1	0	1	0
Fiddes	Whittier, CA	13	16	12	13	8	8
Flescher	Raleigh, NC	1	1	0	1	0	1
Gilderman	Pembroke Pines, FL	2	0	0	0	0	0
Gill	Garden City, NY	1	0	0	0	0	0

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group		Treatment Group		Treatment Group	
		Spar	Oflx	*Spar	Oflx	Spar	Oflx
Gordon	Ambler, PA	2	1	2	1	2	0
Greenberg	Lexington, KY	2	4	2	4	2	3
Gianna	Spartanburg, NC	3	3	2	3	2	2
Harris	Lake Oswego, OR	5	6	5	3	5	3
Ziauch	Charlotte, NC	1	1	1	1	1	1
Henry	Salt Lake City, UT	35	32	33	30	23	24
Hubbard	Shreveport, LA	5	5	5	5	5	4
Ilowite	Mincola, NY	1	0	0	0	0	0
Jacobson	Eugene, OR	3	3	2	3	0	3
Jubran	Hines, IL	19	21	18	21	15	14
Khairi	Indianapolis, IN	4	3	4	3	2	0
Khurana	Evanston, IL	14	14	0	0	0	0
Kimmerling	Dallas, TX	7	7	7	3	3	3
Kish	Lansdale, PA	1	2	1	2	1	1
LaForge	Quebec City, Quebec	10	11	9	10	0	0
Lampasso	Buffalo, NY	1	2	1	2	1	0
Lazarus	La Jolla, CA	11	11	10	9	7	7
LeFrock	Sarasota, FL	0	1	0	0	0	0
Lipsky	Seattle, WA	1	2	1	1	1	1
Mahoney	Voorhees, NJ	2	3	2	2	0	1
Manning	Portland, OR	1	0	0	0	0	0
McCluskey	Mogadore, OH	10	10	10	8	10	7
McElvaine	El Paso, TX	9	10	5	8	5	8

Investigator Name:	Investigator Location:	Enrolled		Clinically Evaluable		Bacteriologically Evaluable	
		Treatment Group	Treatment Group	Treatment Group	Treatment Group	Treatment Group	Treatment Group
		Spar	Oflx	Spar	Oflx	Spar	Oflx
Miller	Morrisville, PA	1	3	1	3	1	2
Montner	Albuquerque, NM	0	2	0	1	0	1
Morales	Santurce, Puerto Rico	3	3	2	1	2	1
Nelson	Kansas City, MO	0	1	0	1	0	1
Nolen	Columbiana, AL	1	0	1	0	1	0
Ondrejicka	Jacksonville Beach, FL	2	2	2	2	1	2
Opipari	Warren, MI	21	22	16	19	12	17
Patei	Dayton, OH	7	8	7	6	6	4
Platt	Cuyahoga Falls, OH	8	10	8	10	6	8
Ramirez	Louisville, KY	1	0	1	0	1	0
Rogers	Tuscon, AZ	3	3	3	3	2	3
Sanford	Portland, OR	2	1	2	1	2	0
Schachter	New York, NY	5	5	5	4	4	2
Schoenberger	Scottsdale, AZ	5	2	5	2	5	1
Shankman	Watertown, MA	2	0	1	0	0	0
Spangenthal	Charlotte, NC	7	7	5	7	5	5
Springmeyer	Seattle, WA	2	2	2	1	2	1
Stein	Rochester, NY	8	10	8	7	8	7
Taylor	Richmond, VA	0	1	0	1	0	0
Tidman	Smyrna, GA	4	3	3	2	2	0
Unnoppet	Birmingham, AL	3	3	3	2	1	1

DRUG ADMINISTRATION**SUMMARY OF DAYS OF STUDY DRUG TREATMENT BY TREATMENT GROUP**

PROTOCOL : RP64206X_356 - SPARFLOXACIN VS OFLOXACIN IN ABECB, N=798

INVESTIGATOR : 68 INVESTIGATORS COMBINED

TREATMENT GROUP : 2 TREATMENT GROUPS COMBINED

DAYS OF STUDY DRUG TREATMENT	TREATMENT GROUP: SPARFLOXACIN		TREATMENT GROUP: OFLOXACIN	
	PATIENTS: N	%	PATIENTS: N	%
TOTAL PATIENTS:	395		403	
0 - 1	8	(2.0%)	13	(3.2%)
2 - 3	11	(2.8%)	17	(4.2%)
4 - 5	19	(4.8%)	18	(4.5%)
6 - 7	6	(1.5%)	7	(1.7%)
8 - 9	7	(1.8%)	3	(0.7%)
10 - 11	337	(85.3%)	335	(83.1%)
12+	7	(1.8%)	10	(2.5%)

The average duration of study drug therapy was 9.4 days (range 1-12 days) for sparfloxacin and 9.3 days (range 1-13 days) for ofloxacin. The mean daily dosage was 220.0 mg for the sparfloxacin group and 800.0 mg for the ofloxacin group. The sparfloxacin and ofloxacin groups were comparable in the number of days of study drug treatment.

Summary of Patient Disposition

Population	Number (%) of Patients		
	Sparfloxacin 400*/200 mg QD	Ofloxacin 400 mg q 12h	Total
All Enrolled (All Randomized)	395 (100)	403 (100)	798 (100)
Completed	316 (80.0)	310 (76.9)	626 (78.4)
Discontinued	79 (20.0)	93 (23.1)	172 (21.6)
Clinically Evaluable	335 (84.8)	337 (83.6)	672 (84.2)
All-Treated With Baseline Pathogen	323 (81.8)	324 (80.4)	647 (81.1)
Bacteriologically Evaluable	253 (64.1)	251 (62.3)	504 (63.2)

* Loading Dose

Summary of Demographic Characteristics (All-Treated Population)*

Characteristic	Sparfloxacin 400*/200 mg QD (n=395)	Ofloxacin 400 mg q 12h (n=403)	Treatment Group Comparison p-value
Age, years			
Mean	51.9	51.7	0.713 ^a
Range	18-93	18-85	
Gender, n (%)			0.162 ^b
Male	195 (49.4)	218 (54.1)	
Female	200 (50.6)	185 (45.9)	
Race, n (%)			0.677 ^b
Caucasian	305 (77.2)	308 (76.4)	
Black	58(14.7)	60 (14.9)	
Oriental	0	2 (0.5)	
Other *	1 (0.3)	2 (0.5)	
Hispanic	31 (7.8)	31 (7.7)	
Body weight lbs.			
Mean	166.8	173.1	0.020 ^a
Range	71-350	81-319	

* Loading Dose

a Two-way analysis of variance on ranks

b Generalized Cochran-Mantel-Haenszel test

Applicant's Summary of Primary Efficacy Results*

Efficacy Parameter (Population Time Point)	Number (%) of Patients		95% CI
	Sparfloxacin n 400*/200 mg QD	Ofloxacin 400 mg q 12h	
Clinical Response Rate Cured + Improved (clinically evaluable, at TOC)	290/335 (86.6)	296/337 (87.8)	-6.3, 3.8
Clinical Cure Rate	194/335 (57.9)	207/337 (61.4)	-10.9, 3.9
Clinical Recurrence Rate (clinically evaluable, at late follow-up)	25/286 (8.7)	30/288 (10.4)	ND
By-Pathogen Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	339/377 (89.9)	331/358 (92.5)	ND
By-Patient Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	221/253 (87.4)	231/251 (92.0)	-10, 0.6
Bacteriologic Relapse Rate	11/253 (5.3)	16/251 (7.8)	ND
Reinfection Rate	2/253 (1.0)	2/251 (1.0)	ND
Relapse + Reinfection Rate (bacteriologically evaluable, at late follow-up)	4/253 (1.9)	4/251 (1.9)	ND
Overall Response Rate - Cured or Improved or Eradicated or Presumed Eradicated (bacteriologically evaluable, at TOC)**	216/253 (85.4)	223/251 (88.8)	-9.3, 2.4

TOC = Test-of-Cure; ND = not done

* Loading Dose

** Primary efficacy parameter

**Applicant's Clinical Response Rate (cure + improvement) by Baseline Pathogen^a
(Bacteriologically Evaluable Population)**

Infection Type	Number (%) of Patients	
	Sparfloxacin 400 [*] /200 mg QD	Ofloxacin 400 mg q 12h
Population Response Rate	250/287 (87.1)	250/278 (89.9)
<i>H. parainfluenzae</i>	100/109 (91.7)	85/95 (89.5)
<i>H. influenzae</i>	49/57 (86.0)	59/65 (90.8)
<i>C. pneumoniae</i> ^b	37/45 (82.2)	36/40 (90.0)
<i>M. catarrhalis</i>	32/38 (84.2)	32/34 (94.1)
<i>S. pneumoniae</i>	30/34 (88.2)	20/22 (90.9)
<i>S. aureus</i>	15/19 (78.9)	12/14 (85.7)
<i>K. pneumoniae</i>	17/17 (100)	15/17 (88.2)
<i>E. cloacae</i>	12/13 (92.3)	11/15 (73.3)
<i>P. aeruginosa</i>	11/13 (84.6)	9/11 (81.8)

* Loading Dose

a Isolated in ≥ 10 patients in either treatment group.

b Results obtained by serology. All other pathogens isolated from sputum.

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Acute Exacerbation of Chronic Bronchitis

Clinical Response at Test of Cure

Clinically Evaluable with Baseline Pathogen

Protocol 356

Sparfloxacin (S)

Ofloxacin

(O)

	S	%	O	%	S	%	O	%
Cure	168	60.9%	171	61.3%	174	63.5%	176	63.8%
Failure	35	12.7%	35	12.5%	31	11.3%	31	11.2%
Improvement	73	26.4%	73	26.2%	69	25.2%	69	25.0%
Indeterminate	0		0		0		0	

Percent = Group Total / Total Number of Patients

(Total Number of Patients does not include indeterminate totals.)

	S	O	S	O	%	%	()	()
Total Number of Patients:	276	279	274	276				
Cured:	168	171	174	176	-2.6%	-2.5%	(-10.7% , 5.5%)	(-10.5% , 5.6%)
+ Improved:	241	244	243	245	-1.4%	-1.3%	(-6.8% , 4.1%)	(-6.7% , 4.1%)

Medical Officer's Comments:

The clinical response (cure + improvement) at test-of-cure for the sparfloxacin group was 244/279 (87.5%) compared to ofloxacin group 245/276 (88.8%). There were three additional patients in the sparfloxacin group and two additional patients in the ofloxacin group that the Medical Officer considered evaluable and the applicant did not. These 5 patients were evaluated one day outside the study test-of-cure window period. The Medical Officer considered that as a minor violation of protocol and included them in the evaluable patient population.

Clinical Response By All Baseline Pathogens

Clinically Evaluable with Baseline Pathogen

Protocol 356

Evaluated by: RPR

Sparfloxacin (S)

Ofloxacin (O)

Pathogen	Sparfloxacin (S) - n	Sparfloxacin (S) - r	Sparfloxacin (S) - c	Sparfloxacin (S) - %	Ofloxacin (O) - n	Ofloxacin (O) - r	Ofloxacin (O) - c	Ofloxacin (O) - %
ACINETOBACTER ANITRATUS	4	3	0	100.0%	4	2	1	85.7%
ACINETOBACTER LWOFFI	3	0	1	75.0%	2	0	1	66.7%
C. PNEU AB	23	11	8	83.0%	29	12	5	89.1%
C. PSITTACI	2	0	0	100.0%	3	1	0	100.0%
C. SPECIES	1	1	0	100.0%	1	1	0	100.0%
COMAMONAS ACIDOVORANS	0	1	0	100.0%	0	0	0	0.0%
ENTEROBACTER AEROGENES	3	0	0	100.0%	0	0	1	0.0%
ENTEROBACTER CLOACAE	11	2	1	92.9%	7	4	4	73.3%
MOPHIUS INFLUENZAE	39	15	9	85.7%	50	18	6	91.9%
HAEMOPHILUS PARAINFLUENZAE	82	32	11	91.2%	71	24	12	88.6%
KLEBSIELLA OXYTOCA	4	1	1	83.3%	6	1	0	100.0%
KLEBSIELLA PNEUMONIAE	11	6	1	94.4%	10	6	2	88.9%
MORAXELLA CATARRHALIS	18	16	6	85.0%	21	11	3	91.4%
NEISSERIA MENINGITIDIS	2	0	2	50.0%	5	4	0	100.0%
PSEUDOMONAS AERUGINOSA	7	5	3	80.0%	10	3	2	86.7%
SERRATIA MARCESCENS	1	0	2	33.3%	4	2	0	100.0%
STAPHYLOCOCCUS AUREUS	15	3	4	81.8%	10	2	2	85.7%
STREPTOCOCCUS AGALACTIAE	1	0	1	50.0%	5	1	0	100.0%
STREPTOCOCCUS GRP G	1	0	0	100.0%	1	0	1	50.0%
STREPTOCOCCUS PNEUMONIAE	24	7	4	88.6%	19	3	2	91.7%
STREPTOCOCCUS PYOGENES	0	0	1	0.0%	1	0	0	100.0%

Clinical Response By All Baseline Pathogens

Clinically Evaluable with Baseline Pathogen

Protocol 356

Evaluated by: FDA

Sparfloxacin (S)

Ofloxacin (O)

Pathogen	S	O	S	O	%	S	O	S	O	%
ACINETOBACTER ANITRATUS	4	3	0	0	100.0%	4	2	1	0	85.7%
ACINETOBACTER LWOFFI	3	0	1	0	75.0%	2	0	1	0	66.7%
C. PNEU AB	28	11	8	0	83.0%	29	12	5	0	89.1%
C. PSITTACI	2	0	0	0	100.0%	3	1	0	0	100.0%
C. SPECIES	1	1	0	0	100.0%	1	1	0	0	100.0%
COMAMONAS ACIDOVORANS	0	1	0	0	100.0%	0	0	0	0	0.0%
ENTEROBACTER AEROGENES	3	0	0	0	100.0%	0	0	1	0	0.0%
ENTEROBACTER CLOACAE	11	2	1	0	92.9%	7	4	4	0	73.3%
HAEMOPHILUS INFLUENZAE	40	15	9	0	85.9%	51	18	6	0	92.0%
HAEMOPHILUS PARAINFLUENZAE	83	32	11	0	91.3%	72	24	12	0	88.9%
KLEBSIELLA OXYTOCA	4	1	1	0	83.3%	6	1	0	0	100.0%
KLEBSIELLA PNEUMONIAE	11	6	1	0	94.4%	10	6	2	0	88.9%
MORAXELLA CATARRHALIS	18	16	6	0	85.0%	21	11	3	0	91.4%
NEISSERIA MENINGITIDIS	2	0	2	0	50.0%	5	4	0	0	100.0%
PSEUDOMONAS AERUGINOSA	7	5	3	0	80.0%	10	3	2	0	86.7%
SERRATIA MARCESCENS	1	0	2	0	33.3%	4	2	0	0	100.0%
STAPHYLOCOCCUS AUREUS	15	3	4	0	81.8%	10	2	2	0	85.7%
STREPTOCOCCUS AGALACTIAE	1	0	1	0	50.0%	5	1	0	0	100.0%
STREPTOCOCCUS GRP G	1	0	0	0	100.0%	1	0	1	0	50.0%
STREPTOCOCCUS PNEUMONIAE	25	7	4	0	88.9%	19	3	2	0	91.7%
STREPTOCOCCUS PYOGENES	0	0	1	0	0.0%	1	0	0	0	100.0%

Medical Officer's Comments:

The clinical outcome (cure+improvement) of sparfloxacin is comparable to the ofloxacin.

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**Clinical Response at Test of Cure
Sustained/Delayed Response (by Patient)**

Clinically Evaluable with Baseline Pathogen

Protocol 356

Sparfloxacin (S)

Ofloxacin (O)

Response	S	%	O	%	S	%	O	%
Delayed Cure	29	10.7%	29	10.5%	28	10.4%	28	10.4%
Early Failure	35	12.9%	35	12.7%	31	11.6%	31	11.5%
Indeterminate	4		4		6		6	
Recurrence	20	7.4%	21	7.6%	25	9.3%	25	9.3%
Sustained Cure	155	57.0%	157	57.1%	158	59.0%	160	59.3%
Sustained Imp.	33	12.1%	33	12.0%	26	9.7%	26	9.6%

Percent = Group Total / Total Number of Patients

(Total Number of Patients does not include Indeterminate totals)

	Sparfloxacin		Ofloxacin		Difference		95% Confidence Interval	
	N	%	N	%	%	%	Lower	Upper
Total Number of Patients:	272		275					
Sustained Cure:	155	57.0%	157	57.1%	-2.0%	-2.2%	(-10.3% , 6.4%)	(-10.4% , 6.1%)
Sustained Cure + Delayed Cure:	184	67.6%	186	67.6%	-1.8%	-2.0%	(-9.6% , 6.1%)	(-9.8% , 5.8%)
Sust. Cure + Del. Cure + Sust. Impr.:	217	79.8%	219	79.8%	0.7%	0.4%	(-6.1% , 7.5%)	(-6.4% , 7.2%)

MEDICAL OFFICER'S COMMENTS:

The failure rate was 12.7% in the sparfloxacin group compared to 11.5% in the ofloxacin group, but the recurrence rate was slightly higher in the ofloxacin group (9.3% compared to 7.6%).

Bacteriologic Response at Test of Cure

Bacteriologically Evaluable

Protocol 356

Sparfloxacin (S)

Ofloxacin (O)

	S (n)	S (%)	O (n)	O (%)	S (n)	S (%)	O (n)	O (%)
Eradicated	31	12.3%	31	12.3%	37	14.7%	37	14.7%
Indeterminate	0		0		0		0	
MPPE	8	3.2%	8	3.2%	3	1.2%	3	1.2%
Persist	5	2.0%	5	2.0%	2	0.8%	2	0.8%
Presu. Eradicated	190	75.1%	190	75.1%	194	77.3%	194	77.3%
Presumed Persist	17	6.7%	17	6.7%	14	5.6%	14	5.6%
Site Infection	2	0.8%	2	0.8%	1	0.4%	1	0.4%

P = Group Total / Total Number of Patients

(Total Number of Patients does not include Indeterminate totals)

	S (n)	S (%)	O (n)	O (%)	95% CI (S)	95% CI (O)
Total Number of Patients:	253	253	251	251		
All Eradicated:	221	221	231	231	-4.7% -4.7%	(-10.0% , 0.6%) (-10.0% , 0.6%)

Medical Officer's Comments:

The eradication/presumed eradication rate for sparfloxacin was 87.4% (221/253) compared to 92% (231/251) for the ofloxacin group.

Acute Exacerbation of Chronic Bronchitis

Bacteriologic Response - By Baseline Pathogen at Test of Cure

Bacteriologically Evaluable

Protocol 356

Evaluated by: FDA

Sparfloxacin (S)

Ofloxacin (O)

Pathogen	S	O	S	O	S	O	S	O	S	O	S	O	S	O	S	O	Percent
ACINETOBACTER A	1	6	0	0	0	0	0	0	100.0%	1	4	0	1	0	0	0	83.3%
ACINETOBACTER L	0	3	0	0	0	0	0	0	100.0%	0	2	0	1	0	0	0	66.7%
C. PNEU AB	0	37	0	8	0	0	0	0	82.2%	0	36	0	4	0	0	0	90.0%
C. PSITTACI	0	2	0	0	0	0	0	0	100.0%	0	4	0	0	0	0	0	100.0%
C. SPECIES	0	2	0	0	0	0	0	0	100.0%	0	1	0	0	0	0	0	100.0%
COMAMONAS ACID	1	0	0	0	0	0	0	0	100.0%	0	0	0	0	0	0	0	0.0%
ENTEROBACTER A	0	3	0	0	0	0	0	0	100.0%	1	0	0	0	0	0	0	100.0%
ENTEROBACTER C	2	10	1	0	0	0	0	0	82.3%	2	10	0	3	0	0	0	80.0%
HAEMOPHILUS INF	7	44	0	6	0	0	0	0	89.5%	15	46	0	4	0	0	0	93.8%
HAEMOPHILUS PAR	21	83	2	3	0	0	0	0	95.4%	15	75	2	3	0	0	0	94.7%
KLEBSIELLA OXYT	0	4	0	0	0	0	0	0	100.0%	1	6	0	0	0	0	0	100.0%
KLEBSIELLA PNEU	2	15	0	0	0	0	0	0	100.0%	2	13	0	2	0	0	0	88.2%
MORAXELLA CATA	12	24	0	2	0	0	0	0	84.7%	5	28	0	1	0	0	0	97.1%
NEISSERIA MENING	0	2	0	2	0	0	0	0	50.0%	2	7	0	0	0	0	0	100.0%
PSEUDOMONAS AE	2	7	2	2	0	0	0	0	69.2%	1	8	1	1	0	0	0	81.8%
STRATIUM MARCES	0	1	1	1	0	0	0	0	33.3%	1	5	0	0	0	0	0	100.0%
PHYLOCOCCUS	3	13	1	2	0	0	0	0	84.2%	3	10	0	1	0	0	0	92.9%
STREPTOCOCCUS	0	0	0	1	0	0	0	0	0.0%	0	5	0	0	0	0	0	100.0%
STREPTOCOCCUS	0	1	0	0	0	0	0	0	100.0%	0	1	0	1	0	0	0	50.0%
STREPTOCOCCUS	3	27	2	2	0	0	0	0	88.2%	3	17	1	1	0	0	0	90.9%
STREPTOCOCCUS	1	0	0	0	0	0	0	0	100.0%	0	1	0	0	0	0	0	100.0%

Percent = (No. of Isolates Eradicated) / (Total No. of Isolates)

Medical Officer's Comments:

The applicant is requesting the following in the Indications and Usage section of the package insert:

Based upon the data submitted, the Medical Officer is recommending the following:

Safety Summary

Safety Parameter	Number (%) Patients		
	Sparfloxacin (N=395)	Ofloxacin (N=403)	p-value
Adverse Event ^a	215 (54.4)	224 (55.6)	ND
Most Common ^b			
Headache	44 (11.1)	35 (8.7)	ND
Insomnia	13 (3.3)	65 (16.1)	ND
Nausea	22 (5.6)	45 (11.2)	ND
Dizziness	23 (5.8)	15 (3.7)	ND
Photosensitivity Reaction	33 (8.4)	3 (0.7)	<0.001
Digestive System	58 (14.7)	99 (24.6)	<0.001
Musculoskeletal System	2 (0.5)	11 (2.7)	ND
Nervous System	60 (15.2)	99 (24.6)	<0.001
Cardiovascular System	17 (4.3)	17 (4.2)	0.970
Adverse Events Related to Study Drug	139 (35.2)	163 (40.4)	ND
Most Common ^b			
Insomnia	6 (1.5)	60 (14.9)	ND
Nausea	17 (4.3)	41 (10.2)	ND
Photosensitivity Reaction	32 (8.1)	3 (0.7)	ND
ND = not done a The majority of adverse events were of mild or moderate severity. b Reported by 5% of patients in either treatment group. c Reported by 2% of patients in either treatment group.			

Safety Summary(Continued)

Safety Parameter	Number (%) Patients		p-value
	Sparfloxacin (N=395)	Ofloxacin (N=403)	
Adverse Events Leading to Discontinuation	21 (5.3)	30 (7.4)	ND
Adverse Laboratory Events Most Common ^c	25 (6.3)	31 (7.7)	ND
↓ White Blood Cell Count	7 (1.8)	13 (3.2)	ND
ND = not done a The majority of adverse events were of mild or moderate severity. b Reported by 5% of patients in either treatment group. c Reported by 2% of patients in either treatment group.			

**Summary of Most Frequently (At Least 2% of Patients in a Treatment Group)
Reported Adverse Events**

	Number (%) of Patients ^a	
	Sparfloxacin (n=395) 400*/200 mg QD	Ofloxacin (n=403) 400 mg q 12h
Patients without Adverse Events	180 (45.6)	179 (44.4)
Patients with Adverse Events	215 (54.4)	224 (55.6)
Body System		
Adverse Event		
BODY AS A WHOLE		
Abdominal Pain	12 (3.0)	13 (3.2)
Accidental Injury	9 (2.3)	3 (0.7)
Headache	44 (11.1)	35 (8.7)
Photosensitivity Reaction ^b	33 (8.4)	3 (0.7)
DIGESTIVE SYSTEM		
Constipation	2 (0.5)	11 (2.7)
Diarrhea	16 (4.1)	15 (3.7)
Dyspepsia	11 (2.8)	19 (4.7)
Nausea	22 (5.6)	45 (11.2)
Vomiting	5 (1.3)	9 (2.2)
NEUROLOGIC SYSTEM		
Dizziness	23 (5.8)	15 (3.7)
Insomnia	13 (3.3)	65 (16.1)
Nervousness	3 (0.8)	8 (2.0)
Vasodilatation	8 (2.0)	2 (0.5)
RESPIRATORY SYSTEM		
Rhinitis	6 (1.5)	9 (2.2)
Sinusitis	14 (3.5)	10 (2.5)
SENSORY SYSTEM		
Taste Perversion	11 (2.8)	11 (2.7)

* Loading Dose

- a Although a patient may have had two or more adverse events in a body system category, the patient was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of patients with any adverse events. If an individual adverse event was reported by the same patient more than once, the adverse event was counted only once.
- b One patient from the sparfloxacin group also reported paresthesia. One patient from the ofloxacin group also reported pruritis.

Medical Officer's Comments and Recommendations:

Although the photosensitivity reactions in the sparfloxacin group are significantly higher than in the ofloxacin group (8.4% versus 0.7%), the majority of these patients were kept on the study drug and completed the treatment.

Based upon the data submitted for efficacy and safety, the following recommendations are made:

Sparfloxacin is recommended for approval for the following indication:

Pages 97-162

Deleted

Not Approved

Indication

**MEDICAL OFFICER'S REVIEW OF THE INTEGRATED SAFETY SUMMARY
NDA 20-677**

Date Reviewed: 11/1/96.

Date Revised: 11/12/96.

The Integrated Safety Summary Analyses were performed by the statistician Dr. Joel Jiang. For a comprehensive review of the safety data, please refer to his review dated October 30, 1996. Some sections of his safety review which are clinically relevant are summarized in this review.

The statistical review includes an integrated summary of data relating to the safety of sparfloxacin for all Phase 3 clinical studies in this NDA submission. Eight Phase 3 clinical studies sponsored by the Applicant were conducted in the U.S.A. and Canada to evaluate the safety of sparfloxacin in patients with Community Acquired Pneumonia (CAP), Acute exacerbation of Chronic Bronchitis (ABECB),

In the CAP, ABECB, indications, sparfloxacin patients received a 10-day treatment course of 400 mg loading dose on the first day, followed by 200 mg daily dose. In the study, sparfloxacin patients received 1-day treatment course of 400 mg single dose or a 3-day treatment course of 400 mg loading dose on the first day, followed by 200 mg daily dose. In order to obtain a better understanding of the safety profile of sparfloxacin, the statistical reviewer performed a combined safety analysis of the Applicant's eight sparfloxacin studies submitted in this NDA in the two groups, respectively, based on the sparfloxacin treatment regimen. One group (all studies excluding includes six studies (301, 352, 356, 358, 359, and 353), and another study) includes the other two studies (355 and 363). In the Medical Officer's review, only data from studies in the first group will be summarized, since the dosing regimen employed in these studies is the one recommended for the proposed indications.

A total of 4510 patients was enrolled in eight Phase 3 clinical studies; 2916 in the first six studies and 1594 in the other two studies. Among all studies excluding 1585 patients were randomized to receive sparfloxacin and 1331 patients were randomized to receive comparators. For all studies, the sparfloxacin and the comparator groups were comparable across all indications with respect to the demographic characteristic of gender, age, and race. The majority of patients in both treatment groups across all indications were white, ranging in mean age from 34.5 years to 51.9 years.

TABLE 1: PHASE 3 CLINICAL STUDIES					
Indication	Study	Study Design	Treatment Duration	Number of Patients	
				Sparfloxacin	Comparators
CAP	301	Double-blind, Randomized, Comparative, Multicenter	10 days	219	209 (Erythromycin)
	352	Double-blind, Randomized, Comparative, Multicenter	10 days	168	162 (Cefaclor)
ABECB	356	Double-blind, Randomized, Comparative, Multicenter	10 days	395	403 (Ofloxacin)
AMS	358	Double-blind, Randomized, Comparative, Multicenter	10 days	252	252 (Clarithromycin)
	359	Open-label, Noncomparative, Multicenter	10 days	253	0 (None)
C-SSSI	353	Double-blind, Randomized, Comparative, Multicenter	10 days	298	305 (Ciprofloxacin)
U-UTI	355	Double-blind, Randomized, Comparative, Multicenter	3 days 1 day	395 394	386 (Ciprofloxacin)
	363	Open-label, Observer-blind, Randomized, Comparative, Multicenter	3 days	204	215 (Ofloxacin)

METHODS

In the eight Phase 3 clinical studies included in this analysis, three sparfloxacin treatment regimens were studied: (1) 200 mg once daily following a 400 mg loading dose given for 10 days of total treatment course, (2) a single 400 mg dose, and (3) 200 mg once daily following a 400 mg loading dose given for 3 days of total treatment course. Separate integrated safety analyses were performed for the above sparfloxacin regimen groups. Although various comparator agents were used in these trials, all the comparator agents were combined to form combined control groups correspondingly.

The rate of patients with adverse events, the rate of adverse events related to study medication, the rate of discontinuation due to adverse events, the rate of serious adverse events, the rate of adverse laboratory events, the rate of sponsor defined clinically significant laboratory adverse events, and the incidence rate of photosensitivity reaction were the safety parameters examined in this analysis. The QT_c interval of electrocardiogram was also evaluated.

All patients who received at least one dose of study medication were evaluable for safety. Treatment comparisons with respect to the safety parameters were conducted for the entire patient population and for the following subpopulations: gender (male, female), age (<60, 65+ years), race (white, nonwhite), and indication.

Safety

The treatment comparison was made using Fisher's exact test, and the test of homogeneity of treatment effect across subgroups was performed using Breslow-Day's test. The 95% confidence interval was computed using a normal approximation method and included a continuity correction. Fisher's exact test differences in the safety parameters were considered significant at the 0.05 level. Breslow-Day's test of homogeneity of treatment effect was deemed significant at the 0.15 level. Changes in the QT_c interval were summarized with descriptive statistics for all Phase 3 clinical studies combined, and by demographic aspects and indication.

In the discussion of subgroup results, it should be noted that in some patient subgroups, the large variation in treatment effect precluded a meaningful pooling of results across studies, or the amount of data in the individual studies was too sparse to obtain a valid estimate of the treatment effect of the study.

RESULTS**ALL STUDIES**

Six studies (301, 352, 356, 358, 359, and 353) were included in this analysis. Sparfloxacin was administered by a daily oral dose of 200 mg following a loading dose of 400 mg on the first day of treatment for 10 days of total treatment course. The safety population for this regimen included a total of 1585 sparfloxacin patients and 1331 combined comparator patients. The comparators in these studies were erythromycin, cefaclor, ofloxacin, clarithromycin, and ciprofloxacin.

Safety data from each of the four comparative studies (301, 352, 356, and 358) are summarized in the tables below:

Table 2 summarizes adverse clinical and adverse laboratory events for study 301. Note that the percentage of patients who experienced a photosensitivity reaction was statistically significantly higher ($p < 0.001$; generalized Cochrane-Mantel-Haenszel Test) in the sparfloxacin group (6.4%, 14/219) as compared with the erythromycin group (0.5%, 1/209). In contrast, the percentage of patients who experienced an adverse event related to the digestive system was statistically lower ($p < 0.001$; generalized Cochrane-Mantel-Haenszel Test) in the sparfloxacin group (21.9%, 48/219) as compared with the erythromycin group (44.5%, 93/209).

Table 2 -Study 301: Clinical and Laboratory Adverse Event Rates

Safety Parameter	Number (%) Patients		
	Sparfloxacin (N=219)	Erythromycin (N=209)	p-value
Adverse Event ^a	136 (62.1)	140 (67.0)	ND
Most Common ^b			
Nausea	13 (5.9)	43 (20.6)	ND
Diarrhea	15 (6.8)	38 (18.2)	ND
Vomiting	12 (5.5)	25 (12.0)	ND
Abdominal Pain	9 (4.1)	24 (11.5)	ND
Headache	16 (7.3)	14 (6.7)	ND
Photosensitivity Reaction	14 (6.4)	1 (0.5)	<0.001
Digestive System	48 (21.9)	93 (44.5)	<0.001
Musculoskeletal System	6 (2.7)	7 (3.3)	ND
Nervous System	28 (12.8)	24 (11.5)	0.494
Cardiovascular System	19 (8.7)	16 (7.7)	0.661
Adverse Events Related to Study Drug	85 (38.8)	108 (51.7)	ND
Most Common ^b			
Diarrhea	14 (6.4)	36 (17.2)	ND
Nausea	9 (4.1)	35 (16.7)	ND
Abdominal Pain	4 (1.8)	22 (10.5)	ND
Vomiting	8 (3.7)	17 (8.1)	ND
Photosensitivity Reaction	13 (5.9)	1 (0.5)	ND
Adverse Events Leading to Discontinuation	21 (10.0)	31 (14.8)	ND
Most Common ^c			
Nausea	2 (1.0)	9 (4.3)	ND
Vomiting	1 (0.5)	9 (4.3)	ND
Pneumonia	2 (1.0)	5 (2.4)	ND
Abdominal Pain	0	6 (2.8)	ND
Adverse Laboratory Events	30 (13.7)	28 (13.4)	ND
Most Common ^c			
↑SGPT	12 (5.5)	9 (4.3)	ND
↑SGOT	9 (4.1)	6 (2.9)	ND
↑Neutrophils	5 (2.3)	5 (2.4)	ND
↑White Blood Cell Count	7 (3.2)	5 (2.4)	ND
↓Platelets	5 (2.3)	2 (1.0)	ND
ND = not done			
a The majority of adverse events were of mild or moderate severity.			
b Reported by 5% of patients in either treatment group.			
c Reported by 2% of patients in either treatment group.			

Table 3 summarizes adverse clinical events and adverse laboratory events for study 352. Note that sparfloxacin is not statistically significantly worse than cefaclor with respect to any of the reported adverse events.

Table 3 - Study 352: Clinical and Laboratory Adverse Event Rates

Safety Parameter	Number (%) Patients		
	Sparfloxacin (n= 168)	Cefaclor (n= 162)	p-value
Adverse Event ^a Most Common ^b	84 (50.0)	80 (49.4)	ND
Headache	18 (10.7)	14 (8.6)	ND
Rhinitis	10 (6.0)	11 (6.8)	ND
Diarrhea	7 (4.2)	10 (6.2)	ND
Digestive System	24(14.3)	21 (13.0)	0.846
Musculoskeletal System	3 (1.8)	3 (1.9)	ND
Nervous System	16 (9.5)	14(8.6)	0.924
Cardiovascular System	12 (7.1)	8 (4.9)	0.446
Photosensitivity Reaction	4(2.4)	1 (0.6)	0.177
Adverse Events Related to Study Drug	37 (22.0)	41 (25.3)	ND
Adverse Events Leading to Discontinuation ^c Most Common ^d	11 (6.5)	9 (5.6)	ND
Pneumonia	1 (0.6)	4 (2.5)	ND
Adverse Laboratory Events Most Common ^d	18 (10.7)	14 (8.6)	ND
↑SGPT	9 (5.4)	6 (3.7)	ND
↑SGOT	8 (4.8)	5 (3.1)	ND
↓Blood Glucose	4 (2.4)	1 (0.6)	ND

ND=not done

- a The majority of adverse events were of mild or moderate severity.
- b Reported by 5% of patients in either treatment group.
- c One additional patient in the cefaclor group experienced an adverse event that led to discontinuation from the study by the investigator; however, the investigator classified the reason for discontinuation for this patient as test drug ineffective in the disposition section of the case report form.
- d Reported by 2% of patients in either treatment group.

Table 4 summarizes the rate of serious adverse events and the rate of adverse laboratory events. No significant differences between treatment groups were detected with respect to all the parameters presented except that the percentages of patients who experienced photosensitivity reaction were significantly higher in the sparfloxacin group than in the ofloxacin group. No deaths were reported in the sparfloxacin group; however, one patient in the ofloxacin group died during the study.

TABLE 4 - STUDY 356: CLINICAL AND LABORATORY ADVERSE EVENT RATES			
Safety Parameter	Sparfloxacin (N=395)	Ofloxacin (N=403)	Fisher's P-value
<u>Patients with Adverse Events</u>	215 (54.4%)	224 (55.6%)	0.776
Headache	44 (11.1%)	35 (8.7%)	0.286
Insomnia	13 (3.3%)	65 (16.1%)	<0.001
Nausea	22 (5.6%)	45 (11.2%)	0.005
Dizziness	23 (5.8%)	15 (3.7%)	0.185
Photosensitivity Reaction	33 (8.4%)	3 (0.7%)	<0.001
Digestive System	58 (14.7%)	99 (24.6%)	<0.001
Musculoskeletal System	2 (0.5%)	11 (2.7%)	0.022
Nervous System	60 (15.2%)	99 (24.6%)	0.001
Cardiovascular System	17 (4.3%)	17 (4.2%)	1.000
<u>AE Related to Study Medication</u>	139 (35.2%)	163 (40.4%)	0.144
Insomnia	6 (1.5%)	60 (14.9%)	<0.001
Nausea	17 (4.3%)	41 (10.2%)	0.002
Photosensitivity Reaction	32 (8.1%)	3 (0.7%)	<0.001
<u>Discontinuation due to AE</u>	21 (5.3%)	30 (7.4%)	0.248
<u>Serious Adverse Events</u>	6 (1.5%)	6 (1.5%)	1.000
<u>Adverse Laboratory Events</u>	25 (6.3%)	31 (7.7%)	0.490
1SGOT	5 (1.3%)	4 (1.0%)	0.750
1SGPT	4 (1.0%)	7 (1.7%)	0.546
1WBC	7 (1.8%)	13 (3.2%)	0.258

Table 5 shows photosensitivity reaction subset by demographic aspects.

TABLE 5 - STUDY 356: PHOTSENSITIVITY REACTION SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=395)	Ofloxacin (N=403)	95% C.I.	P-value Fisher's Exact	P-value Breslow-Day's
Male	22/195 (11.3%)	3/218 (1.4%)	(4.7%, 15.1%)	<0.001	0.277
Female	11/200 (5.5%)	0/185 (0%)	(1.8%, 9.2%)	0.001	
<65	20/271 (7.4%)	3/281 (1.1%)	(2.6%, 10.0%)	<0.001	0.178
≥65	13/124 (10.5%)	0/122 (0%)	(4.3%, 16.7%)	<0.001	
White	33/305 (10.8%)	3/308 (1.0%)	(5.9%, 13.8%)	<0.001	NA
Nonwhite	0/90 (0%)	0/95 (0%)	NA	NA	

Table 6 shows the mean changes in Q_t intervals at selected time points. A significantly greater mean change from baseline to maximum on-treatment value for Q_t interval was observed in the sparfloxacin group as compared with the ofloxacin group.

TABLE 6 - STUDY 356: MEAN CHANGE IN Q_t INTERVALS AT SELECTED TIME POINTS		
Safety Parameter	Sparfloxacin (N=395)	Ofloxacin (N=403)
<u>Day 4</u>		
Number of Patients	357	357
Baseline Mean	0.409	0.408
Mean Change	0.011	0.001
<u>Endpoint</u>		
Number of Patients	387	392
Baseline Mean	0.409	0.409
Mean Change	0.002	0.002
Maximum on Treatment Mean Change and	0.012	0.001
ITS P-value and 95% C.I.	p<0.001, (0.007, 0.014)	

Table 7 presents a summary of mean changes from baseline in QT_c interval at selected time points, subset by gender, age, and race.

TABLE 7 - STUDY 356: MEAN CHANGE IN QT_c INTERVALS AT SELECTED TIME POINTS SUBSET BY DEMOGRAPHIC ASPECTS				
Subset	Sparfloxacin (N=395)		Ofloxacin (N=403)	
GENDER	Male	Female	Male	Female
<u>Day4</u>				
Number of Patients	180	177	195	162
Baseline Mean	0.403	0.146	0.407	0.409
Mean Change	0.009	0.012	-0.001	0.003
<u>Endpoint</u>				
Number of Patients	192	195	212	180
Baseline Mean	0.404	0.414	0.407	0.411
Mean Change	0.001	0.003	0	0.005
AGE	18-64	≥65	18-64	≥65
<u>Day4</u>				
Number of Patients	250	107	250	107
Baseline Mean	0.409	0.410	0.409	0.408
Mean Change	0.010	0.012	0.001	0.001
<u>Endpoint</u>				
Number of Patients	264	123	272	120
Baseline Mean	0.409	0.411	0.409	0.408
Mean Change	0.003	<0.001	0.002	0.002
RACE	White	Nonwhite	White	Nonwhite
<u>Day4</u>				
Number of Patients	276	81	279	78
Baseline Mean	0.410	0.408	0.408	0.411
Mean Change	0.011	0.009	<0.001	0.005
<u>Endpoint</u>				
Number of Patients	300	87	304	88
Baseline Mean	0.410	0.408	0.409	0.410
Mean Change	0.001	0.006	0.001	0.005

Table 8 gives the summaries of the rates of all the clinical and laboratory adverse events. Among the most common adverse events, the percentage of patients who experienced taste perversion was significantly lower in the sparfloxacin group than in the clarithromycin group. However, the percentage of patients who experienced photosensitivity reaction was significantly higher in the sparfloxacin group than the clarithromycin group.

TABLE 8 - STUDY 358: CLINICAL AND LABORATORY ADVERSE EVENT RATES			
Safety Parameter	Sparfloxacin (N=252)	Clarithromycin (N=252)	Fisher's P-value
Patients with Adverse Events	122 (48.4%)	146 (57.9%)	0.040
Headache	27 (10.7%)	31 (12.3%)	0.676
Nausea	15 (6.0%)	22 (8.7%)	0.305
Diarrhea	12 (4.8%)	22 (8.7%)	0.109
Taste Perversion	2 (0.8%)	22 (8.7%)	<0.001
Photosensitivity Reaction	24 (9.5%)	3 (1.2%)	<0.001
Digestive System	43 (17.1%)	63 (25.0%)	0.038
Musculoskeletal System	3 (1.2%)	3 (1.2%)	1.000
Nervous System	19 (7.5%)	18 (7.1%)	1.000
Cardiovascular System	8 (3.2%)	13 (5.2%)	0.373
AE Related to Study Medication	78 (31.0%)	89 (35.3%)	0.344
Insomnia	12 (4.8%)	17 (6.7%)	0.445
Nausea	14 (5.6%)	15 (6.0%)	1.000
Taste Perversion	2 (0.8%)	22 (8.7%)	<0.001
Photosensitivity Reaction	24 (9.5%)	3 (1.2%)	<0.001
Discontinuation due to AE	18 (7.1%)	21 (8.3%)	0.739
Serious Adverse Events	0 (0%)	5 (2.0%)	0.061
Adverse Laboratory Events	17 (6.7%)	15 (6.0%)	0.855
!SGPT	5 (2.0%)	2 (0.8%)	0.450
!Lipase	3 (1.2%)	5 (2.0%)	0.724

Table 9 shows photosensitivity reaction subset by demographic aspects.

TABLE 9 - STUDY 358: PHOTOSENSITIVITY REACTION SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=252)	Clarithromycin n (N=252)	95% C.I.	P-value Fisher's Exact	P-value Breslow-Day's
Male	12/104 (11.5%)	2/95 (2.1%)	(1.6%, 17.2%)	0.011	0.523
Female	12/148 (8.1%)	1/157 (0.6%)	(2.2%, 12.7%)	0.001	
<65	22/237 (9.3%)	3/226 (1.3%)	(3.5%, 12.4%)	<0.001	0.480
≥65	2/15 (13.3%)	0/26 (0%)	(-9.1%, 35.8%)	0.128	
White	22/218 (10.1%)	3/226 (1.3%)	(4.0%, 13.5%)	<0.001	0.659
Nonwhite	2/34 (5.9%)	0/26 (0%)	(-5.4%, 17.2%)	0.501	

Table 10 shows mean changes in Q_t intervals at selected time point. A significantly greater mean change from baseline to maximum on-treatment value for Q_t interval was observed in the sparfloxacin group as compared with the clarithromycin group.

TABLE 10 - STUDY 358: MEAN CHANGE IN Q_t INTERVALS AT SELECTED TIME POINTS		
Safety Parameter	Sparfloxacin (N=252)	Clarithromycin (N=252)
<u>Day 4</u>		
Number of Patients	228	229
Baseline Mean	0.405	0.406
Mean Change	0.007	0.003
<u>Endpoint</u>		
Number of Patients	2470.404	247
Baseline Mean		0.406
Mean Change		0.001
Maximum on Treatment Mean Change and Its P-value and 95% C.I.	0.005	0.003
	p=0.326, (-0.002, 0.007)	

Table 11 presents a summary of mean changes from baseline in QT_c interval at selected time points, subset by gender, age, and race.

TABLE 11 - STUDY 358: MEAN CHANGE IN QT_c INTERVALS AT SELECTED TIME POINT SUBSET BY DEMOGRAPHIC ASPECTS				
Subset	Sparfloxacin (N=252)		Clarithromycin (N=252)	
GENDER	Male	Female	Male	Female
<u>Day4</u>				
Number of Patients	95	133	85	144
Baseline Mean	0.396	0.411	0.397	0.411
Mean Change	0.006	0.007	0.002	0.004
<u>Endpoint</u>				
Number of Patients	102	145	93	154
Baseline Mean	0.395	0.412	0.397	0.411
Mean Change	0.001	-0.003	-0.003	0.004
AGE	18-64	≥65	18-64	≥65
<u>Day4</u>				
Number of Patients	216	12	205	24
Baseline Mean	0.404	0.416	0.403	0.426
Mean Change	0.006	-0.002	0.004	-0.001
<u>Endpoint</u>				
Number of Patients	234	13	222	25
Baseline Mean	0.405	0.408	0.403	0.426
Mean Change	-0.001	0.001	0.002	-0.005
RACE	White	Nonwhite	White	Nonwhite
<u>Day4</u>				
Number of Patients	197	31	205	24
Baseline Mean	0.404	0.408	0.405	0.415
Mean Change	0.007	0.002	0.004	-0.001
<u>Endpoint</u>				
Number of Patients	214	33	223	24
Baseline Mean	0.405	0.409	0.405	0.415
Mean Change	0.001	-0.011	0.001	0.003

All Clinical Adverse Events

Safety results of the difference between sparfloxacin and the combined comparators in clinical adverse events are presented in Table 12. For all six studies, 53.1% of 1585 sparfloxacin patients and 55.9% of 1331 combined comparator patients experienced adverse events. Fisher's exact p-value was 0.136, which indicated that there was no significant difference between sparfloxacin and the combined comparators with respect to the rates of adverse event. No significant differences between sparfloxacin and the combined comparators were also detected with respect to the rates of serious adverse events and the rates of adverse laboratory events. For the patients reporting adverse events related to study medication and the discontinuation due to adverse events, the rates were significantly lower in the sparfloxacin group than in the combined comparator group, respectively ($p=0.003$ and $p=0.021$). However, the sparfloxacin group had a very significantly higher incidence rate of photosensitivity reaction ($p<0.001$). Table 12 also summarizes the incidence of adverse events by body system. A statistically lower percentage of patients in the sparfloxacin group was reported with respect to the rates of adverse events in digestive and nervous systems as compared with the combined comparator group. The percentage of patients who experienced adverse events associated with body as a whole was significantly higher in the sparfloxacin group. The two treatments were statistically comparable for the adverse events that occurred in cardiovascular, respiratory, skin and appendage, special sense, and urogenital systems. Note that the most frequently reported incidences of adverse events in both treatment groups were found in the digestive system and body as a whole.

TABLE 12: COMBINED SAFETY ANALYSIS FOR ALL STUDIES CLINICAL AND SELECTED LABORATORY ADVERSE EVENT RATES			
Safety Parameter	Sparfloxacin (N=1585)	Comparators (N=1331)	P-value Fisher's Exact
<u>Patients with Adverse Events</u>	842 (53.1%)	744 (55.9%)	0.136
Body as a Whole	414 (26.1%)	268 (20.1%)	<0.001
Cardiovascular System	73 (4.6%)	66 (5.0%)	0.664
Digestive System	240 (15.1%)	342 (25.7%)	<0.001
Nervous System	180 (11.4%)	184 (13.8%)	0.049
Respiratory System	182 (11.5%)	144 (10.8%)	0.596
Skin and Appendage	112 (7.1%)	85 (6.4%)	0.505
Special Sense	80 (5.0%)	70 (5.3%)	0.801
Urogenital System	30 (1.9%)	37 (2.8%)	0.136
Photosensitivity Reaction	130 (8.2%)	12 (0.9%)	<0.001
<u>AE Related to Study Medication</u>	518 (32.7%)	505 (37.9%)	0.003
Body as a Whole	223 (14.1%)	117 (8.8%)	<0.001
Cardiovascular System	41 (2.6%)	38 (2.9%)	0.731
Digestive System	184 (11.6%)	274 (20.6%)	<0.001
Metabolism	10 (0.6%)	8 (0.6%)	1.000
Nervous System	121 (7.6%)	151 (11.3%)	0.001
Respiratory System	28 (1.8%)	27 (2.0%)	0.682
Skin and Appendage	70 (4.4%)	47 (3.5%)	0.256
Special Sense	43 (2.7%)	45 (3.4%)	0.328
Urogenital System	15 (0.9%)	24 (1.8%)	0.052
Photosensitivity Reaction	126 (7.9%)	12 (0.9%)	<0.001
<u>Discontinuation due to AE</u>	104 (6.6%)	118 (8.9%)	0.021
<u>Adverse Laboratory Events</u>	115 (7.3%)	99 (7.4%)	0.887
↑SGOT	32 (2.0%)	19 (1.4%)	0.258
↑SGPT	36 (2.3%)	28 (2.1%)	0.801
↓WBC	18 (1.1%)	23 (1.7%)	0.207

Patients with Adverse Events

No statistical significance was detected in age. However, significantly lower rates of adverse events for sparfloxacin were observed in female patients ($p=0.012$) and in nonwhite patients ($p=0.011$).

Safety

Adverse Events Related to Study Medication

Sparfloxacin had significantly lower rates of adverse events related to study medication in female patients of gender subgroup ($p<0.001$), in <65 years patients of age subgroup ($p=0.001$), in nonwhite patients of race subgroup ($p<0.001$), in CAP and LRTI patients of indication subgroup ($p=0.015$ and $p=0.005$).

Discontinuation due to Adverse Events

The results from all subgroup analyses showed that numerically lower rates of discontinuation due to adverse events were observed in the sparfloxacin patients than in the combined comparator patients. Significantly lower rates were also observed in <65 years patients of gender subgroup ($p=0.024$), and in nonwhite patients of race subgroup ($p=0.024$).

Serious Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of serious adverse events are displayed in Table 13. No statistical significance was detected among all demographic subgroups, except in patients of indication subgroup, in which sparfloxacin had a significantly lower rate than the combined comparators ($p=0.017$).

Deaths

A total of 7 patients died in all studies

These deaths were considered by the investigators to be either unrelated or remotely related to study medication. There were 4 deaths in the sparfloxacin group and 3 deaths in the combined comparator group.

TABLE 13: COMBINED SAFETY ANALYSIS FOR ALL STUDIES				SERIOUS	
ADVERSE EVENTS SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION					
Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	43/1585 (2.7%)	47/1331 (3.5%)	(-2.2%, 0.5%)	0.237	
Male	33/819 (4.0%)	34/732 (4.6%)	(-2.8%, 1.5%)	0.617	0.453
Female	10/766 (1.3%)	13/599 (2.2%)	(-2.4%, 0.7%)	0.289	
<65	25/1274 (2.0%)	25/1034 (2.4%)	(-1.7%, 0.8%)	0.475	0.907
≥65	18/311 (5.8%)	22/297 (7.4%)	(-5.9%, 2.7%)	0.513	
White	33/1313 (2.5%)	36/1104 (3.3%)	(-2.2%, 0.7%)	0.273	0.968
Nonwhite	10/272 (3.7%)	11/227 (4.8%)	(-5.2%, 2.8%)	0.655	
CAP	27/337 (7.0%)	24/371 (6.5%)	(-3.3%, 4.3%)	0.885	0.127
ABECB	6/395 (1.5%)	6/403 (1.5%)	(-1.9%, 2.0%)	1.000	
AMS	1/505 (0.2%)	5/252 (2.0%)	(-3.8%, 0.3%)	0.017	
C-SSSI	9/298 (3.0%)	12/305 (3.9%)	(-4.2%, 2.3%)	0.658	

Photosensitivity Reaction

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the incidence rate of photosensitivity reaction and incidence rate of photosensitivity reaction related to study medication are displayed in Table 14 and Table 15, respectively. The results observed in the analyses subset by demographic aspects and indication were consistent with those observed in the overall analysis; that is, in all of the subgroups, sparfloxacin had a very significantly higher incidence rate of photosensitivity reaction and incidence rate of photosensitivity reaction related to study medication ($p < 0.001$ and $p < 0.001$) than the combined comparators.

The comparison results of the day of onset, duration, and number of episodes of photosensitivity reaction is presented in Table 16. A statistically significant difference between sparfloxacin and the combined comparators was only detected in the duration of photosensitivity reaction ($p = 0.043$).

Table 17 displays the results of patients experiencing photosensitivity reaction by selected classes of concomitant medication. The incidences of photosensitivity reaction by all concomitant medications, except tricyclic antidepressants, were significantly higher in the sparfloxacin group.

A summary of the outcome and action taken for photosensitivity reaction is presented in Table 18. There was not a statistically significant difference between the sparfloxacin patients and the combined comparator patients.

It is noteworthy that the US development program was stopped temporarily by the Applicant on Oct. 18, 1993, due to the high frequency of photosensitivity reaction in sparfloxacin studies, and the protocols were amended to provide new information regarding sparfloxacin associated photosensitivity to the investigators and to provide advice and additional precautions to patients regarding sun exposure during treatment with study medication. Upon IRB approval at each site of the Oct. 25, 1993 amendment, the studies resumed. Table 19 presents the incidence rates of photosensitivity reaction pre- and post- Oct. 25, 1993 Amendment. For sparfloxacin, although the rate of post-1993 was numerically decreased slightly as compared with that of pre-1993, it had always very significantly higher rates than its comparators.

TABLE 14: COMBINED SAFETY ANALYSIS FOR ALL STUDIES PHOTOSENSITIVITY REACTION SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION					
Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	130/1585 (8.2%)	12/1331 (0.9%)	(5.8%, 8.8%)	<0.001	
Male	74/819 (9.0%)	9/732 (1.2%)	(5.6%, 10.1%)	<0.001	0.322
Female	56/766 (7.3%)	3/599 (0.5%)	(4.7%, 8.9%)	<0.001	
<65	107/1274 (8.4%)	11/1034 (1.1%)	(5.6%, 9.1%)	<0.001	0.325
≥65	23/311 (7.4%)	1/297 (0.3%)	(3.7%, 10.4%)	<0.001	
White	128/1313 (9.7%)	12/1104 (1.1%)	(6.9%, 10.5%)	<0.001	0.679
Nonwhite	2/272 (0.7%)	0/227 (0)	(-0.7%, 2.2%)	0.503	
CAP	18/387 (4.7%)	2/371 (0.5%)	(1.6%, 6.6%)	<0.001	0.990
ABECB	33/395 (8.4%)	3/403 (0.7%)	(4.5%, 10.7%)	<0.001	
AMS	44/505 (8.7%)	3/252 (1.2%)	(4.4%, 10.6%)	<0.001	
C-SSSI	35/298 (11.7%)	4/305 (1.3%)	(6.2%, 14.6%)	<0.001	

TABLE 15: COMBINED SAFETY ANALYSIS FOR ALL STUDIES PHOTOSENSITIVITY REACTION RELATED TO STUDY MEDICATION SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION					
Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	126/1585 (7.9%)	12/1331 (0.9%)	(5.6%, 8.5%)	<0.001	
Male	72/819 (8.8%)	9/732 (1.2%)	(5.6%, 10.1%)	<0.001	0.329
Female	54/766 (7.0%)	3/599 (0.5%)	(4.7%, 8.9%)	<0.001	
<65	103/1274 (8.1%)	11/1034 (1.1%)	(5.6%, 9.1%)	<0.001	0.304
≥65	23/311 (7.4%)	1/297 (0.3%)	(3.7%, 10.4%)	<0.001	
White	124/1313 (9.4%)	12/1104 (1.1%)	(6.9%, 10.5%)	<0.001	0.674
Nonwhite	2/272 (0.7%)	0/227 (0)	(-0.7%, 2.2%)	0.503	
CAP	17/387 (4.4%)	2/371 (0.5%)	(1.6%, 6.6%)	0.001	0.990
ABECB	32/395 (8.1%)	3/403 (0.7%)	(4.5%, 10.7%)	<0.001	
AMS	43/505 (8.5%)	3/252 (1.2%)	(4.4%, 10.6%)	<0.001	
C-SSSI	34/298 (11.4%)	4/305 (1.3%)	(6.2%, 14.6%)	<0.001	

TABLE 16: COMBINED SAFETY ANALYSIS FOR ALL STUDIES EXCEPT THE DAY OF ONSET, DURATION, AND NUMBER OF EPISODES OF PHOTSENSITIVITY REACTION			
Photosensitivity Reaction	Sparfloxacin (130/1585)	Comparators (12/1331)	P-value: Fisher's Exact
<u>Day of Onset</u> <i>Relative to the First Dose of Study Medication:</i>			
Mean ± S.D. Range	7.5 ± 5.3	9.1 ± 6.3	0.326*
<i>Relative to the Last Dose of Study Medication:</i>			
Mean ± S.D. Range *	-3.5 ± 5.7	-2.8 ± 6.5	0.688*
<u>Duration</u>			
Mean · S.D. Range	13.2 ± 11.0	6.5 ± 9.0	0.043*
<u>Number of Episodes</u>			
1	123 (94.6%)	12 (100.0%)	1.000
2	7 (5.4%)	0	1.000
*: P-value by two-sample t test for independent samples with equal variances.			

**TABLE 17: COMBINED SAFETY ANALYSIS FOR ALL STUDIES
PHOTOSENSITIVITY REACTION BY SELECTED CLASSES OF
CONCOMITANT MEDICATION**

Class of Concomitant Medication	Sparfloxacin (130/1585)	Comparators (12/1331)	P-value: Fisher's Exact
Sunscreens	18/27 (66.7%)	2/13 (15.4%)	0.006
Antihistamines	9/69 (13.0%)	0/66 (0)	0.003
Oral Contraceptives	15/156 (9.6%)	1/106 (0.9%)	0.003
Tricyclic Antidepressants	2/22 (9.1%)	0/14 (0)	0.511
NSAIDS	18/249 (7.2%)	1/208 (0.5%)	<0.001
Diuretics	12/195 (6.2%)	0/184 (0)	<0.001

**TABLE 18: COMBINED SAFETY ANALYSIS FOR ALL STUDIES
PHOTOSENSITIVITY REACTION BY OUTCOME AND ACTION TAKEN**

Outcome or Action Taken	Sparfloxacin (130/1585)	Comparators (12/1331)	P-value: Fisher's Exact
Outcome at End of Study			
Recovered	113 (86.9%)	11 (91.7%)	1.000
Recovered with Sequelae	6 (4.6%)	0	1.000
Ongoing	11 (8.5%)	1 (8.3%)	1.000
Action Taken - Study			
None	114 (87.7%)	11 (91.7%)	1.000
Discontinued	16 (12.3%)	1 (8.3%)	1.000
Action Taken - Other			
None	80 (61.5%)	9 (75.0%)	0.535
Medication	36 (27.7%)	3 (25.0%)	1.000
Other	14 (10.8%)	0	0.608
Discontinued From the Study			
Yes	17 (13.1%)	1 (8.3%)	1.000
No	113 (86.9%)	11 (91.7%)	1.000

TABLE 19: COMBINED SAFETY ANALYSIS FOR ALL STUDIES THE INCIDENCE RATES OF PHOTSENSITIVITY REACTION PRE- AND POST- 1993 AMENDMENT			
Study Period	Sparfloxacin	Comparators	P-value Fisher's Exact
Pre-1993	44/430 (10.2%)	2/428 (0.5%)	<0.001
Post-1993	86/1155 (7.4%)	10/903 (1.1%)	<0.001

Sponsor Defined Clinically Significant Laboratory Adverse Events

Table 20 summarizes the incidence of sponsor defined clinically significant laboratory adverse events. On all variables, a statistically significant difference between the two groups was reported only in WBC which sparfloxacin had a significantly lower incidence rate than the combined comparators (p=0.048).

TABLE 20: COMBINED SAFETY ANALYSIS FOR ALL STUDIES SPONSOR DEFINED CLINICALLY SIGNIFICANT LABORATORY ADVERSE EVENT RATES			
Laboratory Values	Sparfloxacin (N=1585)	Comparators (N=1331)	P-value Fisher's Exact
Creatinine increased	27 (1.7%)	27 (2.0%)	0.582
Eosinophils decreased	27 (1.7%)	28 (1.8%)	0.495
Hemoglobin decreased	146 (9.2%)	130 (9.8%)	0.612
Platelets decreased	5 (0.3%)	3 (0.2%)	0.734
SGOT increased	38 (2.4%)	33 (2.5%)	0.904
SGPT increased	55 (3.5%)	55 (4.1%)	0.380
Total Bilirubin increased	5 (0.3%)	0	0.067
WBC decreased	9 (0.6%)	17 (1.3%)	0.048

Mean Change from Baseline in QT_c Interval

In all six studies, a total of 14 patients (11 in the sparfloxacin group and 3 in the combined comparator group) had one or more on-treatment QT_c values larger than 500 msec. Table 21 shows mean change in QT_c interval from baseline to maximum for on- and off-treatment value. Table 22 presents a summary of mean changes in QT_c interval from baseline to maximum for on- and off-treatment value, subset by gender, age, race, and indication. Summary of the mean change in QT_c interval from baseline to off-treatment value larger than 10% and QT_c interval off-treatment value larger than 400 msec is presented in Table 23. For all six studies as a whole, the sparfloxacin group had significantly more patients who met the level than the combined comparator group (p<0.001), so did the sparfloxacin groups for Study 353 and Study 356, respectively.

TABLE 21: COMBINED SAFETY ANALYSIS FOR ALL STUDIES MEAN CHANGE IN QT_c INTERVAL AT SELECTED TIME POINTS		
Safety Parameter	Sparfloxacin	Comparators
<u>On Treatment</u>		
Number of Patients	1489	1215
Baseline Mean	0.408	0.406
Mean Change	0.010±0.001	0.003±0.001
<u>Off Treatment</u>		
Number of Patients	1435	1198
Baseline Mean	0.408	0.406
Mean Change	0.001±0.001	0.004±0.001

TABLE-22: COMBINED SAFETY ANALYSIS FOR ALL STUDIES						MEAN CHANGE				
IN QT _c INTERVALS AT SELECTED TIME POINTS SUBSET BY DEMOGRAPHIC ASPECTS										
Subset	Sparfloxacin					Comparators				
	Male		Female			Male		Female		
<u>On Treatment</u>	772		717			678		537		
Patients	0.402		0.413			0.402		0.411		
Baseline Mean	0.008±0.001		0.011±0.001			0.003±0.001		0.004±0.001		
Mean Change										
<u>Off Treatment</u>	745		690			654		544		
Patients	0.403		0.413			0.403		0.410		
Baseline Mean	0.001±0.001		0.001±0.001			0.002±0.001		0.007±0.001		
Mean Change										
AGE	18-64		≥65			18-64		≥65		
<u>On Treatment</u>	1202		237			952		263		
Patients	0.406		0.414			0.404		0.412		
Baseline Mean	0.009±0.001		0.013±0.002			0.003±0.001		0.002±0.002		
Mean Change										
<u>Off Treatment</u>	1159		276			933		265		
Patients	0.406		0.414			0.404		0.414		
Baseline Mean	0.001±0.001		0.002±0.002			0.004±0.001		0.004±0.002		
Mean Change										
RACE	White		Non-White			White		Non-White		
<u>On Treatment</u>	1242		247			1019		196		
Patients	0.408		0.408			0.406		0.408		
Baseline Mean	0.010±0.001		0.007±0.002			0.002±0.001		0.006±0.002		
Mean Change										
<u>Off Treatment</u>	1191		244			1000		198		
Patients	0.408		0.409			0.406		0.408		
Baseline Mean	-0.001±0.001		-0.002±0.002			0.004±0.001		0.005±0.003		
Mean Change										
INDICATION	CAP	ABECB	LRTI	AMS	CSSSI	CAP	ABECB	LRTI	AMS	CSSI
<u>On Treatment</u>	363	365	728	482	279	334	363	697	239	278
Patients	0.408	0.410	0.409	0.408	0.404	0.408	0.408	0.408	0.406	0.402
Baseline Mean	0.008±	0.012±	0.010±	0.008±	0.012±	0.004±	0.001±	0.002±	0.003±	0.006±
Mean Change	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.002
<u>Off Treatment</u>	341	355	696	462	277	321	367	688	227	283
Patients	0.409	0.409	0.409	0.409	0.404	0.407	0.409	0.408	0.405	0.402
Baseline Mean	0.001±	0.003±	0.002±	-0.001±	0.000±	0.004±	0.005±	0.004±	0.003±	0.004±
Mean Change	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.002

TABLE 23: COMBINED SAFETY ANALYSIS FOR ALL STUDIES MEAN CHANGE IN QT_c INTERVAL FROM BASELINE TO OFF- TREATMENT VALUE>10% AND QT_c INTERVAL OFF-TREATMENT VALUE>400 msec			
Study	Sparfloxacin (N=1585)	Comparators (N=1331)	P-value Fisher's Exact
All	93/1555 (6.0%)	35/1292 (2.7%)	<0.001
301	12/214 (5.6%)	6/197 (3.0%) Erythromycin	0.235
352	11/163 (6.7%)	7/158 (4.4%) Cefaclor	0.469
353	15/297 (5.1%)	6/298 (2.0%) Ciprofloxacin	0.048
356	26/387 (6.7%)	4/392 (1.0%) Ofloxacin	<0.001
358	14/247 (5.7%)	12/247 (4.9%) Clarithromycin	0.841
359	15/247 (6.1%)	NA	NA

Medical Officer's Comments:

Any patient who met the criteria of having a Qt_c interval of more than or equal to 400 msec at baseline and/or a mean change in the Qt_c interval of >10% from baseline at any point during therapy or after therapy is presented in the above table. Although 6% of patients in the sparfloxacin met the criteria, there was only one patient in study 352, two patients in study 358, and one patient in study 356 on sparfloxacin who developed Right bundle branch block. One patient in study 353 developed Left bundle branch block. Two patients (one in study 353, one in study 356) developed first degree heart block. All these abnormalities noted were not directly related to the prolongation of the Qt_c interval but due to the underlying cardiac problems in these patients.

In the comparator arms, there was one patient with Left bundle branch block in study 353 who received ciprofloxacin. In study 358 where clarithromycin was used as a comparator, one patient developed bigeminy, and one patient had a first degree heart block. In study 352, cefaclor was used as the comparator drug and six patients had right bundle branch block, one patient developed left bundle branch block, and one patient had first degree heart block.

Based upon data from toxicology studies as well as post-marketing data from

Europe, prolongation of Q_t_c interval and subsequent development of ventricular arrhythmias was a concern when studies with sparfloxacin were being initiated in the United States of America and Canada, so when the study protocols were submitted to FDA for review, patients with underlying heart disease were excluded from these studies. That might be the reason prolongation of Q_t_c was not a significant problem leading to clinical abnormalities in patients on sparfloxacin. Since ventricular arrhythmias still remain a concern, the **WARNINGS** and **PRECAUTIONS** sections of the package insert for sparfloxacin should address this issue appropriately.

OVERALL RECOMMENDATIONS:

Based upon the data submitted by the applicant, the following recommendations are made:

INDICATIONS AND USAGE

DOSAGE AND ADMINISTRATION

The package insert for sparfloxacin is reviewed separately. Please refer to the Medical Officer's review dated 11/4/96.

Nasim Moledina

Nasim R. Moledina, M.D.
Medical Officer, FDA.

cc: Orig NDA 20-677
HFD-340
HFD-520
HFD-520/MO/NMoledina
HFD-520/Pharm/AEllis
HFD-520/Micro/PDionne
HFD-520/Chem/VShetty
HFD-520/PMS/FLeSane
nm/11-13-96

concurrence only:

HFD-520/Acting DivDir/DFeigal
HFD-520/TL/MSAlbueme

MDA 11/13/96

DJH 12-16-96

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-677 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF _____ Trade and generic names/dosage form: Zagam (sparfloxacin) 200mg Tablets Action: AP AE NA
Applicant Rhone-Poulenc Rorer Therapeutic Class IS

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate inadequate

Indication in this application Note approval letter (For supplement answer the following questions in relation to the proposed indication.)

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary. ←

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[Signature]
Project Manager
Signature of Preparer and Title

11-14-96
Date

cc: Orig NDA/PLA/PMA # 20-677
HFD 520 /Div File
NDA/PLA Action Package
HFD-006/ SOLmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

Pediatric use: Safety and effectiveness have not been established in patients below the age of 18 years. Quinolones, including sparfloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See WARNINGS.) ←



RHÔNE-POULENC RORER PHARMACEUTICALS INC.
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P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

New Drug Application:#20-677
Form FDA 356h
Item 13

Zagam® (sparfloxacin)

Items 13: Patent Information

The Item 13 Patent Information for the ZAGAM ® (sparfloxacin) New Drug Application is found on the following page.

Item 13. Patent Information

1)	Patent number	4,795,751
2)	Date of expiration	October 28, 2006
3)	Type of patent	Drug, Drug Product and Method of Use (treating of bacterial infectious disease)
4)	Name of patent owner	Dainippon Pharmaceutical Co., Ltd.
5)	U.S. representative	Rhône-Poulenc Rorer Pharmaceuticals Inc.

The undersigned declares that Patent No. 4,795,751 covers the compound, formulation, and method of use for treating bacterial infectious disease. This product is the subject of this application for which approval is being sought.

By: 

Name: Ross J. Oehler

Title: Patent & Trademark Counsel



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**New Drug Application:#20-677
Form FDA 356h
Item 14**

Zagam® (sparfloxacin)

Item 14: Patent Certification

This application does not contain Patent Certification information.

Clin. Pharm

+

Bio

NDA 20,677

DATES of SUBMISSION

December 27, 1995

February 15, 1996

July 29, 1996

August 15, 1996

**CLINICAL PHARMACOLOGY
BIOPHARMACEUTICS REVIEW****Sparfloxacin, 200mg Tablet (ZAGAM)**

Original NDA, 1S, NME

SPONSOR: Rhone-Poulenc Rorer
500 Arcola Road,
P.O.Box 1200,
Collegeville, PA 19426-0107

REVIEWER: He Sun, Ph.D.

I. RECOMMENDATION

The Biopharmaceutics and Pharmacokinetics section of NDA 20, 677 is acceptable to meet the requirement of CFR S320. From a Biopharmaceutics standpoint, all pivotal studies are acceptable, bioequivalence between modified dosage form and clinical trial formulation was established, and the application is approvable provided the information requested in Comments is addressed. The applicant should be informed of comment #16 (page 44) and **COMMENTS ON LABELING** (page 45).

II. SYNOPSIS

The sponsor submitted the original NDA for Zagam (Sparfloxacin) for the treatment of community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis,

Forty-five clinical pharmacology studies conducted in the U.S., Europe and Japan, one population PK study, and dissolution testing results were submitted. Number and type of studies and study findings are summarized at the following:

# of Studies	Description	Results
6	BA and BE.	F=90%. The drug is highly bioavailable. To be marketed formulation BE to clinical trial formulation.
1	Dose proportional study,	Linear kinetics observed in mg range.
2	Food effect studies.	The AUC was unchanged, but lag time was observed after high fat breakfast.
2	Al and Mg affect drug absorption.	Sparfloxacin absorption was unaffected if Ma or Al was given 4 hours after the administration of sparfloxacin.
8	Tissue distribution studies.	Widely distributed into many body fluids and tissues. Tissue concentration equals or greater than plasma concentration.
2	Metabolism studies.	The drug is metabolized by phase II conjugation.
4	Multiple dose PK studies.	Steady-state generally achieved by third or fourth daily dose. Steady-state is predictable from a single dose observation.

5	PK studies in elderly subjects.	PK characteristics consistent with young adults.
1	Gender study	No difference in PK between genders.
6	Drug interaction studies.	Sparfloxacin has demonstrated a lack of interaction with selected model compounds.
6	Pharmacodynamic studies.	Sparfloxacin does not affect the PD of selected drugs.
1	Population PK study.	Covariables such as age, gender, race, body weight, body height, CL _{cr} , Scr were tested. CL correlated with CL _{cr} and V _d correlated with body weight

BRIEF DESCRIPTION OF THESE STUDIES:

The absolute oral bioavailability of sparfloxacin is nearly complete (F=90%) with T_{max} at approximately 4 hours (RP64206-161). The market image formulation is bioequivalent to clinical formulation (RP64206-160, RP64206-164, and CI 978-15, CI 978-18, and CI 978-19) and shows that maximum plasma sparfloxacin concentration following administration of a single 200 mg oral dose reached 0.6 µg/ml and ranged from µg/ml. Mean AUC_{0-∞} values increased linearly with increasing doses up to 1200 mg, and mean C_{max} values increased less than proportionally with increasing doses throughout the dose range (RP64206-162). The extent of oral sparfloxacin absorption was not altered when administered in combination with a standard continental breakfast (AT 107), or a high fat breakfast, or milk (RP64206-157). However, a delay in the onset of absorption was observed when sparfloxacin was administered with a high fat breakfast. The oral absorption of sparfloxacin was decreased when sparfloxacin was administered 2 hours before and 2 hours after administration of a representative calcium and magnesium containing antacid (Maalox) (RP64206-154 and AT 117). The oral absorption of sparfloxacin was not altered when sparfloxacin was administered 4 hours prior to Maalox administration.

The distribution studies indicate, that upon reaching the general circulatory system, sparfloxacin distributes widely into many body fluids and tissues especially tissues of the respiratory system. The protein binding in serum was 42 to 44% over a µg/ml concentration range and 46% in plasma at 0.37 µg/ml. Sparfloxacin concentrations in blister fluid, saliva, sweat, and tears were similar to that in plasma (AT 120 and 124). The sparfloxacin concentration in nasal secretions, vaginal secretions, ejaculate fluid, and prostatic fluid were at least 1.5 times greater than that in plasma. In the (ear, nose, and throat) ENT sphere, bronchial mucosa, epithelial lining, alveolar macrophage, and pulmonary tissues were at least 2 times greater than that in plasma (AT 127, 123, and 128). Intravitreal, aqueous humor, and pleural effusion sparfloxacin concentrations were less than that in plasma (AT 135, 136, and 133). Based on results from the absolute oral bioavailability study (RP64206-161), sparfloxacin appears to have a large volume of distribution with a mean steady-state volume of distribution (V_{dss}) of 198.5 L (3.6 L/kg). The large V_{dss} value is consistent with the ability of sparfloxacin to distribute readily into body tissues.

Metabolite isolation and identification have shown that in man, sparfloxacin is primarily metabolized by Phase II conjugation to form an acylglucuronide. Approximately 50% of the total radioactive dose was recovered in the urine and 48% was recovered in the feces (AT 122). Of the radioactivity recovered in the urine, approximately 35% was identified as unchanged sparfloxacin and 42% was identified as sparfloxacin glucuronide. In a single dose study in patients with biliary tract drainage using non radio-labeled material (AT 111/139), the mean recoveries in urine and bile were 8.8% and 1.5% of the administered dose for sparfloxacin and 39.4% and 11.5% for sparfloxacin glucuronide,

respectively. Mean renal and biliary clearance of sparfloxacin, which represented 10% and 2% of the total apparent oral clearance, were 0.8 and 0.17 L/hr, respectively.

Terminal elimination half-life, $t_{1/2}$, of sparfloxacin in normal healthy subjects ranges between 16 and 30 hours with a mean $t_{1/2}$ value of approximately 20 hours. The $t_{1/2}$ values were generally independent of the administered dose. The apparent oral clearance was relatively slow ranging from - L/hr. The terminal elimination rate of sparfloxacin glucuronide appears to parallel that of sparfloxacin. Several studies (AT 119, CI 978-1, RP64206-153, and AT 102) show that steady-state plasma sparfloxacin concentrations were generally achieved by the third or fourth daily dose, and are generally predictable from single dose data.

Both the single and multiple dose pharmacokinetics of sparfloxacin in the elderly were consistent with that in young subjects. The pharmacokinetics of sparfloxacin were also not altered in subjects with chronic hepatic impairment (AT 103, 116, 110, 108, 104, and RP64206-159). The elimination of sparfloxacin decreased in subjects with moderate ($10 < \text{CLcr} < 29$ ml/min), and severe ($2 < \text{CLcr} < 10$ ml/min) renal impairment following single dose administration. The elimination of sparfloxacin decreased slightly in subjects with mild ($30 < \text{CLcr} < 49$ ml/min) and moderate renal impairment following multiple dose administration.

Any differences in pharmacokinetics between male and female subjects were explained by differences in body weight (RP64206-162), therefore, there is no gender difference of the drug.

It was demonstrated that sparfloxacin does not alter the pharmacokinetics of theophylline (AT 105 and RP64206-156) and digoxin (AT 114 and RP64206-155) and that probenecid and cimetidine (AT 115) do not alter the pharmacokinetics of sparfloxacin. Results of pharmacodynamic studies show that sparfloxacin does not alter the pharmacodynamics of warfarin (AT 113) and terfenadine (RP64206-151). In addition, pharmacokinetic analysis based upon limited plasma samples obtained from the terfenadine interaction study suggest that sparfloxacin does not alter the pharmacokinetics of terfenadine and its acid metabolite, carboxyterfenadine. Therefore, sparfloxacin has demonstrated a lack of interaction with selected model compounds.

A population pharmacokinetic analysis was conducted using plasma samples from 143 patients enrolled in Phase III clinical trials (RP64206-301, -352, -353, -355, -356, -358, and -359). The mixed effect model evaluated the effect of the covariates age, gender, race, body weight, body height, creatinine clearance, serum creatinine, bilirubin, and other liver function tests on the apparent volume of distribution (V) and apparent oral clearance (CL) assuming an open one compartment pharmacokinetic model. Creatinine clearance (CLcr) was the only significant covariate that remained in the final model for CL and was:

$$\begin{aligned} \text{CL (L/hr)} &= 0.206 * \text{Clcr} && \text{(when CLcr} < 80 \text{ ml / min)} \\ \text{CL (L/hr)} &= 16.6 && \text{(when CLcr} \geq 80 \text{ ml / min)} \end{aligned}$$

Total body weight (TBW) was the only significant covariate that remained in the model for V and was:

$$V \text{ (L)} = 120 + 2.48 * \text{TBW} \text{ (Where TBW in unit of Kg)}$$

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III. BACKGROUND

Sparfloxacin is a synthetic, broad spectrum, fluoroquinolone anti-infective agent for oral administration. Sparfloxacin is an amino-difluoroquinolone with the chemical name 5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difloro-1,4-dihydro-4-oxo-3quinolinecarboxylic acid. The laboratory codes for Sparfloxacin are AT-4140, CI-978, PD 131501 and RP 64206. Sparfloxacin has a molecular formula of $C_{19}H_{22}F_2N_4O_3$, its molecular weight is 392.41. The dissociation constants are: $pK_{a1} = 6.33$ and $pK_{a2} = 8.94$. The partition coefficient is: $\log P = -0.11$ n-octanol/ H_2O , $25^\circ C$, at $pH = 6.80$.

Sparfloxacin was selected for development due to its superior activity against bacteria found commonly in community acquired respiratory tract infections. Stability studies for 3 lots of Sparfloxacin show an acceptable stability profile for the drug substance for up to 24 months when packaged in a double polyethylene bags in a fiber drum and stored at room temperature.

IV. DRUG FORMULATION

The drug substance, sparfloxacin, is manufactured by

The to be marketed dosage form, Zagam, is an immediate release, round, white film-coated tablet imprinted with the letters "RPR" and number "201". It contains the following components:

Ingredient	% W/W	mg
<u>Tablet Core</u>		
Sparfloxacin		
✓ Microcrystalline Cellulose		
✓ Corn (Maize) Starch		
✓ L-Hydroxypropylcellulose		
✓ Magnesium Stearate		
✓ Colloidal Anhydrous Silica		
<u>Coating Suspension</u>		
✓ Methylhydroxypropylcellulose		
✓ Polyethylene Glycol 6000		
✓ Titanium Dioxide		

1. MANUFACTURER:

Rhone-Poulenc Rorer Pharmaceuticals Limited NENAGH
Lisbunny industrial Estate
Nenagh, Co. Tipperary
Republic of Ireland

The commercial method of manufacture is a standard dry compaction granulation, compression into tablet cores and coating with aqueous suspension.

2. STABILITY:

Zagam tablets are stable for at least 24 months when packaged either in vinyl blisters with a foil backing or in HDPE bottles with a polypropylene screw cap.

3. INVESTIGATIONAL FORMULATIONS

The development of Sparfloxacin 200 mg tablets was initiated by

States, clinical and market image formulation development was begun by in August 1989. Later, had entered a joint venture with Rhone-Poulenc S.A. to develop Sparfloxacin in Europe. In the merger between Rhone-Poulenc and Rorer, the joint venture became a part of RPR. By the time handed the development of the market image formulation to RPR-US, the European joint venture (Rhone had completed the development of their product. A decision was made within RPR to use one worldwide market image and product globally. A bioequivalence trial was undertaken, and the Rhone formula was found to be bio-inequivalent to the product.

A table listing the clinical trial number, drug product lot number and dosage form and strength is provided below. The formulations used in clinical trials are provided in Appendix I in more detail.

Table of Drug Formulations

Clinical Study Number	Drug Product Lot Number	Dosage Form and Strength
301	9111357 (CB05136)	100 mg tablets
	9208221 (CM0980692)	200 mg tablets
352	9111357 (CB05136)	100 mg tablets
	9208221 (CM0980692)	200 mg tablets
	9308817 (CM0030193)	200 mg tablets
353	9111357 (CB05136)	100 mg tablets
	9204834 (ZFTA0240A)	100 mg tablets
	9208221 (CM0980692)	200 mg tablets
356	9208221 (CM0980692)	200 mg tablets
	9212494 (CM0560392)	200 mg tablets
358	9308817 (CM0030193)*	200 mg tablets
359	9208221 (CM0980692)	200 mg tablets
363	9308817 (CM0030193)	200 mg tablets
151	9204834 (ZFTA0240A)	100 mg tablets
153	9204834 (ZFTA0240A)	100 mg tablets
155	9208221 (CM0980692)	200 mg tablets
156	9208221 (CM0980692)	200 mg tablet
157	9411419(8151)	Nenagh 200 mg tablets
159	9212494 (CM0560392)	200 mg tablets
160	9408311 (CM0030193)	200 mg tablets
	9403094(6534)	Nenagh 200 mg tablets
	9308817(CM0030193)	Nenagh 200 mg tablets
161	9411419(8151)	Nenagh 200 mg tablets
	64206/08-1A-1	Sparfloxacin iv 250 mg/5 ml
162	9408311 (CM0030193)	200 mg tablets
163	9408311 (CM0030193)	200 mg tablets
164	9408311 CM0030193	200 mg tablets

* Tablets in capsules for blinding purpose

V. HUMAN PHARMACOKINETIC STUDY SUMMARY

1. ORAL ABSORPTION

Study #RP64206-161.

µg/ml The absolute oral bioavailability of sparfloxacin was assessed in a randomized 2-way crossover study in 12 healthy male volunteers between 21 and 36 years of age. Sparfloxacin was administered under fasting conditions as a 200 mg (1x200 mg tablet) single oral dose as the market image formulation or as a 4-hour intravenous infusion (50 mg/hr x 4 hr). Using AUC values, the mean (CV%) absolute oral bioavailability was 90%(12%). Based on the results of this study, the oral absorption of sparfloxacin is nearly complete, but relatively slow ($T_{max} = 4.2$ hours).

Pharmacokinetic parameters are summarized below:

Administration Dosage Form	Dose (mg)	C _{max} (µg/ml)	T _{max} (hr)	Vd/f (L)	AUC _{inf} (µg/ml/hr)	T1/2 (hr)	Ae (%Dose)	CL _{p/f} (L/hr)	CL _r (L/hr)	Comments
IV (single dose)	200(n=12)	0.90(19)	4.1(3.3)	286(24)	19.3(34)	22.1	N/A	11.4(31)	N/A	
PO (single dose)	200(n=12)	0.67(27)	4.2(55)		17.3(31)	20.1	N/A		N/A	F=0.90

IV dose: 250mg/5ml, 64206/08-LA-1
PO dose: 200mg, 9411419

Studies # RP64206-164, RP64206-160, CI-978-19, CI-978-18, CI-978-15

Bioequivalency studies that have been conducted to establish a market image formulation have provided considerable information about the typical plasma sparfloxacin concentration-time profile following administration of single 200 mg (1x200 mg tablet) oral doses. These studies were conducted under fasting conditions in 24 healthy male volunteers between 18 and 45 years of age using repeated measures (#RP64206-160, CI-978-19, CI-978-18) or crossover designs (RP64206-164, CI-978-15). Maximum plasma sparfloxacin concentrations (C_{max}) generally reached 0.6 µg/ml and ranged from _____ µg/ml following administration of a single 200 mg oral dose. These C_{max} values are generally comparable to the MIC values for most of the relevant pathogens. AUC_{0-t} values were approximately 17.0 µg*hr/ml and ranged from _____ µg*hr/ml. The time to reach maximum plasma concentrations was highly variable, with T_{max} values ranging from _____ hours. The results of these bioequivalence studies, specifically RP64206-164, established a market image formulation that was bioequivalent to the formulation used in pivotal clinical safety and efficacy studies. The following table is a summary of these biopharmaceutic studies discussed.

Study Number		Dose(Sub.)	C _{max} (µg/ml)	T _{max} (hr)	Vd/f (L)	AUC _{inf} (µg/ml/hr)	TL/2 (hr)	A _e (%Dose)	CL _{p/f} (L/hr)	CL _r (L/hr)	Batch No.
RP164	PO (s.d) ¹	200 (n=22)	0.59 (32)	5.0 (31)	N/A	16.7(29)	21.1	N/A	N/A	N/A	9308817
	PO (s.d)	200 (n=22)	0.64 (32)	3.9 (48)	N/A	17.0 (21)	20.2	N/A	N/A	N/A	9403094
	PO (s.d)	200 (n=22)	0.61 (38)	4.7 (64)	N/A	16.7 (27)	20.9	N/A	N/A	N/A	9411419
RP160	PO (s.d)	200 (n=34)	0.58 (26)	5.0 (35)	N/A	16.9 (16)	19.1	N/A	N/A	N/A	9308817
	PO (s.d)	200 (n=35)	0.63 (21)	4.9 (82)	N/A	18.6 (21)	19.1	N/A	N/A	N/A	9403094
CI-978-19 ²	PO (s.d)	200 (n=36)	0.60 (30)	4.5 (53)	N/A	16.2 (26)	17.8	N/A	N/A	N/A	cm0560392
	PO (s.d)	200 (n=36)	0.66 (23)	4.1 (90)	N/A	17.5 (18)	18.3	N/A	N/A	N/A	cm189111
CI-978-18	PO (s.d)	200 (n=35)	0.61 (25)	3.8 (32)	N/A	16.4 (23)	19.0	N/A	N/A	N/A	cm0550392
	PO (s.d)	200 (n=36)	0.69 (24)	3.8 (50)	N/A	18.6 (20)	19.1	N/A	N/A	N/A	cm189111
CI-978-15	PO (s.d)	400 (n=18)	1.27 (47)	5.7 (37)	N/A	37.0 (37)	19.2	N/A	N/A	N/A	cm189111
	PO (s.d)	400 (n=18)	1.11 (48)	6.5(100)	N/A	32.8(39)	19.7	N/A	N/A	N/A	cm323109
	PO (s.d)	400 (n=18)	1.21 (42)	4.5 (44)	N/A	36.1(32)	19.0	N/A	N/A	N/A	cm324109

1. (s.d) = Single Dose, (m.d) = Multiple dose

2. CI-978-19, CI-978-18 and CI-978-15 used different formulations.

2. DOSE PROPORTIONAL STUDIES.

Studies RP64206-162, AT-121, AT-101

The dose proportional behavior of sparfloxacin absorption was assessed at single oral doses up to 1600 mg as part of an ascending-dose safety, tolerance, and electrocardiographic pharmacodynamic study (RP64206-162). Single 400, 800, 1200, and 1600 mg oral doses (2-8 x 200 mg tablets) were administered under fasting conditions to 23 healthy male and female volunteers in a double-blind, randomized, ascending-dose, crossover design. Mean AUC_{inf} values generally increased in a linear fashion with increasing doses up to 1200 mg, which exceeds the expected recommended doses (Figure 1). Less-than-proportional increases in AUC_{inf} values appear to begin at about 1200 mg single doses. Mean AUC_{inf} values were 32.2, 65.9, 94.0, and 116.2 µg*hr/ml following administration of single oral 400, 800, 1200, and 1600 doses, respectively. Mean C_{max} values increased in a less-than-proportional manner with dose (Figure 2). This deviation from linearity for C_{max} was considerably more pronounced than that observed for AUC_{inf} and occurred throughout the dose range. Mean C_{max} values were 1.41, 2.39, 3.16, and 3.64 µg/ml at single oral doses of 400, 800, 1200, and 1600 mg, respectively. Additionally, T_{max} values appeared to increase with increasing dose. Mean T_{max} values were 3.4, 5.4, 5.2, and 7.5 hours following single oral 400, 800, 1200, and 1600 mg doses, respectively. Hence, it appears that sparfloxacin exhibited some rate-limited oral absorption at high doses that did not generally affect the extent of absorption. Similar results were observed in a dose-linearity study (AT 121) conducted in 12 healthy male volunteers where sparfloxacin was administered in a randomized crossover fashion as single oral 200, 400, 600, and 800 mg doses. Less than dose-proportional increases in mean AUC_{inf} and C_{max} values were also observed in an initial ascending dose tolerance study (AT 101) conducted in parallel groups of 5 healthy male volunteers using single oral 100, 200, 300, 400, 600, and 800 mg sparfloxacin doses.

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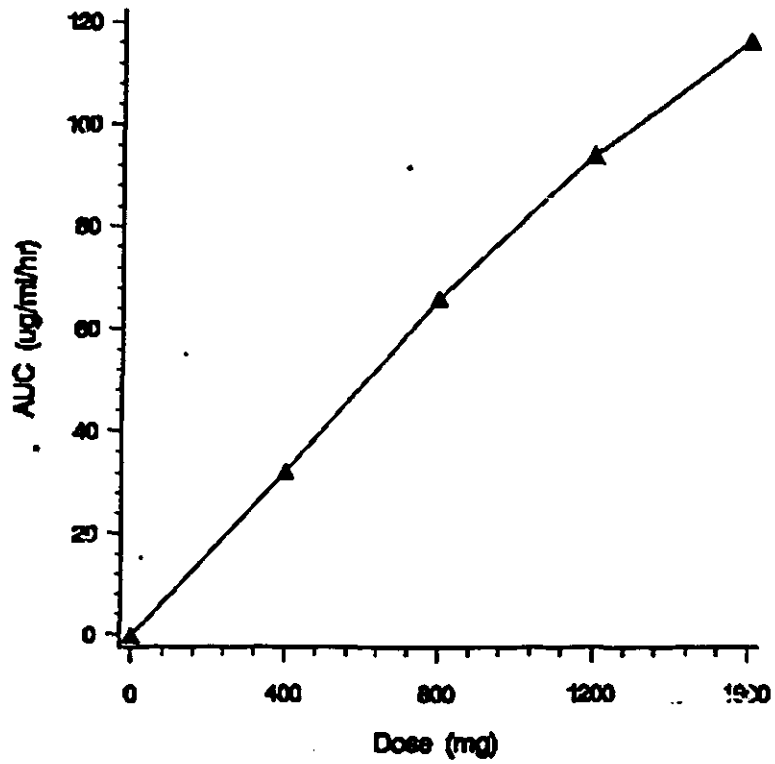


Figure 1: Mean ~~C_{max}~~^{AUC} values as a function of the oral sparfloracin dose (N=23/dose).

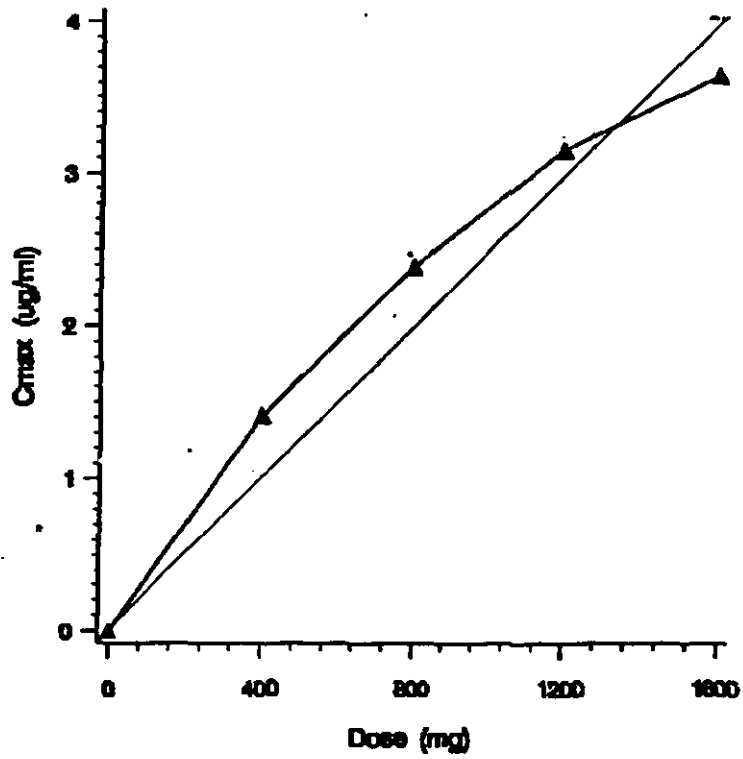


Figure 2: Mean C_{max} values as a function of the oral sparfloxacin dose (N=23/dose).

Pharmacokinetic parameters are summarized below:

Study Number	Dose (Sub.)	C _{max} (µg/ml)	T _{max} (hr)	V _d /f (L)	AUC _{inf} (µg/ml/hr)	T _{1/2} (hr)	A _s (%Dose)	CL _{p/f} (L/hr)	CL _r (L/hr)	Conjugated (%Dose)
RP162 Crossover	PO (s.d) 400 (n=23)	1.41 (34)	3.4 (42)	N/A	32.2 (29)	16.0	N/A	N/A	N/A	
	800 (n=23)	2.39 (27)	5.4 (38)	N/A	65.9 (30)	16.8	N/A	N/A	N/A	
	1200 (n=22)	3.16 (38)	5.2 (54)	N/A	94.0 (31)	18.4	N/A	N/A	N/A	
	1600 (n=21)	3.64 (41)	7.5 (127)	N/A	116 (33)	18.8	N/A	N/A	N/A	
AT121 Crossover	PO (s.d) 200 (n=12)	0.71 (23)	3.6 (32)	N/A	18.7 (9.5)	20.8	10.2 (24)	11.0 (21)	1.12 (17)	22.4 (20)
	400 (n=12)	1.18 (24)	4.5 (31)	N/A	32.7 (18)	18.2	9.30 (22)	12.8 (13)	1.20 (13)	21.3 (20)
	600 (n=12)	1.65 (35)	4.4 (39)	N/A	45.8 (22)	20.4	8.80 (24)	13.7 (25)	1.19 (12)	18.3 (23)
	800 (n=12)	1.97 (32)	4.3 (27)	N/A	57.5 (25)	20.0	14.8 (28)	14.8 (27)	1.21 (18)	16.9 (33)
AT101 Parallel	PO (s.d) 100 (n=5)	0.22 (15)	4.8 (56)	N/A	5.71 (4.8)	19.2	10.1 (33)	N/A	N/A	25.5 (43)
	200 (n=5)	0.40 (42)	5.6 (16)	N/A	10.5 (32)	17.8	14.7 (31)	N/A	N/A	36.8 (14)
	300 (n=5)	1.14 (16)	7.2 (15)	N/A	31.5 (12)	16.1	9.20 (26)	N/A	N/A	26.1 (23)
	400 (n=5)	1.36 (43)	5.8 (58)	N/A	30.5 (23)	15.1	10.9 (36)	N/A	N/A	26.8 (37)
	600 (n=8)	1.06 (21)	6.0 (18)	N/A	31.3 (38)	19.5	9.20 (15)	N/A	N/A	23.2 (12)
	800 (n=5)	1.44 (18)	5.6 (39)	N/A	41.8 (19)	18.9	10.6 (81)	N.R	N/A	26.1 (27)

3. FOOD EFFECT STUDIES

A. Studies RP64206-157, AT 107

The effect of a high fat breakfast or milk on the oral absorption of sparfloxacin was evaluated in a randomized 3-way crossover study (RP64206-157) in 24 healthy male volunteers between 19 and 41 years of age. Sparfloxacin was given as single oral 200 mg doses using the market image tablet formulation intended for the U.S. market. A plot of mean plasma sparfloxacin concentration-time profiles is presented in Figure 3. The extent of absorption of sparfloxacin was not affected by concomitant administration with a high fat breakfast or milk. Mean AUC_{inf} values were 18.5, 17.7, and 19.2 µg*hr/ml following administration of a single oral 200 mg dose after an overnight fast, with a high fat breakfast, and with milk, respectively. Corresponding mean C_{max} values were 0.69, 0.70, and 0.76 µg/ml, respectively. Absorption was delayed somewhat following administration with the high fat meal as evidenced by the slight increase in T_{max} values. Mean T_{max} values were 3.6, 3.8, and 5.4 hours after an overnight fast, with a high fat breakfast, and with milk, respectively. This later T_{max} value appeared to be associated with a delay in the onset of absorption (lag time) rather than a decreased rate of absorption. These results are generally consistent with an earlier study (AT 107) conducted in 10 healthy male volunteers that showed that the oral absorption of single 400 mg doses of sparfloxacin was not affected when administered with food (standard European breakfast).

Pharmacokinetic parameters from study RP64206-157 are listed below:

Study Number	Dose (Sub.)	C _{max} (µg/ml)	90%CI*	T _{max} (hr)	AUC _{inf} (µg/ml/hr)	90%CI*	T _{1/2} (hr)	Comments and Batch No. (hr)
RP 157	PO (s.d) 200 (n=24)	0.69 (24)	—	3.6 (60)	18.5 (24)	—	19.8	Overnight fast #9414419
	PO (s.d) 200 (n=24)	0.70 (17)	(93.9-114.5)	3.8 (29)	17.7 (17)	(90.3-106.4)	18.8	8 oz of Skim Milk
	PO (s.d) 200 (n=24)	0.76 (19)	(100.7-122.8)	5.4 (48)	19.2 (23)	(95.7-112.7)	20.3	High Fat Breakfast excluding milk

* Compared to treatment A—overnight fast condition on log transform: $\times 2$ data.

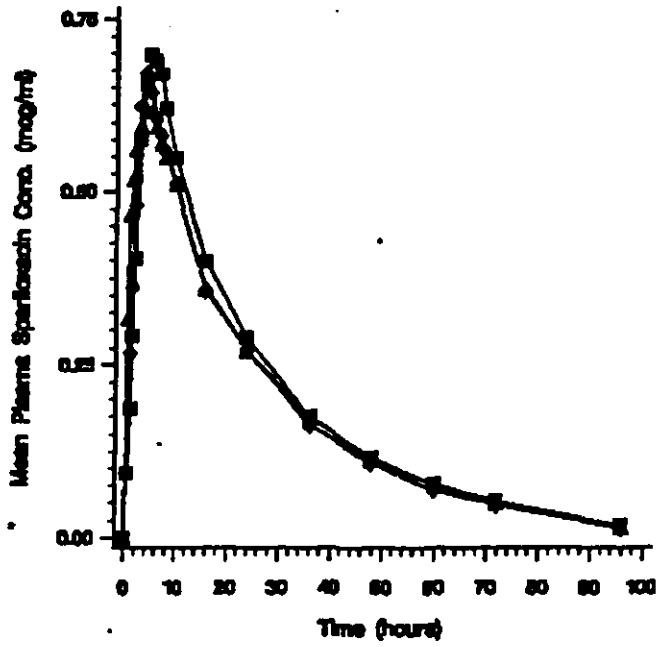


Figure 3: Mean (N=24) plasma sparfloxacin concentrations following a single 200 mg oral sparfloxacin dose after an overnight fast (◆), with skim milk (▲), and with a standard high fat breakfast excluding milk (■).

Pharmacokinetic parameters from study AT 107 are listed below:

Study Number	Dose (Sub.)	C _{max} (µg/ml)	T _{max} (hr)	V _d /f (L)	AUC _{inf} (µg/ml/hr)	T _{1/2} (hr)	A _e (%Dose)	CL _p /f (L/hr)	CL _r (L/hr)	Comments and Batch No.
AT 107	PO(s.d) 400 (n=10)	1.48 (24)	4.7 (43)	N/A	41.6(27)	19.6	8.9(34)	9.62(25)	0.86(30)	#CB 3976
	PO (s.d) 400 (n=10)	1.46 (23)	3.1 (52)	N/A	40.8(33)	20.9	9.1(27)	10.2(32)	0.93(26)	With Continental Breakfast

4. Mg and Al EFFECT.

Studies #RP64206-154, and AT 117

The oral absorption of sparfloxacin appears to be decreased when administered in combination with magnesium and aluminum containing antacids. The effect of staggered dosing of Maalox on the oral absorption of sparfloxacin was assessed in a randomized, 4-way crossover study (RP64206-154) in 20 healthy male volunteers between 18 and 38 years of age. Sparfloxacin was administered as a single 400 mg (2x200 mg tablets) oral dose without Maalox, 2 hours before Maalox, 2 hours after Maalox, and 4 hours before Maalox. Maalox was given as a single 30 ml liquid oral dose. The mean plasma sparfloxacin concentration-time profiles are presented in Figure 4. Mean AUC_{inf} values were 33.5(19), 25.8(38), 27.7(26), and 31.7(23) µg*hr/ml following single 400 mg dose of sparfloxacin alone. Maalox two hours before sparfloxacin, Maalox at > 2 hours after sparfloxacin, and Maalox at 4 hours after sparfloxacin, respectively. Administration of Maalox 2 hours before and 2 hours after sparfloxacin caused a mean decrease of 23% and 17% for AUC_{inf} and 29% and 13% for C_{max}, respectively. However, the oral absorption of sparfloxacin was not decreased by Maalox when given 4 hours after drug administration (Figure 4). A reduction in oral sparfloxacin absorption was also observed in an earlier study (AT 117) conducted in 10 healthy volunteers who received 2 Maalox tablets at thirty minutes prior to single 400 mg oral doses.

Study Number	Dose (Sub.)	C _{max} (µg/ml)	T _{max} (hr)	V _d /f (L)	AUC _{inf} (µg/ml/hr)	T _{1/2} (hr)	A _e (%D)	CL _p /f (l/hr)	CL _r (l/hr)	Comments	Batch No.
RP-154	PO (s.d)400 (n=20)	1.09 (19)	4.4 (46)	N/A	33.5 (19)	20.40	N/A	N/A	N/A	Used Maalox	920821
	400 (n=20) ¹	0.77 (37)	5.4 (51)	N/A	25.8 (38)	22.44	N/A	N/A	N/A	Liquid, total of	
	400 (n=20) ²	0.95 (28)	3.8 (45)	N/A	27.7 (26)	21.75	N/A	N/A	N/A	30 ml.	
	400 (n=20) ³	1.17(30)	3.9 (46)	N/A	31.7 (23)	21.76	N/A	N/A	N/A		
AT- 117	PO(s.d) 400(n=10)	1.41 (36)	3.6(40)	N/A	39.9(40)	20.60	10.0(47)	N/A	0.98(22)	Used 2 Maalox	CB3976
	400(n=10) ⁴	0.74 (78)	5.1(56)	N/A	22.2(71)	20.97	6.3(78)	N/A	1.10(38)	Tablets.	

1. Administration of Maalox at two hours before sparfloxacin
2. Administration of Maalox at two hours after sparfloxacin
3. Administration of Maalox at four hours after sparfloxacin
4. Administration of Maalox at 30 minutes before sparfloxacin, different formulation.

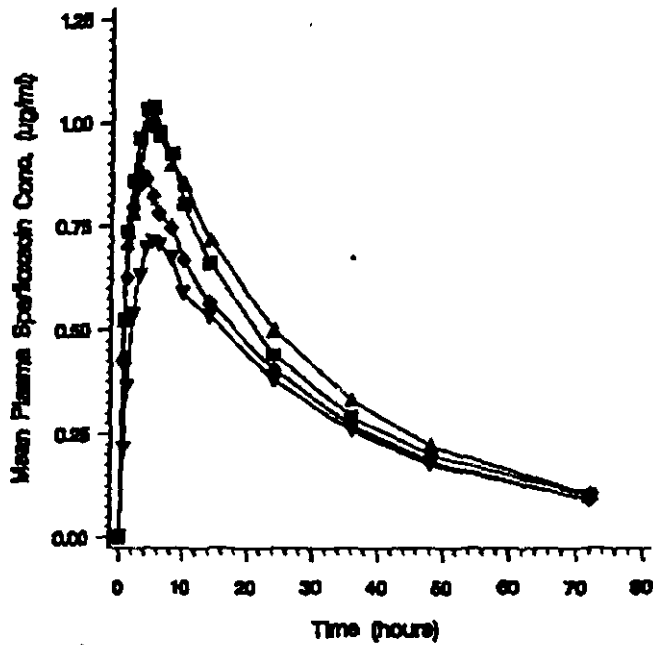


Figure 4: Mean (N=20) plasma sparfloxacin concentrations following administration of sparfloxacin alone (▲), Maalox at two hours prior to sparfloxacin administration (▼), Maalox at two hours after sparfloxacin administration (◆), and Maalox® at four hours after sparfloxacin administration (■).

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5. DISTRIBUTION

Study #RP64206-161

Several studies indicate that upon reaching the general circulation, sparfloxacin is capable of widely distributing into many body tissues and fluids. Based on results of a previously described study (RP64206-161, see section 1. ORAL ABSORPTION) which included an intravenous infusion, sparfloxacin appears to have a large volume of distribution with a mean steady-state volume of distribution (V_{dss}) of 198.5(27%) L (3.6 L/kg). Sparfloxacin also exhibits low plasma protein binding. Using equilibrium dialysis, the protein binding in serum was 42 to 44% over a 0.087 to 1.90 $\mu\text{g/ml}$ concentration range and 46% in plasma at 0.37 $\mu\text{g/ml}$.

6. TISSUE PENETRATION

Studies #AT 120, AT 124, AT 127, AT 123, AT 128, AT 133, AT 135, AT 136

The ability of sparfloxacin to penetrate into inflammatory fluid was evaluated in 6 healthy male volunteers between 18 and 45 years of age who received single 400 mg (2x200 mg tablets) oral doses of sparfloxacin (AT 120). Inflammatory fluid produced in blisters induced by cantharides-impregnated plasters was collected at the same time as plasma samples for up to 52 hours after drug administration. The mean C_{max} value for blister fluid was similar (1.3 $\mu\text{g/ml}$) to the value for plasma (1.6 $\mu\text{g/ml}$). The mean (CV%) blister fluid to plasma ratio for $AUC_{0-\infty}$ value was 1.2 ($\pm 18\%$) also showing similar extent of exposure. Blister fluid concentrations reached a maximum (T_{max}) at approximately two hours later than the corresponding plasma concentrations. The mean $t_{1/2}$ value for sparfloxacin in blister fluid was also similar to the mean value in plasma. The results of this study illustrated that sparfloxacin readily distributes into and out of inflammatory fluid. The ability of sparfloxacin to distribute into various body fluids such as saliva, sweat, tears, nasal secretions, vaginal secretions, prostatic fluid, and ejaculate was assessed in 12 healthy male or female volunteers who received single 400 mg (2x200 mg tablets) oral doses of sparfloxacin (AT 124). Mean body fluid to plasma concentration ratios were close to unity for saliva, tears, and sweat. Mean (CV%) body fluid to plasma ratios were 0.77($\pm 31\%$), 0.80($\pm 36\%$), and 0.79($\pm 25\%$) for $AUC_{0-\infty}$ and 0.97($\pm 24\%$), 0.98($\pm 95\%$) and 0.67($\pm 13\%$) for C_{max} in saliva, sweat, and tears, respectively. Maximum body fluid concentrations of these three fluids generally occurred later than those values observed in plasma. Corresponding mean (CV%) ratios of T_{max} values were 1.6 ($\pm 143\%$), 1.2 ($\pm 81\%$), and 3.2 ($\pm 83\%$) hours for saliva, sweat, and tears, respectively. Body fluid to plasma concentration ratios were higher than that in plasma for nasal secretions, vaginal secretions, ejaculate, and prostatic fluid. Mean (CV%) body fluid to plasma ratios were 3.7 ($\pm 51\%$) and 13.1 ($\pm 35\%$) for $AUC_{0-\infty}$ and 4.4 ($\pm 23\%$) and 5.1 ($\pm 19\%$) for C_{max} in nasal and vaginal secretions, respectively. Mean body fluid to plasma concentration ratios were 1.5 ($\pm 25\%$) and 1.7 ($\pm 36\%$) $\mu\text{g/ml}$ at 4 and 12 hours post dose for ejaculate and 2.0 ($\pm 40\%$) $\mu\text{g/ml}$ at 4 hours post dose for prostatic fluid. T_{max} values were also longer for nasal and vaginal secretions than in plasma with mean (CV%) T_{max} ratios of 4.5 ($\pm 123\%$) and 26 ($\pm 117\%$), respectively. It was concluded that sparfloxacin penetrates well into relevant body fluids as reflected by sparfloxacin concentrations in body fluids that were equal to or greater than corresponding plasma concentrations.

A study (AT 127) to assess the penetration of sparfloxacin into the ear, nose, and throat (ENT) sphere following single oral 200 (N=4) or 400 (N=31) mg doses was conducted in 35 adult male or female patients that underwent surgery for ENT sphere tumors (N=24) or chronic maxillary sinusitis (N=11). Sparfloxacin concentrations in (ENT) and in respiratory tract tissues generally exceeded corresponding plasma concentrations. Mean (CV%) tissue to plasma sparfloxacin concentration ratios for the ENT system taken at 2 to 6.75 hours after drug administration are listed below:

Mean (CV%) ENT sphere tissue concentration ($\mu\text{g/g}$) to plasma concentration ($\mu\text{g/ml}$) ratios

Tissue	Mean Ratio	N
sinus mucosa	9.0 (42.6%)	8
salivary glands	8.9 (83.4%)	5
skin	5.5 (44.0%)	9
oropharyngeal mucosa	5.4 (61.2%)	9
thyroid	5.1 (55.6%)	11
tonsils	4.8 (34.8%)	9
muscle	3.9 (36.4%)	10
lymph nodes	2.9 (87.3%)	4
cartilage	2.9 (30.0%)	17
adipose tissue	0.7 (78.1%)	14

Consistent with the previously described studies, it was concluded that sparfloxacin penetrates well into relevant body tissues after single oral administration as reflected by ENT sphere tissue concentrations that generally exceeded the MIC_{90} for most of the relevant pathogens (0.25 $\mu\text{g/ml}$).

The ability of sparfloxacin to diffuse into bronchial mucosa, epithelial lining fluid (ELF) and alveolar macrophages was evaluated in 31 male and female patients scheduled for fiberoptic bronchoscopy due to suspicion of lung cancer (AT 123). Patients were administered a single oral 400 mg dose (N=21) or multiple doses (400mg/200mg) for three days. Representative tissue concentrations consistently exceeded the plasma concentrations. Mean (CV%) serum and tissue sparfloxacin concentrations at selected times after drug administration are presented at the following:

Mean (CV%) bronchial sparfloxacin concentrations after 400mg single dose.

Time (h)	Serum ($\mu\text{g/ml}$)	Mucosa ($\mu\text{g/g}$)	Macrophages ($\mu\text{g/g}$)	ELF ($\mu\text{g/ml}$)
3-6(n=5)	0.78(130%)	2.37(112%)	34.1 (115%)	10.3(148%)
12(n=5)	1.22(36%)	2.60(30%)	61.3 (51%)	9.75(59%)
24(n=5)	0.57(32%)	1.64(30%)	36.3 (30%)	10.2(44%)
48(n=5)	0.30(63%)	1.11(51%)	37.9 (119%)	4.64(83%)

Multiple Dose (400 mg on Day 1 and 200 mg on Days 2-3)

3-6 (n=11)	1.20(34%)	4.40(68%)	53.7 (72%)	15.0 (56%)

It was concluded that sparfloxacin penetrates well into bronchial tissues after single and multiple oral doses, with apparent steady-state concentrations in tissues higher than single dose concentrations, as expected. Again, both serum and tissues concentrations exceeded the MIC_{90} for most relevant pathogens.

The penetration of sparfloxacin into pulmonary tissues following a single oral 400 mg (2x200 mg tablets) dose was evaluated in 15 male and female patients that underwent surgery for bronchial or pulmonary cancer (AT 128). Tissue to serum sparfloxacin concentration ratios of representative pulmonary tissues that were collected at 2-6 and 12-24 hours after drug administration are listed below.

Mean (CV%) pulmonary tissue to plasma concentration ratios:

Tissue	2-6 hr (n=8)	12-24 (n=7)
pulmonary parenchyma	5.9 (15%)	15.8 (32%)
tumor tissue	4.0 (13%)	5.0 (24%)
bronchus wall	2.8 (16%)	5.7 (25%)
pulmonary artery wall	2.7 (10%)	4.7 (22%)
erythrocytes	1.1 (43.6%)	1.1 (7.3%)
intra-bronchial mucus proximal to tumor	2.0 (24%)	2.4 (20%)
Intra-bronchial mucus distal to tumor	2.7 (24%)	2.7 (22%)

The pulmonary tissue to plasma concentration ratios ranged from 1.35 to 36.32 cross individual subject. Based on this single dose data, it was concluded that sparfloxacin will penetrate very well into broncho-pulmonary tissues over the anticipated multiple dosing interval of 24 hours, with tissue concentrations exceeding the MIC₉₀ for most relevant pathogens.

The diffusion of sparfloxacin into pleural effusion fluid following a single oral 400 mg dose was assessed using 24 adult male and female patient volunteers with suspected pleural exudative effusion (AT 133). Pleural effusion concentrations of sparfloxacin were less than corresponding concentrations in plasma, but appeared to increase with time. Mean (CV%) pleural effusion to plasma sparfloxacin concentration ratios were 0.34 ($\pm 35\%$) at 4 hours post dose and 0.69 ($\pm 33\%$) at 20 hours post dose.

Additional studies have been conducted to assess the ability of sparfloxacin to penetrate into fluids associated with the eye. The penetration of sparfloxacin into the aqueous humor following a single oral 400 mg (2x200 mg tablets) dose was assessed in 31 adult male and female patient volunteers that underwent cataract surgery (AT 135). Serum sparfloxacin concentrations were generally greater than that in the aqueous humor except the 24-hour sample. Mean (CV%) aqueous humor to serum concentration ratios are presented in the table below:

Mean (CV%) Aqueous Humor to Serum Concentration Ratios

Time (h)	n	Ratio of aqueous humor to serum
2	5	0.16 (14%)
5	5	0.19 (10%)
8	4	0.21 (7.0%)
10	5	0.27 (5.0%)
12	4	0.28 (5.0%)
24	5	1.15 (75%)

Based on these results, sparfloxacin does not appear to penetrate well into fluids associated with the eye after single oral doses.

The intravitreal pharmacokinetics of sparfloxacin following a 4-day multiple dose regimen (400 mg/200 mg) was also evaluated in 8 adult male and female patient volunteers that underwent a vitrectomy (AT 136). Vitreal sparfloxacin concentrations sampled at 4 to 8 hours following the last dose were less than that in plasma. The mean (CV%) vitreal to plasma concentration ratio was 0.47 ($\pm 23\%$). Consistent with the previously described single dose study, sparfloxacin does not appear to penetrate well into fluids of the eye after multiple oral doses.

Study Number	Dose (Sub.)	C _{max} ($\mu\text{g/ml}$)	T _{max} (hr)	V _{d/f} (L)	AUC _{inf} ($\mu\text{g/ml/hr}$)	T _{1/2} (hr)	A _e (%D)	CL _{p/f} (L/hr)	Cl _r (L/hr)	Comments
AT-124 PO (sd) 400 (n=12)		1.5(36)	2.9(73)	304(36)	33.5(40)	15.6	9.6(25)	233(104)	20.7(6.6)	Unchanged Drug
		0.9(35)	2.1(53)	N/A	15.1(32)	16.3	28.1(24)			184(75)
AT-120 PO (sd) 400 (n=6)		1.6(19)	2.7(78)	N/A	32.3(12)	17.6	8.8(20)	N/A	N/A	Micro. Assay, Unchanged Drug
		1.3(23)	5.0(34)	N/A	37.4(39)	19.7	N/A			N/A

Studies AT 128 (400mg, n=15), AT 127 (400mg, n=29 and 200mg n=3), AT 133 (400mg, n=25), AT 123 (400mg, n=21 and 400/200 mg, n=11), AT 135 (400mg, N=28) and AT 136 (400/200 mg, n=8) have no pharmacokinetic parameter estimation. Therefore, are ignored from the table.

7. METABOLISM AND EXCRETION

Studies #AT 122, AT 111/139, AT 138, AT 106

A. Metabolite identification.

Metabolite isolation and identification have been performed in plasma, urine, and feces following administration of single oral 200 mg doses and in bile following a single oral 300 mg dose from a study conducted in Japanese volunteers. Metabolites were first isolated by high performance liquid chromatography (HPLC), then determined by mass spectrometry and H-nuclear magnetic resonance spectrometry. Results from metabolite profiling showed that only unchanged sparfloxacin and one polar metabolite, an acylglucuronide, could be isolated in plasma, urine and bile. Only unchanged sparfloxacin was detected in the feces. The degradation half-life of the glucuronide at 37 °C was 22, 114, and 261 hours in plasma, urine, and bile, respectively. The acylglucuronide was also rapidly hydrolyzed in alkaline medium with degradation half-lives of 1.4 and 0.09 hours at 37 °C in pH 9.0 and pH 11.0 buffers and 82 hours in pH 7.4 buffer.

B. Mass balance studies.

In a mass balance study (AT 122), six healthy male volunteers between 18 and 40 years of age received single 400 mg oral doses of sparfloxacin. Of the 400 mg oral dose, 300 mg was non-labeled (3x100 mg tablet) sparfloxacin while the remaining 100 mg was a ¹⁴C-labeled homogeneous carboxymethylcellulose suspension (50 pCi) of sparfloxacin. Mean (CV%) recovery of the total radioactive dose was 49.9% ($\pm 3.4\%$) in urine and 48.2% ($\pm 11\%$) in feces within 240 hours after drug administration. Of the amount of radioactivity recovered in the urine, approximately 35% and 42% was further identified as unchanged sparfloxacin and sparfloxacin glucuronide, respectively. Further analysis to determine the relative fractions of sparfloxacin and sparfloxacin glucuronide present in the feces was not performed.

The pharmacokinetics of ^{14}C -radioactivity and sparfloxacin were also assessed in this study. The mean (CV%) plasma to blood concentration ratio for total radioactivity was 0.8 ($\pm 16\%$) for C_{max} and 0.7 ($\pm 16\%$) for AUC_{inf} , indicating that sparfloxacin and its metabolites do not concentrate in red blood cells. More important, HPLC analysis of plasma samples also showed that unchanged sparfloxacin accounted for approximately 80% of the plasma radioactivity. Additionally, the mean $t_{1/2}$ values for unchanged sparfloxacin and plasma ^{14}C -radioactivity were 19.55 hours and 18.86 hours, respectively. Based on the results of this study, it was concluded that most of the radioactivity in the plasma was associated with unchanged sparfloxacin, that sparfloxacin is excreted into the urine primarily as unchanged drug or its glucuronide and that sparfloxacin is not retained by human body tissues.

Study Number	Dose (Sub.)	C_{max} ($\mu\text{g/ml}$)	T_{max} (hr)	V_d/f (L)	AUC_{inf} ($\mu\text{g/ml/hr}$)	$T_{1/2}$ (hr)	A_e (%D)	CL_p/f (L/hr)	CL_r (L/hr)	Comments
AT-122 PO (sd)	400 (n=6)	3.51(36)	0.75(37)	N/A	50.7 (17)	20.4	38.2(4.3)	N/A	N/A	total sparfloxacin in plasma
		4.28 (20)	0.75(37)	N/A	75.2 (21)	20.2		N/A	N/A	total sparfloxacin in blood
		2.59 (33)	0.75 (37)	N/A	40.8 (17)	19.6	17.5(20)	N/A	N/A	unchanged sparfloxacin

Data are ^{14}C Mass Balance Study. Data represent PK results for total radioactivity.

C. Excretion

Single 400 mg oral doses of sparfloxacin were administered to 12 adult male and female patients with biliary tract drainage to further assess the metabolism and excretion of sparfloxacin (AT 111/139). Urine and bile were collected up to 96 and 72 hours following drug administration, respectively. Based upon HPLC analysis of urine and bile samples, mean (CV%) recovery of unchanged sparfloxacin in urine and bile following administration of a single 400 mg oral dose were 8.8% ($\pm 35\%$) and 1.5% ($\pm 67\%$), respectively. Corresponding mean recoveries of sparfloxacin glucuronide were 39.4% ($\pm 29\%$) and 11.5% ($\pm 60\%$) in urine and bile, respectively. The mean (CV%) renal clearance of unchanged sparfloxacin, which accounted for approximately 10% of the total apparent oral clearance was 0.8 ($\pm 27\%$) L/hr.

Mean (CV%) biliary clearance of sparfloxacin accounted for only 2% of the total apparent oral clearance and only 2.5% of the total non-renal clearance and was 0.17 ($\pm 62\%$) L/hr. Based on the results of this study, sparfloxacin appears to be eliminated primarily by the hepatic Phase II glucuronidation pathway.

Another single dose study using only 4 adult male and female patients with biliary tract drainage assessed the excretion of sparfloxacin in bile following administration of a single 400 mg oral dose (AT 138). Mean (CV%) biliary clearance and fractional recoveries were 0.24 ($\pm 17\%$) L/hr and 3.0% ($\pm 24\%$), respectively. The biliary clearance and fractional recovery of sparfloxacin in bile were generally consistent with that in Study AT 111/139.

The previously described studies readily demonstrated that sparfloxacin is excreted unchanged in the

urine. Therefore, the ability of sparfloxacin to crystallize in urine was assessed in a study (AT 106) conducted in 12 healthy male volunteers who were given Chlorammonice or Alcaphor to acidify or alkalinize their urine. Except small amounts in one subject, sparfloxacin crystals were not found in urine samples taken up to 24 hours after drug administration. The PK parameters are listed below.

Study Number	Dose (Sub.)	C _{max} (µg/ml)	T _{max} (hr)	V _{d/f} (L)	AUC _{inf} (µg/ml/hr)	T _{1/2} (hr)	A _e (%D)	CL _{p/f} (L/hr)	Cl _r (L/hr)	Comments
AT-111/139	PO(sd)400(n=12)	2.56(39) 2.38(55)	15.8(97) 14.5(90)	272(50) N/A	48.5(24) 81.0(48)	21.3 20.8	8.8(35) 39.4(29)	8.7(23) N/A	0.78(27) 3.93(61)	
AT-138	PO(sd) 400(n=4)	2.86(60)	5(105)	N/A	52.7(28)	21.2	N/A	N/A	N/A	in serum
AT-106	PO(sd) 400(n=12)	N/A	N/A	N/A	N/A	N/A	1.5(36)	N/A	N/A	(S+C)

D. Elimination

Studies #AT 119, CF-978-1, RP64206-153, AT 102

A compilation of data collected from many pharmacokinetic studies shows that the terminal elimination half life ($t_{1/2}$) of sparfloxacin in normal healthy subjects ranges between 16 and 30 hours with a mean $t_{1/2}$ of approximately 20 hours. The $t_{1/2}$ is generally independent of the administered dose which suggests that sparfloxacin obeys linear elimination pharmacokinetics over the dosage range of 200 mg to 1600 mg and encompasses the anticipated therapeutic dosing regimen. The apparent oral clearance is relatively slow, ranging between 8 and 14 L/hr.

The terminal elimination rate of sparfloxacin glucuronide appears to parallel the elimination rate of the parent compound. The $t_{1/2}$ for sparfloxacin glucuronide varies between 10 and 23 hours with a mean of approximately 16 hours. Therefore, the data suggest that sparfloxacin glucuronide elimination was formation-rate limited. A comparison of the plasma sparfloxacin and sparfloxacin glucuronide concentration-time profiles is illustrated in Figure 5.

multiple dose pharmacokinetics of sparfloxacin were predictable from single dose data.

In another multiple dose study (AT 102), the pharmacokinetics of sparfloxacin were to be assessed following administration of a single 200 or 400 mg dose followed by a 7 day washout to parallel groups of healthy male volunteers. At the end of the washout period, sparfloxacin was administered as a once daily 400 mg dose (q24h) or a twice daily 200 mg dose (q12h).

The multiple dose pharmacokinetics were not assessed because subjects discontinued from the study early due to photosensitivity reactions. Pharmacokinetic parameters of these studies are listed below.

Study Number	Dose (Sub.) (µg/ml)	C _{max} (µg/ml)	T _{max} (hr)	V _d /f (L)	AUC _{0-∞} (µg/ml/hr)	T _{1/2} (hr)	A _e (%D)	CL _{p/f} (L/hr)	CL _r (L/hr)	Comments
CI-978-1 PO(md)	200/100 (n=8)q24h	0.22(23)	4.4(51)	N/A	8.50(25)	21.8	11.2(40)	12.5(28)	N/A	Steady-State Values
	400/200 (n=8)q24h	0.31(28)	4.3(46)	N/A	11.3(27)	24.6	7.71(38)	18.8(27)	N/A	Steady-State Values
	600/300 (n=8)q24h *	0.63(15)	4.3(41)	N/A	23.2(19)	22.7	7.37(53)	13.3(18)	N/A	Steady-State Values
AT- 119 PO (md)	200/100 (n=8)q24h	0.72(15)	3.3(61)	N/A	11.0(10)	20.9	10.4(14)	N/A	N/A	Steady-State Values
	400/200 (n=8)q24h	1.36(27)	3.5(61)	N/A	20.4(22)	20.3	8.52(24)	N/A	N/A	Steady-State Values
	600/300 (n=8)q24h	2.07(23)	5.5(41)	N/A	34.6(21)	22.3	8.44(42)	N/A	N/A	Steady-State Values
	800/400 (n=8)q24h	2.87(21)	3.8(37)	N/A	45.3(31)	17.8	7.9(41)	N/A	N/A	Steady-State Values
AT-102 PO(ad)	200(n=4)	0.85(16)	4.1(75)	N/A	20.9(14)	16.7	11.3(21)	9.8(16)	N/A	
	400(n=4)	1.05(18)	6.0(67)	N/A	31.5(13)	18.8	7.39(12)	12.9(13)	N/A	
	200,q24h	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(Steady-state values not reported because subjects discontinued due to photosensitivity reactions)
RP 153, PO (md)	200/100 q24 h (n=23)	0.75 (18)	3.2 (34)	N/A	12.1 (16)	N/A	N/A	N/A	N/A	Day 1
	(n=23)	0.66 (14)	2.8 (40)	N/A	10.4 (14)	N/A	N/A	N/A	N/A	Day 3
	(n=23)	0.63 (14)	2.8 (37)	N/A	10.3 (17)	N/A	N/A	N/A	N/A	Day 4
	(n=22)	0.63 (19)	2.5 (35)	N/A	10.7 (14)	N/A	N/A	N/A	N/A	Day 2
	400/200 q24 h (n=23)	1.26 (16)	3.3 (44)	N/A	20.6(15)	N/A	N/A	N/A	N/A	Day 1
	(n=23)	1.14 (18)	2.5 (32)	N/A	19.0 (15)	N/A	N/A	N/A	N/A	Day 2
	(n=23)	1.15 (14)	3.1 (37)	N/A	19.2 (15)	N/A	N/A	N/A	N/A	Day 3
	(n=22)	1.13 (13)	2.8 (43)	N/A	18.7 (14)	N/A	N/A	N/A	N/A	Day 4
	800/400 q24 h (n=22)	2.27 (15)	3.9 (37)	N/A	38.9 (16)	N/A	N/A	N/A	N/A	Day 1
	(n=22)	2.29 (14)	2.8 (30)	N/A	38.9 (13)	N/A	N/A	N/A	N/A	Day 2
	(n=22)	2.16 (15)	3.5 (34)	N/A	37.2 (15)	N/A	N/A	N/A	N/A	Day 3
	(n=22)	2.13 (17)	2.8 (39)	N/A	35.4 (16)	N/A	N/A	N/A	N/A	Day 4

1. Mean (%CV) Clearance in bile = 0.17 (62%) L/hr for sparfloxacin and 1.28 (78%) L/hr for sparfloxacin glucuronide.

2. Sparfloxacin Glucuronide

3. Mean (%CV) Clearance in bile = 0.24 (17%) L/hr for sparfloxacin.

F. Special populations

Studies #AT 103, AT 104

The pharmacokinetics of sparfloxacin in elderly healthy volunteers were studied following single ascending doses of 100, 200, 300, and 600 mg (4 subjects per gender, ages 62-77 years) and following a seven-day multiple dose regimen (5 subjects per gender, ages 60-74 years) using a 400 mg loading dose followed by single daily 200 mg doses for 6 days (AT 103, AT 104). The pharmacokinetics of sparfloxacin following single dose administration over the dose range studied were similar to results in healthy young volunteers. Mean (CV%) $AUC_{0-\infty}$ values were 8.8 ($\pm 12\%$), 18.5 ($\pm 16\%$), 35.2 ($\pm 17\%$), and 47.5 $\mu\text{g}\cdot\text{hr}/\text{ml}$ for the 100, 200, 400, and 600 mg doses, respectively. Corresponding mean C_{max} values were 0.31 ($\pm 22\%$), 0.68 ($\pm 23\%$), 1.35 ($\pm 24\%$), and 1.71 ($\pm 20\%$). Mean $t_{1/2}$ values were approximately 19 hours. As was observed in normal healthy subjects, sparfloxacin exhibited dose proportional increases in plasma concentrations with increasing dose. The multiple dose pharmacokinetics of sparfloxacin in the elderly were consistent with that observed in normal healthy subjects. Mean (CV%) steady-state AUC_{0-24} and C_{max} values were 17.6 ($\pm 17\%$) $\mu\text{g}/\text{ml}/\text{hr}$ and 1.3 ($\pm 17\%$) $\mu\text{g}/\text{ml}$, respectively. The observed and theoretical accumulation factors were 1.63 and 1.73 respectively, and in good agreement with previous studies in young volunteers. Therefore, age alone does not appear to alter the pharmacokinetics of sparfloxacin.

Study Number	Dose (Sub.) ($\mu\text{g}/\text{ml}$)	C_{max} ($\mu\text{g}/\text{ml}$)	T_{max} (hr)	V_d/T (L)	$AUC_{0-\infty}$ ($\mu\text{g}/\text{ml}/\text{hr}$)	$T_{1/2}$ (hr)	A_e (%D)	CL_p/T (L/hr)	CL_r (L/hr)	Comments
AT-104 PO (md) 200 (n=10) q24h		1.30 (17)	3.0 (65)	N/A	17.7 (17)	19.9	11.2 (22)	116 (16)	128 (24)	steady-state conditions
AT 103 PO (sd)	100(n=6)	0.35 (22)	4.0 (0)	N/A	8.8	N/A	N/A	N/A	N/A	
	200(n=6)	0.68(23)	4.7(35)	N/A	18.5(16)	19.2	9.2(41)	11.0(14)	1.07(36)	
	400(n=6)	1.35(24)	6.0(37)	N/A	35.1(17)	18.8	7.6(26)	11.7(18)	0.93(29)	
	600(n=6)	1.71(19)	6.0(37)	N/A	47.5(12)	18.9	7.7(14)	12.8(11)	1.06(14)	

G. Hepatic insufficiency

Studies # AT 116, AT 110,

The pharmacokinetics of sparfloxacin were studied in 12 male and female patients with mild and moderate liver cirrhosis (Pugh scores of 6 to 12) following a single oral 400 mg dose (AT 116). The mean $t_{1/2}$ of 22.3 hours was similar to the typical 20-hour $t_{1/2}$ observed in healthy subjects. Mean (CV%) total CL and renal clearance (CL_r) were 9.8 ($\pm 44\%$) and 0.8 (61%) L/hr, respectively. It was concluded that the pharmacokinetics of sparfloxacin in patients with liver disease was consistent with that in healthy volunteers. This lack of effect of liver disease on the pharmacokinetics of sparfloxacin is not surprising since hepatic insufficiency may or may not alter the glucuronidation process. The impact of liver disease on glucuronidation which appears to be the primary pathway for metabolism of sparfloxacin depends upon the severity of the disease, whether the glucuronide is an ester or ether, heterogeneity of glucuronyltransferase, protein binding, and endocrine/nutritional status of the patient. In another study (AT 110) conducted also in patients with liver cirrhosis, only data from two subjects

were reported. Hence, the study could not be used to support any dosing recommendations. PK parameters are summarized below.

Study Number	Dose (Sub.) (µg/ml)	C _{max} (µg/ml)	T _{max} (hr)	V _{d/f} (L)	AUC _{inf} (µg/ml/hr)	T _{1/2} (hr)	A _e (%D)	CL _{pf} (L/hr)	CL _r (L/hr)	Comments
AT- 116 PO (ad)1400 (n=12)		1.64 (29)	5.1(41)	N/A	47.3 (37)	22.3	8.8(55)	9.8(44)	0.86 (61)	Sparfloxacin Spar. Glucuronid
		0.87 (57)	9.23 (60)	N/A	33.9 (82)	24.9	44.8(22)	N/A	8.4 (74.4)	
AT-110 PO (ad) 400(n=2)		2.34	N/A	45.7	16.4	N/A	8.8	N/A	N/A	subject subject
		1.3	2	N/A	65.4	20.6	N/A	6.1	N/A	

H. Renal insufficiency

Studies #AT 108, AT 121, RP64206-159

The effect of varying degrees of renal insufficiency on the pharmacokinetics of sparfloxacin have been studied following both single and multiple dose administration in male and female subjects. In the single dose study (AT 108), the pharmacokinetics of sparfloxacin was studied in 7 patients with moderate ($10 < \text{CLcr} < 30 \text{ ml/min/1.73 m}^2$) and 7 patients with severe ($2 < \text{CLcr} < 10 \text{ ml/min/1.73 m}^2$) renal insufficiency following a single 400 mg dose. The elimination of sparfloxacin was decreased in both groups of renal insufficiency when compared to data for 6 normal healthy subjects from another study (AT 121). Mean $t_{1/2}$ values were 34.9 hours and 38.5 hours in subjects with moderate and severe renal insufficiency, respectively, compared to 19.1 hours in normal healthy subjects. Renal excretion of sparfloxacin also decreased with a decrease in renal function. Mean (CV%) values for CL_r were 0.41 (34%) and 0.29 (26%) L/hr for moderate and severe renal impaired subjects, respectively compared to 1.26 (16%) L/hr for normal subjects. The mean (CV%) values for the amount of sparfloxacin excreted in the urine (fu) was 4.0% (47%) and 3.2% (28%) for moderate and severe renal impaired subjects, respectively, compared to 9.7% (24%) for normal subjects. CL_{pf} was not significantly altered.

The pharmacokinetics of sparfloxacin glucuronide were also studied in this single dose study. The elimination of sparfloxacin glucuronide was only slightly decreased in subjects with moderate renal insufficiency, but significantly decreased for subjects with severe renal insufficiency. Mean $t_{1/2}$ values were 23.7 hours and 35.0 hours in subjects with moderate and severe renal insufficiency, respectively, compared to 15.3 hours in normal healthy subjects in Study AT 121. Mean (CV%) A_e values were also correspondingly lower, 9.8%(58%) and 8.4%(52%) L/hr respectively, when compared to 18.6%(26%) L/hr for normal subjects. The results of this study indicated that renal insufficiency could significantly decrease the elimination of both sparfloxacin and its glucuronide metabolite.

In the multiple dose study (RP64206-159), the pharmacokinetics of sparfloxacin were evaluated in patients with renal function of CL_{cr} > 50 ml/min (n=14), mild renal insufficiency (30 < CL_{cr} < 49 ml/min; n=8), and moderate renal insufficiency (10 < CL_{cr} < 29 ml/min; n=8) following multiple dose administration using the anticipated therapeutic regimen of a 400 mg loading dose followed by once daily 200 mg maintenance doses. In this study, subjects with normal renal function were age, weight,

and sex-matched to subjects having mild and/or moderate renal insufficiency. The multiple dose regimen consisted of a single 400 mg loading dose followed by once daily 200 mg maintenance doses for 9 days for subjects with normal and mild renal insufficiency and a single 400 mg loading dose followed by 200 mg every other day for subjects with moderate renal insufficiency. Mean plasma sparfloracin concentration-time profiles for the three groups after the last multiple dose are presented in Figure 6. Unexpectedly, the mean $t_{1/2}$ for the mild renal insufficiency group was longer (27.7 hours) than the mean values for subjects with normal renal function (18.7 hours) or moderate renal insufficiency (20.4 hours). However, Figure 6 readily demonstrates that daily sparfloracin doses in subjects with mild renal insufficiency generally produces much higher steady-state plasma drug concentrations when compared to normal subjects. Mean (CV%) AUC_{τ} values were 11.5 (32%), 25.4 (20%), and 19.2 (35%) $\mu\text{g/ml/hr}$ for subjects with normal renal function, mild renal insufficiency, and moderate renal insufficiency, respectively. Steady-state urinary excretion pharmacokinetic parameters also generally decreased. Mean (CV%) values for mild and moderate renal insufficiency were 0.74(32%), and 0.3(38%) L/hr for CL_r and 9.2% (30%), and 2.8% (55%) for Fr , respectively. Mean values for subjects with normal renal function were 1.5 (32%) and 8.3% (35%) for CL_r and Fr , respectively. Linear regression analysis of the data also showed that AUC_{τ} and CL were related to CL_{Cr} (Figure 7).

It was concluded that an adjustment in dosing frequency from a once daily sparfloracin dose (24-hour dosing interval) to a single dose every alternate day (48-hour dosing interval) may be appropriate for most patients with mild and moderate renal insufficiency if it is desirable to produce steady-state plasma concentrations that are similar to those values observed in normal healthy subjects taking sparfloracin on a 24-hour dosing interval.

As was observed in the single dose study, steady-state sparfloracin glucuronide pharmacokinetic parameters were altered only slightly in subjects with moderate renal impairment. Mean $t_{1/2}$ values, which expected is increased as renal function decreased, were 18.2, 23.9, and 24.8 hours for subjects with normal renal function, mild renal insufficiency, and moderate renal insufficiency, respectively. The mean (CV%) steady-state urinary excretion pharmacokinetic parameters were 16.5 (103%), 17.6 (164%), and 3.1 (69%) L/hr for CL_r and 8.8% (49%), 15.9% (54%), and 10.5% (37%) for Fr , respectively. Linear regression analysis showed that AUC_{τ} , but not CL_r were related to CL_{Cr} (Figure 8).

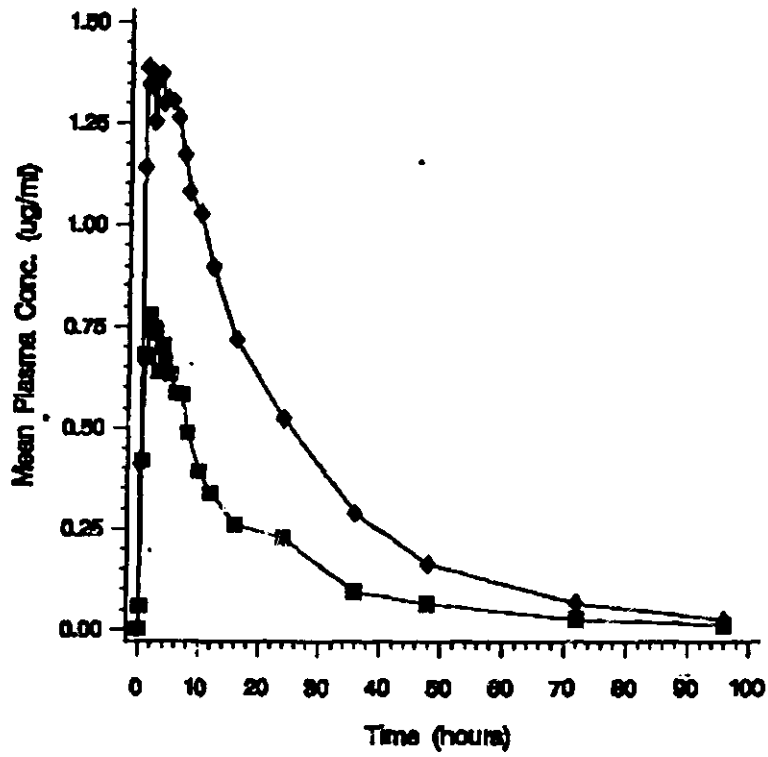


Figure 5: Mean (N=12) plasma sparfloxacin (◆) and sparfloxacin glucuronide (■) concentration-time profiles following administration of a single 400 mg oral sparfloxacin dose. [6.16]

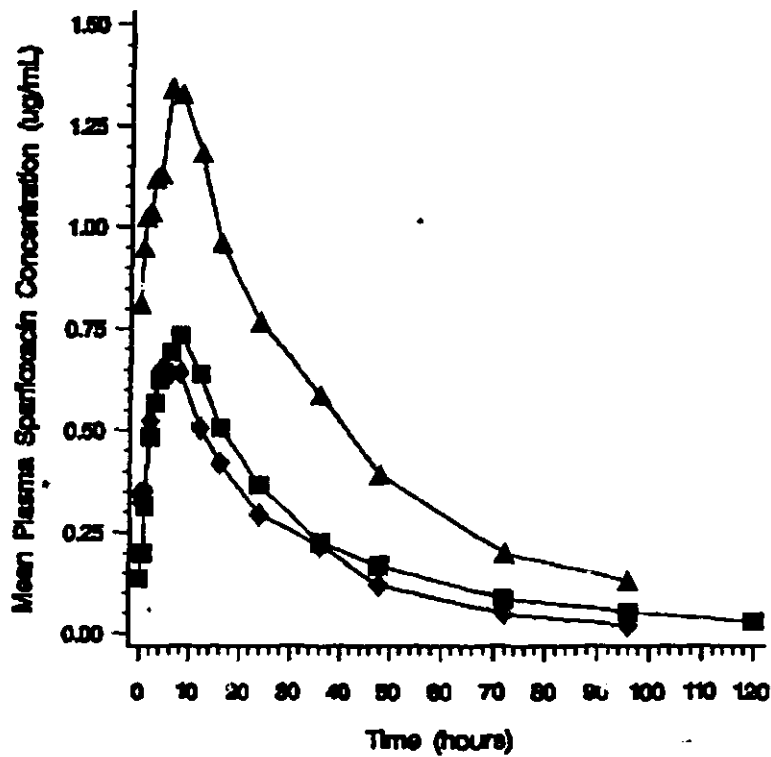


Figure 6: Mean plasma sparfloxacin concentrations for subjects with normal renal function (◆) (N=12), mild renal insufficiency (▲) (N=7), and moderate renal insufficiency (■) (N=8) following the last multiple oral dose (200 mg) administration of Sparfloxacin. Subjects were excluded for previously stated reasons

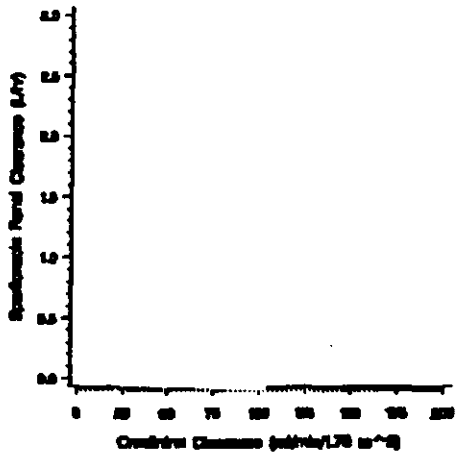
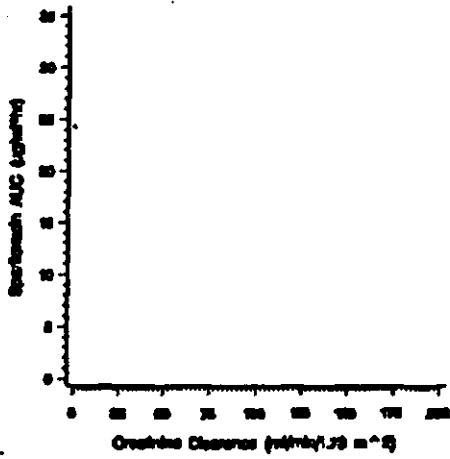


Figure 7: Scatter plots of steady-state sparfloxacin $AUC_{0-\infty}^{\infty}$, (top), and CL_r^{∞} (bottom), versus creatinine clearance.

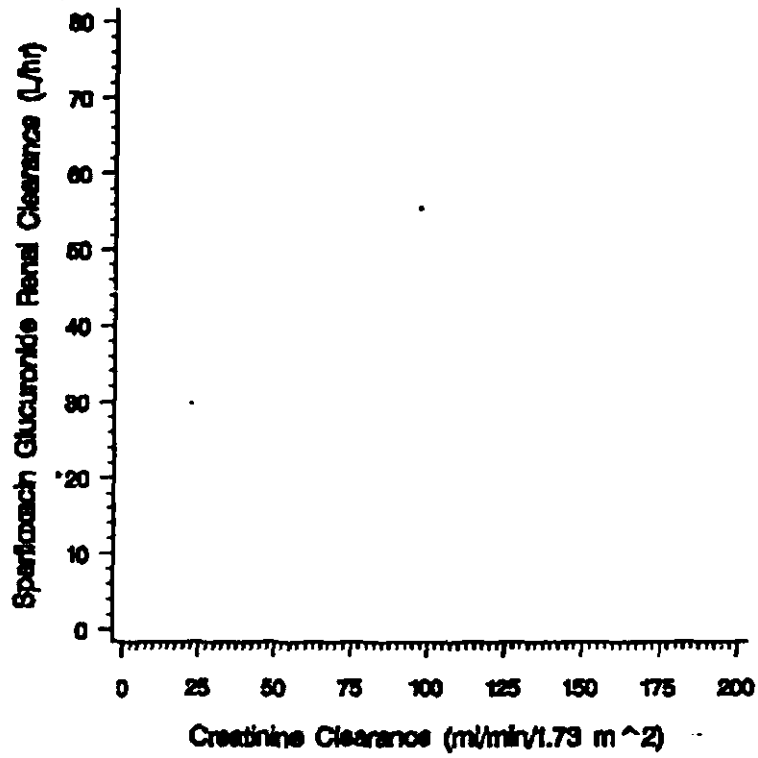


Figure 8: Scatter plot of the steady-state sparfloxacin glucuronide renal clearance versus creatinine clearance.

Pharmacokinetic parameters of these studies are preset below.

Study Number	Dose (Sub.)	C _{max} (µg/ml)	T _{max} (hr)	V _d /f (L)	AUC _{0-∞} (µg/ml/hr)	T _{1/2} (hr)	A _e (%D)	CL _{cr} /f (L/hr)	CL _r (L/hr)	Comments
RP-159 PO(oad)	400/200 ³	0.75(29)	5.9(47)	N/A	11.5(32)	18.7	8.3(35)	N/A	1.5(32)	normal renal function moderate renal insufficiency severe renal insufficiency
	(n=14)q24	0.18(37) ¹	6.0(71)	N/A	2.17(72)	26.71	8.8(49)	N/A	16.5(103)	
	400/200 ³	1.46 (17)	4.9 (38)	N/A	25.4 (20)	27.7	9.2 (30)	N/A	0.74 (32)	
	(n=8)q24h	0.41 (79) ¹	14.1(139)	N/A	4.66(65)	22.41	15.9 (54)	N/A	17.6 (164)	
	400/200 ⁴	0.80 (28)	6.3 (35)	N/A	19.2 (35)	20.4	2.8 (62)	N/A	0.30 (48)	
	(n=8)q24h	0.51 (60) ¹	12.6 (54)	N/A	11.5 (74)	18.71	10.5 (37)	N/A	3.06 (69)	
AT 108 PO(oad)	400(n=7) ¹	1.43(45)	3.9(57)	N/A	44.2(43)	35	4.1(47)	10.6(41)	0.41(34)	
		0.68(27) ¹	8.6 (88)	N/A	25.5(28)	24	9.8 (44)	N/A	1.89 (58)	
	400(n=7) ²	1.31 (33)	4.9 (32)	N/A	49.4 (23)	39	3.2 (30)	8.5 (22)	0.29 (26)	
		0.98 (60) ¹	15 (58)	N/A	64.9 (57)	135	8.4 (56)	N/A	0.84(52)	

1. Sparfloxacin Glucuronide
2. CL_{cr} > 50 ml/min/1.73 m²
3. 30 < CL_{cr} < 50 ml/min/1.73 m²
4. 10 < CL_{cr} < 30 ml/min/1.73 m²
5. 2 < CL_{cr} < 10 ml/min/1.73 m²

L Gender difference

Where it was possible to evaluate, the pharmacokinetics of sparfloxacin did not appear to be different between males and females with one exception. In a previously discussed ascending dose tolerability study (RP64206-162), mean AUC_{0-∞} and C_{max} values were higher in females than in males. Mean (CV%) AUC_{0-∞} values for females and males were 38.0 (18%) and 26.7 (29%) µg/ml/hr at the 400 mg dose, 73.2 (31%) and 59.1 (25%) µg/ml/hr at the 800 mg dose, 109 (28%) and 81.2 (27%) µg/ml/hr at the 1200 mg dose, and 130(36%) and 106(27%) µg/ml/hr at the 1600 mg dose, respectively.

Corresponding mean C_{max} values were 1.80 (18%) and 1.06 (24%) µg/ml, 2.74 (26%) and 2.08 (19%)µg/ml, 3.87(27%) and 2.51(36%)µg/ml, and 4.62(37%) and 3.15(30%)µg/ml, respectively. However, these differences could be explained by the differences in mean body weight between the male and female subjects. The mean body weight for males subjects (83 kg) was approximately 30% greater than the mean body weight for female subjects (63.6 kg) and weight-normalized pharmacokinetic parameters for the two groups were similar.

J. Drug-drug interaction studies.

a. Drug-drug interaction on pharmacokinetics

Studies #RP64206-156, AT 114, RP64206-155, AT 115, AT 105

The effect of multiple oral doses of sparfloxacin on the single dose pharmacokinetics of theophylline were evaluated in 10 healthy male volunteers between 18 and 40 years of age (AT 105). Sparfloxacin was administered orally as a single 400 mg loading dose on Day 1 followed by single 200 mg doses

on Days 2 through 6. Theophylline was administered by short term intravenous infusion (176 mg) on Day 6. Mean(CV%) theophylline AUC_{0-8} values were 54.5 (42%) $\mu\text{g/ml/hr}$ following administration of theophylline alone and 53.2 (36%) $\mu\text{g/ml/hr}$ following administration of theophylline and sparfloracin. Corresponding mean (CV%) C_{max} values were 5.9 (33%) and 5.3 (19%), respectively.

The effect of multiple oral doses of sparfloracin on the multiple dose pharmacokinetics of theophylline was also evaluated in 20 normal healthy male (N=10) and female (N=10) volunteers (RP64206-156). After an initial theophylline dosing phase to establish appropriate individual dosing regimens for the subjects, theophylline was administered orally as a 100 or 200 mg dose every 8 hours. Sparfloracin was administered as a 400 mg loading dose followed by once daily single 200 mg doses for three days. The mean steady-state theophylline concentration-time profiles when administered alone or with sparfloracin are presented in Figure 9. Consistent with results from the single dose study, the steady-state AUC_{0-8} values were 56.1(27%) $\mu\text{g/ml/hr}$ following administration of theophylline alone and 54.9(25%) $\mu\text{g/ml/hr}$ following administration of theophylline and sparfloracin. Corresponding steady-state mean (CV%) C_{max} values were 9.1(28%) and 9.0(25%), respectively. Based on the results of these two studies, it was concluded that the pharmacokinetics of theophylline are not altered by multiple dose treatment with sparfloracin.

A study (AT 114) conducted to assess the effect of single dose sparfloracin administration on the steady-state pharmacokinetics of digoxin in 10 healthy male volunteers between 20 and 40 years of age showed a significant increase in AUC_{0-24} values when digoxin was administered with sparfloracin. However, blood samples for plasma digoxin determination were obtained on Day 7 (digoxin alone) and on Day 10 (digoxin and sparfloracin). Since digoxin typically takes 10 days to reach steady-state conditions the plasma concentration-time profile obtained following administration of digoxin alone (Day 7) probably did not represent steady-state conditions. Therefore, an additional study was conducted to further evaluate the interaction between the steady-state pharmacokinetics of digoxin when administered in combination with multiple dose sparfloracin administration.

The second study (RP64206-155) to assess the effect of sparfloracin on the pharmacokinetics of digoxin was conducted as a double-blind, placebo controlled, multiple dose, two-way crossover study in 24 healthy male volunteers between the ages of 20 and 49. Subjects were maintained on 0.3 mg of digoxin (3x0.1 mg Lanoxicaps) orally throughout both study periods. Subjects receiving sparfloracin were given a 400 mg oral loading dose (2x200 mg tablets) followed by a single 200 mg oral dose once a day for the next nine days. Subjects receiving placebo followed the same regimen with placebo tablets. The mean steady-state digoxin concentration-time profiles in subjects receiving digoxin alone or with sparfloracin are presented in Figure 10. Mean (CV%) AUC_{0-24} values were 28.4(14%) and 28.9(15%) $\text{ng}\cdot\text{hr/ml}$ for digoxin alone and when administered concomitantly with sparfloracin, respectively. Corresponding mean steady-state C_{max} values were 3.9(24%) and 3.6(23%) ng/ml . Based on the results of these two studies, it was concluded that multiple oral doses of sparfloracin do not alter the steady-state pharmacokinetics of digoxin.

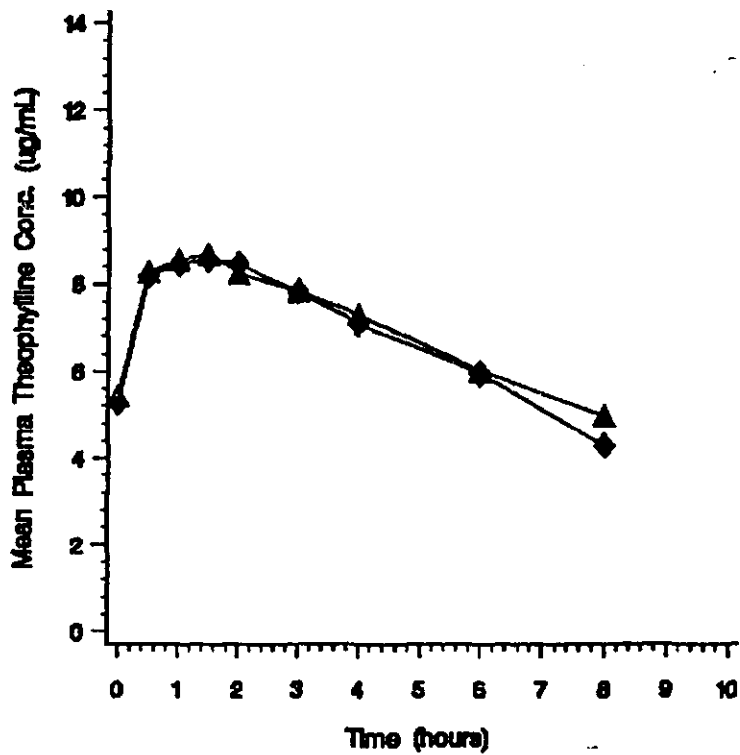


Figure 9: Mean (N=17) Plasma Theophylline Concentration-Time Plots For Subjects Taking Theophylline Alone (▲) and For Subjects Taking Theophylline and Sparfloxacin (◆).

The ability of multiple oral doses of cimetidine to affect the pharmacokinetics of sparfloxacin was evaluated in 10 normal healthy male volunteers between 18 and 40 years of age (AT 115). Cimetidine was administered orally three times daily (q8h) as a single 400 mg dose for 8 days to establish steady-state conditions. On Day 8 sparfloxacin was administered as a single 400 mg oral dose. As shown in Figure 11, the single dose pharmacokinetics of sparfloxacin were not altered by concomitant multiple dose administration of cimetidine. Mean (CV%) AUC_{inf} values were 58.1 (20%) $\mu\text{g/ml/hr}$ following administration of sparfloxacin alone and 51.5 (34%) $\mu\text{g/ml/hr}$ following administration of sparfloxacin and cimetidine. Corresponding mean (CV%) C_{max} values were 1.95 (31%) $\mu\text{g/ml}$ and 1.65 (43%) $\mu\text{g/ml}$ respectively. Based on the results of this study, it was concluded that multiple dose administration of cimetidine does not alter the pharmacokinetics of sparfloxacin.

The ability of probenecid to affect the pharmacokinetics of sparfloxacin was assessed since probenecid has been shown to inhibit renal excretion and glucuronidation of other drugs. The effect of probenecid on the pharmacokinetics of sparfloxacin was conducted in a crossover fashion in 6 healthy male volunteers. Sparfloxacin was administered as a single 200 mg oral dose. Probenecid was administered as a 1.5 g oral dose. The mean sparfloxacin concentration-time profiles in subjects given sparfloxacin alone or with probenecid are presented in Figure 12. Mean (CV%) AUC_{inf} values were 21.1 (16%) $\mu\text{g/ml/hr}$ following administration of sparfloxacin alone and 20.1 (10%) $\mu\text{g/ml/hr}$ following administration of sparfloxacin and probenecid, respectively. Corresponding mean (CV%) C_{max} values were 0.87 (11%), and 0.81 (10%), respectively. The results of this study indicate that the pharmacokinetics of sparfloxacin were not altered by concomitant probenecid administration.

PK parameters of these studies are presented below.

Study Number	Dose (Sub.)	C_{max} ($\mu\text{g/ml}$)	T_{max} (hr)	V_d/f (L)	AUC_{inf} ($\mu\text{g/ml/hr}$)	$T_{1/2}$ (hr)	A_e (%D)	CL_p/f (L/hr)	Cl_r (L/hr)	Comments
RP-136 PO (sd) ¹	300 (n=19)	N/A	N/A	N/A	119.6(28)	7.7	N/A	33.6(34)	N/A	Theophylline alone
	PO (md) ² 100 or 200	9.08(28)	1.2 (50)	N/A	56.1(27)	N/A	N/A	32.3(26)	N/A	Theophylline + Spar
	q8h (n= 17) ³	8.99(23)	1.2 (58)	N/A	54.9(25)	N/A	N/A	33.2(25)	N/A	
AT-105 IV (sd)	176	5.87(19)	0.7(59)	35.1(23)	54.5(42)	7.1	N/A	37.6(42)	N/A	Theophylline
	(n= 10)	5.31(19)	0.7(26)	34.1(19)	53.2(36)	7.0	N/A	37.0(36)	N/A	Theophylline + Spar
RP-155 PO(md)	0.3(n=23) ⁴	3.91(24)	0.9(35)	N/A	28.4(14)	N/A	N/A	N/A	N/A	Digoxin
	q24h	3.59(23) ⁵	0.2(39)	N/A	28.9(15)	N/A	N/A	N/A	N/A	
AT-115 PO(sd)	400(n=10)	1.95(31)	3.5(49)	N/A	58.1(20)	26.2	13.0(21)	7.2(24)	0.94(21)	Sparfloxacin + placebo
		1.65(43)	4.3(70)	N/A	51.5(34)	25.5	12.3(21)	8.5(30)	0.99(24)	Cimetidine + sparfloxacin
		N/A	N/A	N/A	N/A	N/A	24.8(22)	N/A	N/A	Spar + placebo, conjugate
		N/A	N/A	N/A	N/A	N/A	23.5(26)	N/A	N/A	Spar + Cime, conjugate

1. Theophylline Alone; 2. Theophylline and Sparfloxacin; 3. Steady State Conditions; 4. Digoxin Alone; 5. Digoxin and Sparfloxacin

Figure 10

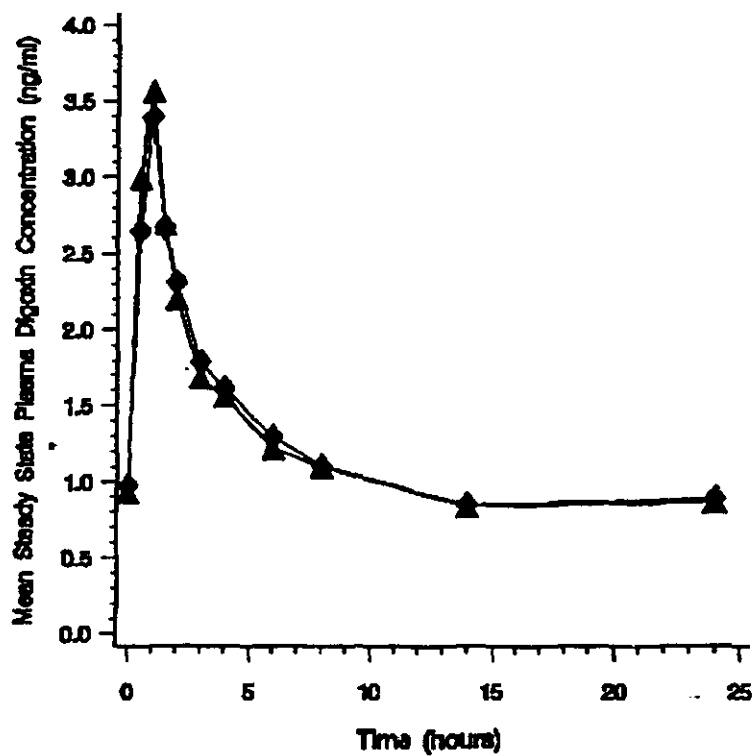


Figure 10: Mean (N=23) steady-state plasma digoxin concentrations following multiple dose administration of digoxin and sparfloxacin placebo (▲) and digoxin and active sparfloxacin (◆).

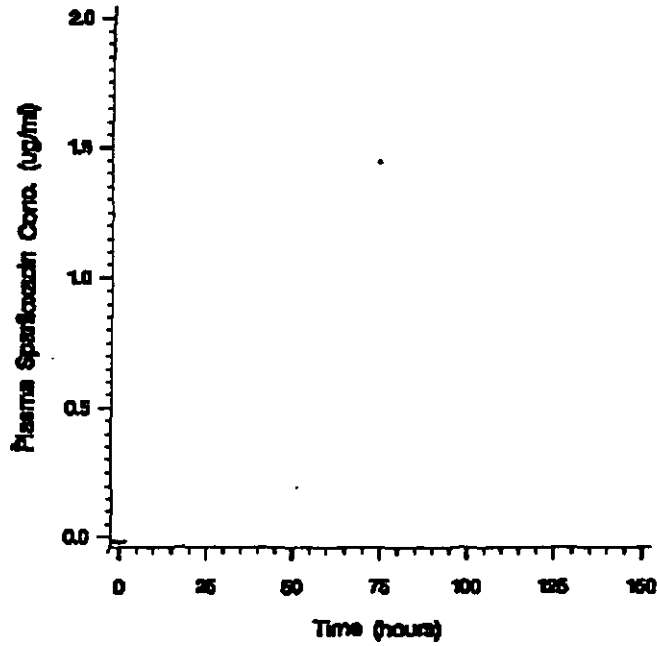


Figure 11: Mean (N=10) plasma sparfloxacin concentration-time profile following administration of sparfloxacin (■) and following administration of sparfloxacin and cimetidine (◆).

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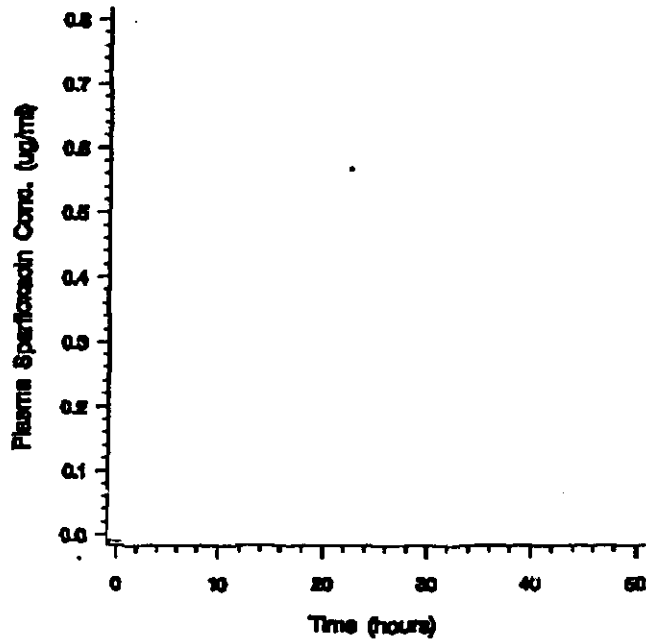


Figure 12: Mean (N=6) sparfloxacin concentration-time profile following administration of sparfloxacin alone (■) and following administration of sparfloxacin and probenecid (◆).

J. Drug-drug interaction study (continued).

b. Drug-drug interaction which primarily for pharmacodynamics with some PK data

Study #RP64206-162, AT 112, AT 113, RP64206-151

Pharmacokinetic sampling has been conducted to varying degrees in support of pharmacodynamic studies. These studies include the effect of sparfloxacin on cardiac function, the effect of sunscreens on phototoxicity, the effect of sparfloxacin on fecal flora, the effect of sparfloxacin on warfarin pharmacodynamics, and the effect of sparfloxacin on the pharmacokinetics and QTc pharmacodynamics of terfenadine. In these studies, plasma concentrations of sparfloxacin were within expected values.

In addition to the single dose cardiac safety study (RP64206-162) previously discussed in Dose Proportional Studies, sufficient plasma concentration data for a complete assessment of sparfloxacin pharmacokinetics were obtained from the study of fecal flora. The study (AT 112) to assess the effect of sparfloxacin on fecal flora was conducted in 12 normal healthy male volunteers between 21 and 49 years of age. Mean(CV%) AUC_{0-4} values were 16.4 (14%) and 18.3 (23%) $\mu\text{g/ml/hr}$ on Days 1 and 4, respectively. Corresponding mean (CV%) C_{max} values were 0.56 (23%) and 0.61 (26%) $\mu\text{g/ml}$, respectively. Mean(CV%) faeces concentration were 759.6(63%) and 671.7(70%) mg/kg on Days 1 and 4, respectively. The %eliminated via Faeces were 47.5%(63%) and 31.4%(66%) on Days 1 and 4, respectively. The mean $t_{1/2}$ value was 18.3 hours. Based on cross study comparisons, the pharmacokinetic parameters for sparfloxacin in this study were consistent with historical values at comparable doses.

The effect of multiple doses of sparfloxacin on the pharmacodynamics of warfarin was evaluated in 10 healthy male subjects between 18 and 45 years of age (AT 113). Warfarin was administered as a single 10 mg dose on Days 1 and 2 followed by a dosage adjustment if needed to maintain steady-state INR (International Normalised Ratio) values in the 1.3 to 1.7 range. The final warfarin dose was fixed at least 3 days prior to sparfloxacin administration. Sparfloxacin was administered as a single 400 mg oral loading dose on Day 11 followed by single daily 200 mg doses on Days 12 through 17. In this study, steady-state plasma sparfloxacin concentrations did not appear to alter the prothrombin time when administered in combination with warfarin. Mean values of difference between the mean steady-state INR on warfarin alone and measurements made on warfarin plus sparfloxacin are shown in the appendixes.

The effect of sparfloxacin on the QTc pharmacodynamics of terfenadine were evaluated in a parallel group safety and tolerance study (RP64206-151) using 88 normal healthy male subjects between 18 and 49 years of age. Sparfloxacin was administered as a single oral 400 mg loading dose on Day 1 followed by single 200 mg maintenance doses on Days 2 through 4. Terfenadine was administered as a 60 mg oral dose every 12 hours. Based upon limited blood samples, terfenadine was shown not to alter the pharmacokinetics of sparfloxacin. Mean (CV%) steady-state AUC_{0-24} values were 18.1(15%) $\mu\text{g/ml/hr}$ when sparfloxacin was administered alone and 18.2 (22%) $\mu\text{g/ml/hr}$ when sparfloxacin was administered with terfenadine. Corresponding mean (CV%) C_{max} values were 1.13 (22%) $\mu\text{g/ml}$ and 1.14 (21%) $\mu\text{g/ml}$, respectively. Sparfloxacin was also shown not to alter the

pharmacokinetics of terfenadine. The mean plasma concentration-time profiles are illustrated in Figure 13. Mean (CV%) steady-state AUC_{inf} values were 25.0 (69%) ng/ml/hr when terfenadine was administered alone and 22.0 (65%) ng/ml/hr when terfenadine was administered with sparfloxacin. Corresponding mean (CV%) C_{max} values were 2.42 (31%) $\mu\text{g/ml}$ and 2.69(100%) $\mu\text{g/ml}$, respectively. It was concluded that sparfloxacin and terfenadine do not affect the pharmacokinetics of each other.

At steady-state, sparfloxacin alone prolonged the mean QTc by 14 msec (placebo-adjusted change, $p = 0.002$); for terfenadine alone, a trend towards an increase was observed (7 msec, $p=0.060$). Combination treatment resulted in a placebo-adjusted increase in mean QTc of 22 msec ($P<0.001$). No QTc pharmacodynamic interaction between terfenadine and sparfloxacin was demonstrated ($p=0.946$).

PK parameters of these studies are presented at the following.

Study Number	Dose (Sub.)	C_{max} ($\mu\text{g/ml}$)	T_{max} (hr)	V_d/T (L)	AUC_{inf} ($\mu\text{g/ml/hr}$)	$T_{1/2}$ (hr)	$A_e(24)$ (%D)	$CL_{p/f}$ (L/hr)	Cl_r (L/hr)	Comments
AT-112 PO (md)	400/200	0.56(23)	3.5(26)	N/A	16.4(14)	18.3	5.9(24)	N/A	N/A	Day 1
	q24h (n=12)	0.61(26)	N/A	N/A	18.3(28)	N/A	6.58(48)	N/A	N/A	Day 8
AT-113 PO (md)	400/200	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Pharmacodynamic INR measurement are presented in the appendixes.

8. POPULATION PHARMACOKINETICS

A population pharmacokinetic analysis was conducted using plasma samples from 143 patients enrolled in Phase III clinical trials. Patients were administered a 400 mg loading dose followed by daily 200 mg maintenance doses over nine additional days. Blood samples for analysis of sparfloxacin in plasma were collected according to one of two sampling schedules at Visit 2 (Day 4+1 of treatment).

Schedule 1: Prior to (trough) and 1.5 hours following administration.

Schedule 2: 4 and 6 hours following administration.

Plasma samples were assayed for sparfloxacin using a high performance liquid chromatography method that was linear over a 0.025 to 20 $\mu\text{g/ml}$ range with a minimum quantitation limit of 0.025 $\mu\text{g/ml}$. Population pharmacokinetic modeling was performed using nonlinear mixed effect modeling (NONMEM) and Bayesian estimation.

The mixed effect model evaluated the effect of the covariates age, gender, race, body weight, body height, creatinine clearance, serum creatinine, bilirubin, and other liver function tests on the apparent volume of distribution (V) and apparent oral clearance (CL) assuming an open one compartment pharmacokinetic model. The well observed distribution of these covariables are shown in the appendixes.

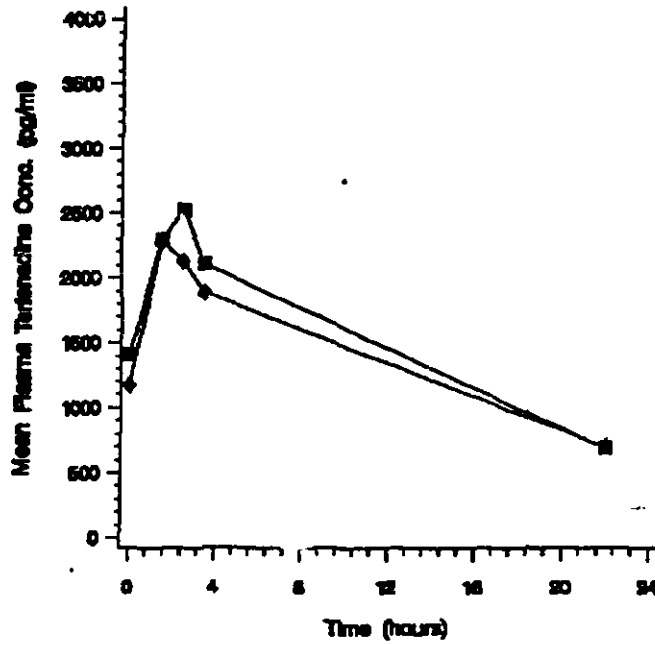


Figure 13: Mean (N=22) plasma terfenadine concentration-time profiles following administration of terfenadine (◆) and following administration of terfenadine and sparfloxacin (■).

Intersubject variability in CL and V was best modeled with a proportional error model as follows:

$$Cl_j = CL * \exp(\eta_{jCL})$$

$$V_j = V * \exp(\eta_{jV})$$

where η_{jCL} and η_{jV} are normally distributed random variables with a mean of zero and variances of ω^2_{CL} and ω^2_V . Cl_j and V_j are the predicted oral clearance and volume of distribution of the j th individual and CL and V are the population mean values. The exponential form of the proportional error model was used so that individual estimates of CL and V would be properly constrained to be positive. The residual variability was also best modeled with a proportional error model:

$$C_{ij} = Cm_{ij} * (1 + \epsilon_{ij})$$

where Cm_{ij} is the i th model predicted plasma concentration of the j th individual and ϵ_{ij} is a normally distributed random variable which describes the residual variability.

The final population pharmacokinetic model was developed using stepwise regression to determine the relationship between the covariates and CL and V. During the development of the base model, the intersubject variability term for absorption rate constant (k_a) was removed. Creatinine clearance (CLcr) was the only significant covariate that remained in the final model for CL and was:

$$CL \text{ (L/hr)} = 0.206 * CLcr, \text{ for conditions that } CLcr < 80 \text{ ml/min}$$

$$CL \text{ (L/hr)} = 16.6, \text{ for conditions that } CLcr \geq 80 \text{ ml / min}$$

Body weight (BW) was the only significant covariate that remained in the model for V and was:

$$V \text{ (L)} = 120 + 2.48 * BW, \text{ where BW in units of Kg.}$$

In conclusion, the addition of these covariates in the model explained more of the variability in the pharmacokinetic parameters and caused a 5.3% reduction of the intersubject variability on CL and a 14.1% reduction of the intersubject variability on V, from 97% to 83%.

Dr. Ette also reviewed this population pharmacokinetics portion. His comment is incorporated in specific comment #17.

VI. DISSOLUTION TESTS

Dissolution tests were conducted along the formulation development process. USP method 2 (50 rpm, paddle method) with 900 ml pH 4.0 acetate buffer at 37°C was applied. Samples were collected at 5, 15, and 30 minutes. The to-be marketed formulation, sparfloxacin 200mg, lot #9411419, dissolves 96-99% ($97.4 \pm 11\%$) during these times.

The proposed dissolution specification is that NLT 70% of the label amount of sparfloxacin is dissolved in 30 minutes.

VI. SPECIFIC COMMENTS

1. Study RP64206-164 demonstrated the bioequivalence between the to be marketed formulation (Modified RPR Nenagh, Lot # 9411419) vs. the clinical trial formulation (Lot # 9308817), the study is acceptable.
2. The four other bioequivalence studies (RP64206-169, CI 978-15, CI 978-18, and CI 978-19) are acceptable. However, they were conducted during the development process, and are less related to the current submission.
3. All dose proportionality studies (RP64206-162, AT 121, AT 101) used formulations other than the to be marketed formulation. The study results may not represent the exact situation of the to be marketed formulation. However, they covered a large dose range (up to 1600 mg), and are acceptable to support the dose proportionality of the drug absorption. Since drug elimination is formulation independent, the conclusion of linear elimination kinetics derived from these studies are acceptable.

Regression analyses were conducted for data submitted. The results are presented in appendixes.

4. Study RP64206-161 shows the drug has an absolute bioavailability of 90% and is acceptable. Information is also included in the drug labeling.
5. RP64206-157 used the to be marketed formulation for determining food effect on sparfloxacin absorption. The study is acceptable. Study AT-107 used the CB3976 Batch that is not acceptable directly to support the food effect of the formulation, but the data can be accepted to support the results of RP64206-157.
6. In studying the effect of Mg and Al on sparfloxacin absorption, the sponsor determined timing factors of co-administration of Maalox, and stated that Maalox should be given at least 4 hours after the administration of sparfloxacin. The study results and statement are acceptable (see COMMENTS ON LABELING below).
7. All tissue distribution/penetration studies, studies #AT 120, AT 124, AT 127, AT 123, AT 128, AT 133, AT 135, and AT 136, were conducted in the years of 1990-1992 in Europe. Although the formulations used were different from the to-be-marketed formulation, these studies are acceptable because tissue distribution is drug dependent rather than formulation dependent. Sparfloxacin concentration in most tissues exceeds the MIC₉₀ for most relevant pathogens.
8. Studies #AT 122, AT 111/139, AT 138, and AT 106 were conducted in Europe and Japan for determining drug metabolism and excretion. The assay methods used — HPLC with MS and H-nuclear magnetic resonance spectrometry, and ¹⁴C-radioactivity, are acceptable. The results of these studies are acceptable.

9. The $t_{1/2}$ of the drug varies largely between subjects. However, as shown in the population pharmacokinetic study, the CL of the drug among patients with normal renal function ($Cl_{cr} > 80 \text{ ml/min}$) are consistent. Therefore, the large variation in $t_{1/2}$ may be due to the large difference in Vd (variability is 83% in population PK study) which is a dependent variable of TBW.

The conclusions regarding linear elimination kinetics for both (1) single dose from 200mg to 1600mg condition, and (2) multiple dose condition, are acceptable.

10. Studies AT 103, AT 104, AT 116, AT 110, AT 108, AT 121 and RP64206-159, special population pharmacokinetics, are acceptable. Methods used in data analysis are relevant and supportive.
11. Drug interaction studies, #RP64206-156, AT 114, RP64206-155, AT 115, and AT 105 concentrate on the effect of sparfloxacin on other model drugs. These studies are important, especially about the effect on the QTc intervals. Dose and dose regimen used, subjects selection and PK/PD measurement are relevant and acceptable.
12. The effect of sparfloxacin prolongation QTc interval is a big concern. Data presented in the Biopharmaceutics Section of this submission (RP64206-162, AT 112, AT 113, RP64206-151) shows that the increase of QTc intervals after the administration of sparfloxacin (400/200 mg multiple dose) is small (3.5% or 16 msec) and within the upper limit of normal values.
13. Overviews all the studies in which adverse effect and safety were evaluated, two subjects were withdrawn from these studies due to serious side effect. Although the rate of withdrawal from specific Biopharmaceutics studies was high (about 1 to 3 subjects withdraw from many European studies of 10 to 36 subjects included), the reasons for withdrawal were limited due to personal reasons, protocol violations, or the co-administration of other medication in drug-drug interaction studies. This finding may be of interest to the Medical Officer.
14. Phototoxicity effect was checked with caution during the review. At most times, this side effect is mild or moderate. The rate of occurrence is significantly increased when dose exceeded 600 mg while minimum at 200 mg dose level. After 400mg single dose, nearly all subjects have various degree of phototoxicity. In these 46 studies, phototoxicity caused one subject to withdraw from one study (CI 978-1). This finding should be also examined by the medical officer.
15. The conclusion that sparfloxacin was not different between males and females is well supported by study RP64206-162, the population pharmacokinetic study, and some other study data.
16. The 200mg sparfloxacin tablet is manufactured by a standard dry compaction granulation and compression into tablet cores and coating with aqueous suspension. A fast dissolution is

expected. Data presented show that, at 5 min, the amount dissolved reaches a mean of 96%. It is recommended that the sponsor use USP apparatus 2 at 50 rpm. The tablet should dissolve NLT 90% (Q) at 15 minutes in 900 ml acetate buffer, pH 4.0.

17. Although the individual concentration were well predicted as checked by Dr. Ette, the sponsor did not test the predictive performance of the population model developed. The sponsor is encouraged to conduct such predictive testing in the future. This is of great importance because of the exploratory nature of the technique. (Incorporated from Dr. Ette's comments)

VII. COMMENTS ON LABELING

In patient package Insert:


10/25/96

He Sun, Ph.D.

Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D.



cc:

NDA 20,677

HFD-520. (Clinical)

✓ HFD-880. (DPE III, Pelsor, Sun)

HFD-340. (Viswanathan)

✓ HFD-870. Drug File (Clarence Bott, PKLN Rm. 13B-31)

APPENDIX 1.

1. INVESTIGATIONAL FORMULATIONS

The development of Sparfloxacin 200 mg tablets was initiated by

After entering into a joint-venture with in the United States, clinical and market image formulation development was begun by in August 1989. Originally, 25mg, 100mg, and 200mg tablets were developed for use in clinical trials. These formulations were based on the Japanese formulations, with a few minor changes to incorporate domestic ingredients to conform to USP/NF standards.

Dainippon had entered a joint venture with Rhone-Poulenc S.A. to develop Sparfloxacin in Europe. In the merger between Rhone-Poulenc and Rorer, the joint venture became a part of RPR. By the time handed the development of the market image formulation to RPR-US, the European joint venture (Rhone had completed the development of their product. A decision was made within RPR to use one worldwide market image and product globally. A bioequivalence trial was undertaken, and the Rhone- formula was found to be bio-inequivalent to the product.

Rhone- formulators investigated two dry processes: direct compression and dry granulation using roller compaction. Development efforts were initiated to modify the existing compaction process in order to produce tablets more closely mimicking the dissolution profile.

Three batches were prepared at 130 Kg (intended production batch size) at the intended commercial facility in Nenagh, Ireland using the compaction parameters. The remainder of the manufacturing process, i.e., blending, compression, coating, were not changed from the process currently being run at Nenagh. No difficulties were encountered in the preparation of these three batches. All three batches were placed on stability, and to date, no changes have been reported. Material from the first commercial scale batch (RP 64206/05-1A-1, Nenagh #08151) was used in a bioequivalence trial, with favorable results.

A table listing the clinical trial number, drug product lot number and dosage form and strength is provided in 3, INVESTIGATIONAL FORMULATIONS, on page 4.

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APPENDIX III

DISSOLUTION TESTING

Table 2.1. DRUG PRODUCT DISSOLUTION TESTING

Date of Test	Dosage Form and Strength	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation/Flow	Collection Times	Units Tested/ Range/Mean % Dissolved/% CV
12/19/89	100 mg tablet	WFTA 0204A	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range: 98.1% - 99.1% mean: 98% %CV 4.7 %
12/19/89	100 mg tablet	WFTA 0208A	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range: 100.1% - 101.1% mean: 101% %CV 0.8 %
1/23/90	100 mg tablet	WFTA 0209A	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range: 98.1% - 99.1% mean: 99% %CV 0.8 %
5/18/90	100 mg tablet	XFTA 0212A	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range: 100.1% - 101.1% mean: 101% %CV 1.6 %
7/3/91	100 mg tablet	YFTA 0228A	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range: 98.1% - 99.1% mean: 99% %CV 1.3 %
2/24/92	100 mg tablet	ZFTA 0240A	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range: 99.1% - 100.1% mean: 100% %CV 2.2 %

Table 2.2. DRUG PRODUCT DISSOLUTION TESTING

Date of Test	Dosage Form and Strength	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation/Flow	Collection Times	Units Tested/ Range/Mean % Dissolved/% CV
3/21/91	100 mg	CM 027021	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range % mean: 101% %CV 1.7%
3/21/91	100 mg	CM 028021	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range % mean: 100% %CV 1.4%
11/16/89	100 mg	CM 323109	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range % mean: 101% %CV 1.4%
11/16/89	200 mg	CM 324109	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range % mean: 102% %CV 1.2%
5/13/92	100 mg	CM 0550392	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range % mean: 103% %CV (NR)
5/12/92	200 mg	CM 0560392	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range % mean: 102% %CV 1.0%

Table 2.3. DRUG PRODUCT DISSOLUTION TESTING

Date of Test	Dosage Form and Strength	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation/Flow	Collection Times	Units Tested/ Range/Mean % Dissolved/% CV
7/17/92	200 mg	CM 0980692	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range mean 103% %CV 0.9%
2/22/93	200 mg	CM 0030193	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=12 range mean 102% %CV 1.0%
	200 mg	9403094	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	mean 99.4%
11/14/94	200 mg	9411419	paddle	pH 4.0 Acetate buffer / 37 °C	50 rpm	min	n=6 range mean 97.4% %CV 1.1%

APPENDIX IV

INDIVIDUAL STUDIES

18 Pages

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Individual data

APPENDIX V

DRUG LABELING

26 Pages
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Draft Labeling

TABULATED SUMMARY REPORT

Title of study (Phase):	An Open-Label, Two-Way, Randomized, Crossover Study of the Absolute Oral Bioavailability of Sparfloxacin in Healthy Male Subjects, Protocol RP 64206X-161 (Phase I)
Investigator:	
Publication (reference):	None
Study period:	First Subject Treated: 11 March, 1995 Last Subject Discharged: 29 March 1995
Study center:	
Objectives:	To determine the absolute bioavailability of sparfloxacin following administration of a single 200-mg tablet.
Methodology:	This single-dose, open-label, randomized, two-way crossover study was conducted at a single study center. Treatments consisted of a single 4-hour constant rate (50 mg/hr) intravenous (IV) infusion of sparfloxacin (Treatment A) and a single 200-mg oral market-image sparfloxacin tablet (Treatment B), both following at least a 10-hour overnight fast. Subjects were randomized into one of two treatment sequence groups, as follows: Sequence Group 1: A, B Sequence Group 2: B, A
Number of subjects:	12 enrolled, 12 completed all study procedures.
Diagnosis and criteria for entry:	Healthy, adult, nonsmoking, male volunteers between the ages of 18 and 45 years with normal screening physical and laboratory examinations and electrocardiograms (ECGs) were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200-mg oral dose tablets, modified Nenagh process, manufactured by Rhône-Poulenc Rorer Lot number: 9411419
Duration of treatment:	Single dose in each of two periods (14-day washout interval between periods).
Reference therapy: dose, route of administration, lot number:	Sparfloxacin IV infusion 200 mg (50 mg/hr) 250 mg/5-mL vials, manufactured by Rhône-Poulenc Rorer Lot number: 64206/08-1A-1
Safety measurements:	Vital signs, adverse events, physical examinations, 12-lead ECG, telemetry, and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis).
Pharmacokinetic parameters:	Area under the plasma sparfloxacin concentration-time curve ($AUC(0-\infty)$), maximum plasma concentration (C_{max}) and the time at which it occurred relative to the administered oral dose (T_{max}), half-life ($t_{1/2}$), volume of distribution (V_{dss}), total body clearance (Cl), and absolute oral bioavailability (F).
Statistical methods:	Pharmacokinetic data were summarized by the use of descriptive statistics.
Results:	Safety and Tolerance: No adverse clinical experiences were reported for any subject, and no subject was discontinued from the study due to an adverse laboratory experience. Evaluation of physical examination, vital sign, ECG, telemetry, and clinical laboratory data revealed no differences between oral and IV sparfloxacin. One subject in the oral/IV sequence group experienced a transient increase in ALT/SGPT and AST/SGOT values following administration of sparfloxacin IV (reported as adverse laboratory experiences with a possible relationship to study drug). Pharmacokinetics: The plasma sparfloxacin concentration-time profiles following IV and oral administration were virtually superimposable at most sampling time points, with the exception of the mean C_{max} value, which was 33% higher at the time of termination of the infusion compared to the value obtained following oral administration. The mean absolute oral bioavailability was 90%.
Conclusions:	• A 200 mg sparfloxacin dose was well tolerated when administered intravenously and orally. • Sparfloxacin is absorbed well following oral administration of the market-image tablet, as evidenced by the 90% mean absolute oral bioavailability.

RP 161

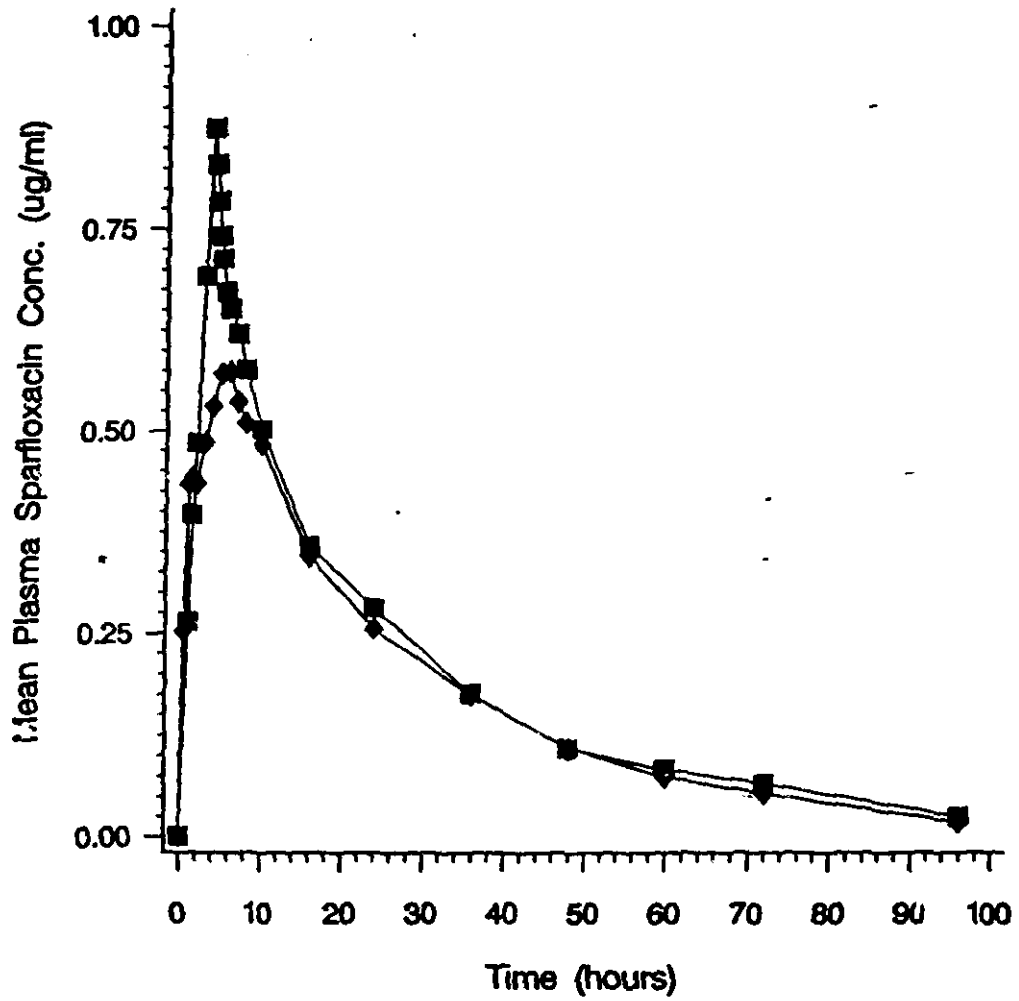


Figure 1. Mean Plasma Sparfloxacin Concentration-Time Profile Following a 4-Hour Intravenous Infusion of 200 mg of Sparfloxacin at a Rate of 50 mg/hour (■) and following a single oral 200 mg dose (◆).

RP161

NDA 28-677

3 OF 8

TABULATED SUMMARY REPORT

Title of study (Phase):	An Open-Label, Three-Way Crossover Study with Repeated Measures to Assess the Bioequivalence of Two Sparfloxacin Formulations in Healthy Volunteers, Protocol RP 64206X-160 (Phase I).
Investigator:	
Publication (reference):	None
Study period:	First Subject Treated: May 1, 1994 Last Subject Discharged: June 9, 1994
Study center:	
Objectives:	To assess the bioequivalence of the Nenagh production tablets relative to the ~~reference~~ tablets used in clinical studies.
Methodology:	This bioequivalence study was conducted as a randomized, open-label, three-way crossover, single-center study with a repeated measures component. Treatments consisted of a single 200-mg oral dose of sparfloxacin (1 x 200 mg tablets) manufactured by direct compression at Nenagh (Treatment A) and a single 200-mg oral dose of sparfloxacin (1 x 200 mg tablets) manufactured by wet granulation by ~~reference~~ (Treatment B). Subjects were randomized into one of two treatment sequence groups, as follows: Sequence Group 1: A, B, B Sequence Group 2: B, A, A
Number of subjects:	27 enrolled; 26 completed all study procedures.
Diagnosis and criteria for entry:	Healthy adult non-smoking male volunteers between the ages of 18 to 45 years with normal screening physical and laboratory examinations and electrocardiograms (ECGs) were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200 mg tablets, manufactured by Rhône-Poulenc Rorer at the Nenagh, Ireland facility. Oral Lot number: 9403094
Duration of treatment:	Single dose in each of three crossover periods (14-day washout interval between study periods).
Reference therapy: dose, route of administration, lot number:	Sparfloxacin 200 mg tablets, manufactured by ~~reference~~ Oral Lot number: 9308817
Safety measurements:	Vital signs, adverse events, physical examinations, 12-lead ECG, and clinical laboratory evaluations (hematology, blood chemistry and urinalysis).
Pharmacokinetics parameters:	Area under the plasma sparfloxacin concentration-time curve (AUC(0-∞)), maximum plasma concentration (C _{max}) and the time at which it occurred relative to the administered dose (T _{max}), terminal elimination rate constant (k _{term}), and half-life (t _{1/2}).
Statistical methods:	An analysis of variance (ANOVA) for repeated measures was used to test for differences in the test means (Nenagh) for each pharmacokinetic parameter compared to the reference means (~~reference~~) at an alpha level of 0.05. Ninety percent confidence intervals calculated from a two one-sided test were determined from natural logarithmically (ln) transformed data for AUC(0-∞) and C _{max} values. The Wilcoxon signed rank test was used to test for differences in T _{max} .

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Results:	Safety and Tolerances: Sparfloxacin appears to be absorbed to a greater extent from the Nenagh tablets. A similar proportion of subjects reported adverse clinical experiences while receiving the [redacted] and Nenagh tablets of sparfloxacin. The most frequently reported AE (COSTART Term) during administration of the [redacted] tablets was headache (four reports), and during administration of the Nenagh tablets was syncope (vasovagal episode, three reports). None of the adverse events was considered serious or rated as severe in intensity. No subject discontinued from the study due to an adverse clinical or laboratory experience. Pharmacokinetics: Sparfloxacin was absorbed to a greater extent from the Nenagh tablets. The mean AUC(0-∞) and Cmax values following administration of the Nenagh tablets were 9.5% and 7.0% higher than the corresponding mean values following administration of the [redacted] tablets. Results of ANOVA showed a significant treatment effect for AUC(0-∞) (p=0.0464) and Cmax (p=0.0495). Ninety percent confidence intervals for ln transformed data demonstrated that, although AUC results met the criteria for bioequivalence (confidence limits = 101.6% to 117.4%), the Nenagh tablets were not bioequivalent to the [redacted] tablets with respect to Cmax (confidence limits = 102.3% to 127.9%). Mean Tmax and t1/2 values were virtually identical for both tablets, indicating no difference in the rates of absorption and elimination between the treatments.
Conclusions:	• Both sparfloxacin tablets were well tolerated. • Sparfloxacin tablets manufactured by direct compression (Nenagh) are not bioequivalent by the most strict definition to those manufactured by the wet granulation process [redacted]. • There is no difference in the rates of absorption or elimination between the two tablets.

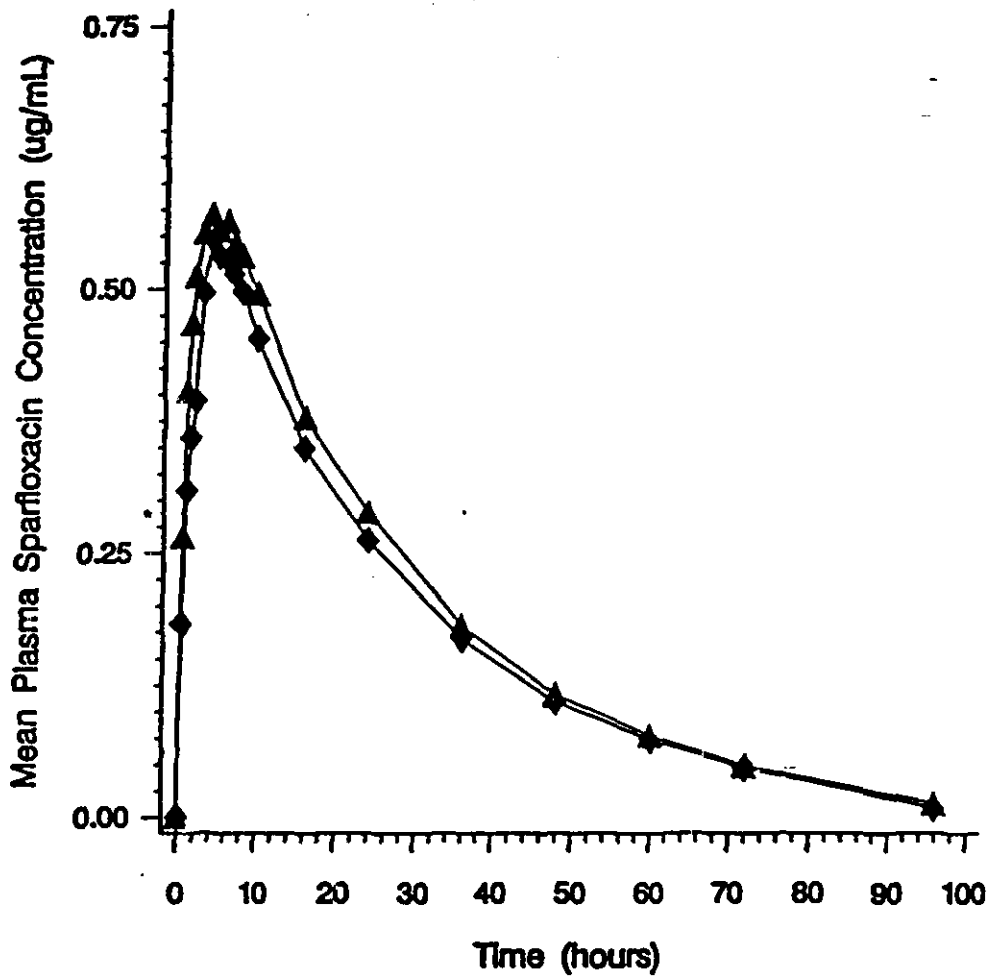


Figure 3. Mean Plasma Sparfloxacin Concentrations Following Single Dose Administration of 200 mg of Sparfloxacin Tablets Manufactured by Nenagh (▲) and Parke-Davis (◆). Excluding Subject [REDACTED]

RP160

TABULATED SUMMARY REPORT	
Title of study (Phase):	An Open-Label, Three-Way Crossover Study to Assess the Bioequivalence of Three Sparfloxacin Formulations in Healthy Volunteers, Protocol RP 64206X-164 (Phase I)
Investigator:	
Publication (reference):	None
Study period:	First Subject Treated: December 3, 1994 Last Subject Discharged: January 1, 1995
Study center:	
Objectives:	To assess the bioequivalence of tablets from two Nenagh production batches (original and modified) relative to the Parke-Davis tablets used in clinical trials.
Methodology:	This bioequivalence study was conducted as a randomized, open-label, three-way crossover, single-center study. Treatments consisted of a single 200-mg oral dose of sparfloxacin (1 x 200 mg tablet) manufactured by [redacted] (Treatment A), manufactured by the original process at RPR's Nenagh, Ireland facility (Treatment B), and manufactured by a modified process at Nenagh (Treatment C). Subjects were randomized into one of six treatment-sequence groups, as follows: Sequence Group 1: B, A, C Sequence Group 2: A, C, B Sequence Group 3: C, B, A Sequence Group 4: B, C, A Sequence Group 5: C, A, B Sequence Group 6: A, B, C
Number of subjects:	29 enrolled, 27 completed all study procedures.
Diagnosis and criteria for entry:	Healthy, adult, nonsmoking, male volunteers between the ages of 18 and 45 years with normal screening physical and laboratory examinations and electrocardiograms (ECGs) were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200 mg tablets, manufactured by Rhone-Poulenc Rorer at the Nenagh, Ireland facility (original and modified) Oral Lot numbers: 9403094 (original) and 9411419 (modified)
Duration of treatment:	Single dose in each of three crossover periods (minimum 10-day washout interval between study periods).
Reference therapy: dose, route of administration, lot number:	Sparfloxacin 200 mg tablets, manufactured by [redacted] Oral Lot number: 9308817
Safety measurements:	Vital signs, adverse events, physical examinations, 12-lead ECG, and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis).
Pharmacokinetics parameters:	Area under the plasma sparfloxacin concentration-time curve (AUC(0-∞)), maximum plasma concentration (C _{max}) and the time at which it occurred relative to the administered dose (T _{max}), terminal elimination rate constant (k _{term}), and half-life (t _{1/2}).
Statistical methods:	An analysis of variance (ANOVA) was used to test for differences in the test means (original and modified processes at the Nenagh facility) for each pharmacokinetic parameter compared to the reference means [redacted] at an alpha level of 0.05. Ninety percent confidence intervals calculated from a two one-sided test were determined from natural logarithmically (ln) transformed data for AUC(0-∞) and C _{max} values. The Wilcoxon signed rank test was used to test for differences in T _{max} .
Results:	Safety and Tolerance: All three sparfloxacin tablets were well tolerated. The most frequently reported adverse event was infection (one subject following treatment with the [redacted] tablet, two subjects following treatment with the original Nenagh tablets and one subject following treatment with the modified Nenagh tablets). All of the adverse experiences were mild in intensity with the

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TABULATED SUMMARY REPORT

	exception of severe cholecystitis. Two subjects discontinued from the study due to an adverse clinical experience (severe cholecystitis and mild hypertension, both considered unrelated to study drug). No subject discontinued from the study due to an adverse laboratory experience. All AEs were considered to have no relationship or only a remote relationship to study drug by the investigator. <u>Pharmacokinetics:</u> The market image sparfloxacin tablet manufactured using the modified Nenagh process was bioequivalent to the [redacted] tablet used in clinical trials with respect to both AUC(0-∞) and C_{max}. Confidence intervals comparing the original Nenagh and [redacted] tablets were not within the 80% to 125% range for C_{max}.
Conclusions:	• All three sparfloxacin tablets were well tolerated. • The market image sparfloxacin tablet manufactured using the modified Nenagh process was bioequivalent to the [redacted] tablet used in clinical trials with respect to both AUC(0-∞) and C_{max}.

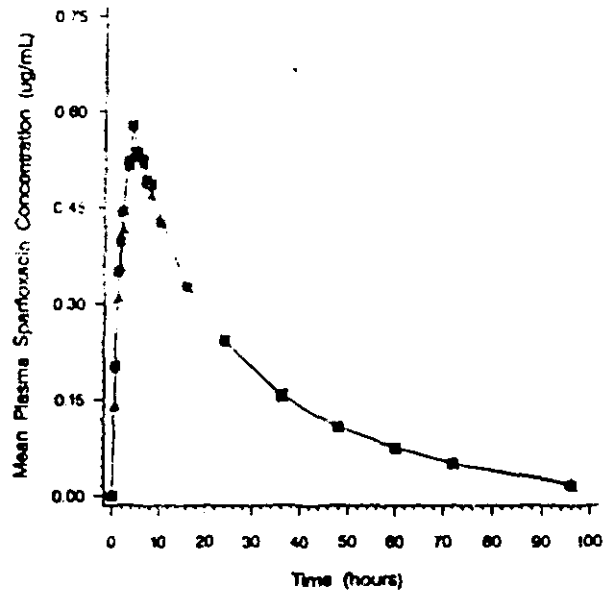
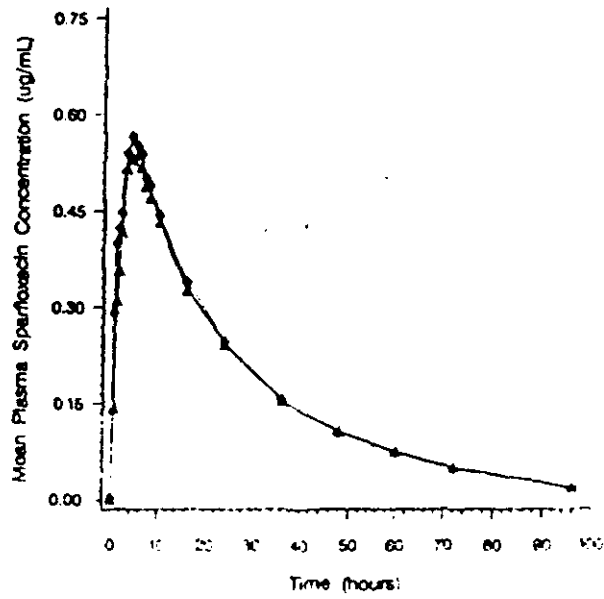


Figure 3 Mean plasma sparfloxacin concentrations following a single 200 mg oral sparfloxacin dose from the original tablets (▲) and original Nenagh process tablets (◆) (top), original tablets (▲) and modified Nenagh process tablets (■) (bottom) Excluding Subject

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TABULATED SUMMARY REPORT

Title of study (Phase):	Double-Blind, Randomized, Ascending-Dose with Parallel Placebo Group, Study of the Safety, Tolerance, and Electrocardiographic (ECG) Pharmacodynamics of Sparfloxacin Given as Single Doses of 400, 800, 1200, and 1600 mg in Healthy, Male and Female Subjects, Protocol RP 64206 (-162) (Phase I)
Investigator:	
Publication (reference):	None
Study period:	First Subject Treated: November 22, 1994 Last Subject Discharged: February 1, 1995
Study center:	
Objectives:	- Define the safety, tolerance, and ECG pharmacodynamics of sparfloxacin at up to four-fold the usual therapeutic loading dose of 400 mg (i.e., single dose of 1600 mg). - Delineate the QTc effect of sparfloxacin at the highest dose. - Determine, within the constraints of sample size, if there is a difference in QTc effect between males and females at the highest dose. - Assess the amount of dispersion of ventricular repolarization, if any, at the highest dose. - Confirm a direct dose- and/or plasma concentration-QTc response relationship. - Assess the QTc effect of sparfloxacin re-administration in subjects experiencing a QTc interval increase from baseline of ≥ 75 msec. or $\geq 20\%$.
Methodology:	This double-blind, randomized, placebo-controlled, five-period, ascending-dose study was conducted at a single center. Treatments consisted of single doses of 400, 800, 1200, and 1600 mg of oral sparfloxacin (2 x 200 mg, 4 x 200 mg, 6 x 200 mg, and 8 x 200 mg tablet, respectively). Subjects were stratified by gender and assigned randomly (4:1 ratio, sparfloxacin : placebo) to one of two treatment sequence groups, as follows: Sequence Group 1 (N = 23): 400 mg, 800 mg, 1200 mg, 1600 mg, Rechallenge at the lowest dose that induced QTc increase ≥ 75 msec. or $\geq 20\%$ Sequence Group 2 (N = 6): Placebo (P x 2; tablet number matched to active), P x 4, P x 6, P x 8, Rechallenge as above
Number of subjects:	29 enrolled (15 males, 14 females), 27 completed the study.
Diagnosis and criteria for entry:	Healthy, adult, male and nonpregnant/nonlactating female volunteers between the ages of 18 and 50 years with normal screening physical and laboratory examinations and ECGs were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200 mg tablets, manufactured by Oral Lot number: 9408311
Duration of treatment:	Single dose in each of four or five study periods (14-day washout interval between study periods).
Reference therapy: dose, route of administration, lot number:	Placebo tablets, manufactured by Oral Lot number: 9308816
Safety measurements:	Vital signs, adverse experiences, physical examinations, 12-lead ECG, Holter monitoring, and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis).
Pharmacokinetics parameters:	Area under the plasma sparfloxacin concentration-time curve (AUC(0- ∞)), maximum plasma concentration (C _{max}) and the time at which it occurred relative to the administered dose (T _{max}), terminal elimination rate constant (k _{term}), elimination half-life (t _{1/2}), as well as dose-normalized AUC(0- ∞) (nAUC(0- ∞)) and C _{max} (nC _{max}).

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TABULATED SUMMARY REPORT

Statistical methods:

ECG Pharmacodynamics:

Ninety-five percent (95%) confidence intervals around the QTc means were determined for each dose level (all subjects regardless of gender) and for each dose level stratified by gender. To assess whether baseline (Period 1) QTc values were re-established for Periods 2-5, a two-way analysis of variance (ANOVA) model was used to compare each period's predose value to the Period 1 predose value. An absence of treatment effect in this model would indicate that the -0.5 hour, Period 1 QTc value could be used as the baseline value for all study periods. Subsequently, one-sided treatment contrasts were constructed from two-way ANOVA models for the mean and maximum changes in QTc (up to 14 hours post-dose) for each study period. The main effects model contained a gender variable; an interaction model was also run in which a treatment-by-gender interaction term was included. Similar models were constructed for dispersion of ventricular repolarization. Finally, to assess the pharmacodynamic relationship between QTc and both dose level and pharmacokinetic parameters, regression of mean and maximum change in QTc on sparfloxacin dose, plasma AUC(0-∞) and plasma Cmax were prepared for each subject at each dose level, and the mean regression slope tested for the null hypothesis of a mean slope equal to zero.

Pharmacokinetics:

Linear regression of nAUC(0-∞) and nCmax as a function of the administered dose was performed by PROC REG within SAS. Dose proportionality was assessed by testing the hypothesis that the slope of the regression was equal to zero at an alpha level of 0.05.

Results:

Safety and Tolerance:

The proportion of subjects reporting adverse clinical experiences at sparfloxacin doses of 1200 and 1600 mg (47.8% and 50.0%, respectively) was higher than that observed in subjects receiving 400 and 800 mg (21.7% at each dose level). Four of the six placebo subjects reported one or more adverse clinical experiences. The most frequently reported adverse clinical experiences among sparfloxacin subjects were nausea and dizziness; among placebo subjects, nausea was the most frequently reported adverse clinical experience. All adverse experiences were mild or moderate in intensity, with the exception of a serious adverse experience of severe cholecystitis with no relationship to study drug, which resulted in premature discontinuation of a sparfloxacin subject. No subject discontinued from the study due to an adverse laboratory experience.

ECG Pharmacodynamics:

Mean baseline QTc intervals were not significantly different across all study periods. Accordingly, the pre-treatment QTc value for Study Period 1 was employed as the baseline value for analyses for all study periods. QTc interval changes on treatment are summarized below:

TABULATED SUMMARY REPORT

Results (Continued):

ECG and Holter Measurements (Continued):

QTc Variable	Study Periods			
	1 (400 mg)	2 (800 mg)	3 (1200 mg)	4 (1600 mg)
Mean Change From Baseline (msec) (S.E.)	21 (3)	35 (4)	45 (5)	47 (5)
Placebo-Adjusted Mean Change from Baseline (msec) (S.E.)	16 (7)	33 (9)	49 (11)	55 (11)
Maximum Change From Baseline (msec) (S.E.)	37 (4)	50 (8)	62 (5)	65 (6)
Placebo-Adjusted Maximum Change from Baseline (msec) (S.E.)	16 (8)	29 (11)	51 (12)	59 (12)

S. E. = Standard Error

For each of Study Periods 1 to 4, the mean QTc change and the maximum change for the sparfloxacin treatment group were significantly different from those for the placebo group. Gender was not significantly associated with QTc effect nor was there a gender-by-treatment interaction.

Pre-treatment values for dispersion of ventricular repolarization (hereinafter dispersion) for each study period were similar, such that the Period 1 pre-treatment value for dispersion was used as a baseline for all subsequent calculations. At baseline for Study Period 1, subjects in the placebo group demonstrated mean dispersion of 36 msec, whereas those in the sparfloxacin group had mean dispersion of 34 msec. For Study Periods 1-4, the mean and/or maximum change in dispersion for sparfloxacin subjects was somewhat greater than that for subjects in the placebo group (range in mean maximum difference: 2-16 msec). No consistent statistically significant treatment effect was demonstrated nor were the changes judged clinically relevant by the investigator.

Regression of mean and maximum change in QTc on sparfloxacin dose, plasma AUC(0-∞), and plasma Cmax demonstrated that for dose and AUC, the mean regression slope decreased as the dose level increased: the mean slope for the two highest dose levels was not significantly different from zero. For Cmax, the mean slope remained significantly different from zero at these dose levels.

Of the 23 sparfloxacin subjects, two, zero, one and four were rechallenged at 400, 800, 1200, and 1600 mg, respectively. One of six subjects who received placebo was rechallenged. The mean absolute QTc values and maximum change from baseline (Study Period 1) were similar for the initial and rechallenge periods for all rechallenged subjects.

Pharmacokinetics: Mean (%CV) pharmacokinetic parameters were as follows:

TABULATED SUMMARY REPORT

Results (Continued)

Pharmacokinetics (Continued)

Parameter	Sparfloxacin Dose (mg)			
	400 (N = 23)	800 (N = 23)	1200 (N = 22)	1600 (N = 21)
AUC _{0-∞} (µg/ml·hr)	32.151 (28.6)	65.864 (30.0)	93.951 (31.1)	116.23 (33.0)
C _{max} (µg/mL)	1.414 (33.5)	2.391 (27.1)	3.139 (38.5)	3.778 (35.9)
T _{max} (hr)	3.4 (42.3)	5.4 (87.8)	5.3 (51.7)	5.6 (58.8)
k _{elim} (hr ⁻¹)	0.0433 (20.2)	0.0413 (17.8)	0.0377 (22.9)	0.0368 (20.9)
t _{1/2} (hr)	16.0	16.8	18.4	18.8

Sparfloxacin demonstrated dose-proportional increases for AUC(0-∞), but not C_{max}, at doses up to 1600 mg, suggesting some rate-limited oral absorption at high doses that did not affect the extent of absorption. Mean T_{max} values tended to increase with increasing dose. The t_{1/2} increased slightly with increasing dose. Mean AUC(0-∞) and C_{max} values were higher for females than for males; gender differences were explained by differences in body weight.

Conclusions:

- Sparfloxacin doses up to four-fold the usual therapeutic loading dose were generally well tolerated; however, gastrointestinal and nervous system tolerances at three-fold and four-fold the therapeutic loading dose were less favorable than those observed at lower doses.
- Sparfloxacin demonstrated dose-proportional increases for AUC(0-∞), but not C_{max}, at doses up to 1600 mg, suggesting some rate-limited oral absorption at high doses that did not affect the extent of absorption. No gender differences were observed in C_{max} and AUC(0-∞), other than those explained by differences in body weight.
- Subjects demonstrated less than dose-proportional increases in QTc interval, with a similar QTc effect seen in subjects receiving the 1200 mg and 1600 mg doses. Regression analyses indicated that the QTc pharmacodynamic effect at the two higher doses correlated better with plasma C_{max} than with dose level or plasma AUC(0-∞).
- No consistent treatment effect was demonstrated for dispersion of ventricular repolarization. No clinically relevant changes (mean absolute and maximum) in dispersion of ventricular repolarization were observed in either the sparfloxacin or the placebo group.
- No gender effect or treatment-by-gender interaction was demonstrated for either QTc change or dispersion of ventricular repolarization.

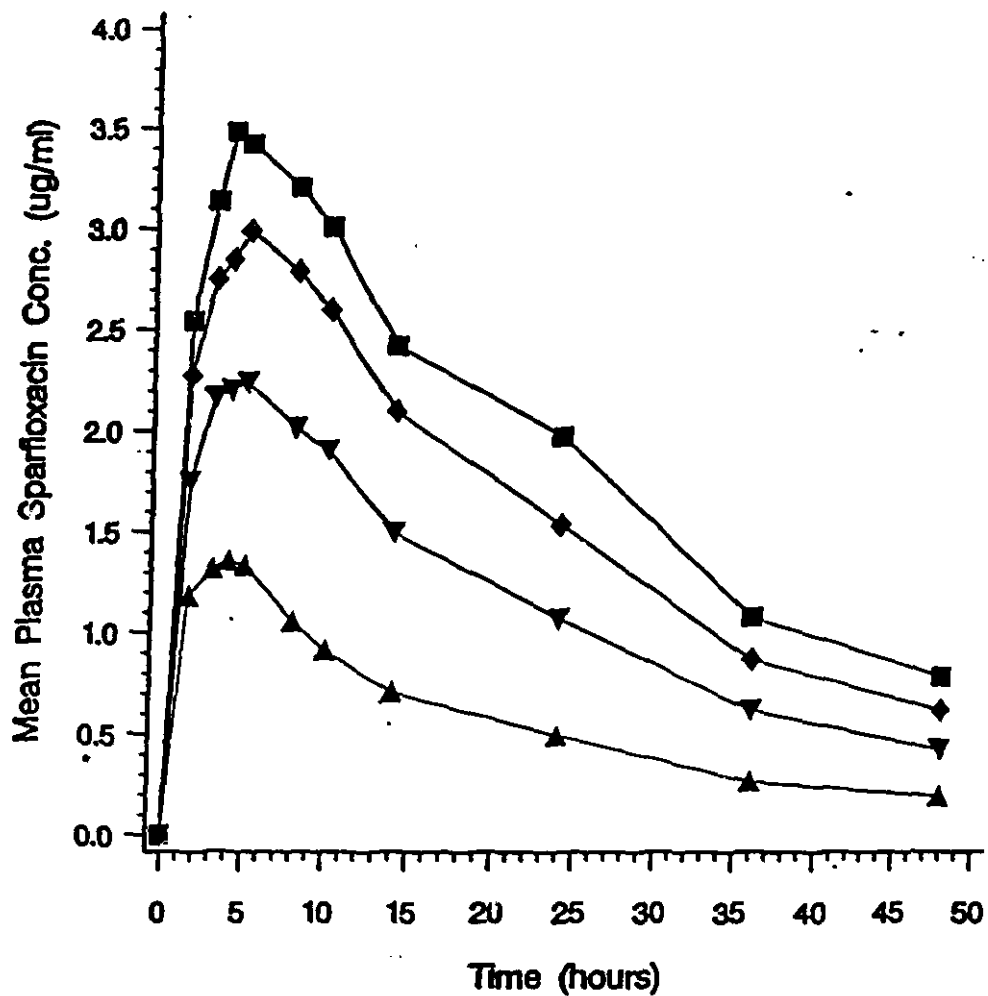


Figure 3. Mean plasma sparfloxacin concentrations following administration of single oral 400 mg (▲; n=23), 800 mg (▼; n=23), 1200 mg (◆; n=22), and 1600 mg (■; n=21) doses.

Mean (%CV) pharmacokinetic parameters by gender are presented in Table 2.

Table 2. Mean (%CV) Sparfloxacin Pharmacokinetic Parameters by Gender Following Administration of 400, 800, 1200, and 1600 mg Single Oral Sparfloxacin Doses.

Males				
Parameter	Sparfloxacin Dose (mg)			
	400 (n=12)	800 (n=12)	1200 (n=12)	1600 (n=12)
$AUC_{0-\infty}$ ($\mu\text{g/ml}\cdot\text{hr}$)	26.746 (29.3)	59.130 (24.8)	81.203 (27.1)	105.80 (27.4)
C_{max} ($\mu\text{g/ml}$)	1.061 (23.9)	2.075 (18.7)	2.508 (36.4)	3.145 (29.9)
T_{max} (hr)	3.3 (51.2)	4.6 (59.7)	5.1 (56.4)	6.3 (63.3)
k_{elim} (hr^{-1})	0.039 (18.1)	0.040 (14.9)	0.035 (27.0)	0.034 (18.7)
$t_{1/2}$ (hr)	17.8	17.3	19.8	20.4
Females				
Parameter	Sparfloxacin Dose (mg)			
	400 (n=11)	800 (n=11)	1200 (n=10)	1600 (n=9)
$AUC_{0-\infty}$ ($\mu\text{g/ml}\cdot\text{hr}$)	38.047 (17.8)	73.210 (30.9)	109.25 (27.9)	130.14 (35.6)
C_{max} ($\mu\text{g/ml}$)	1.799 (18.4)	2.736 (26.1)	3.869 (27.2)	4.621 (30.5)
T_{max} (hr)	3.5 (33.6)	6.3 (100)	5.7 (54.9)	4.6 (36.7)
k_{elim} (hr^{-1})	0.048 (17.1)	0.043 (20.5)	0.0414 (15.1)	0.040 (20.0)
$t_{1/2}^a$ (hr)	17.8	16.3	16.7	17.3

^a Harmonic mean

Mean $AUC_{0-\infty}$ and C_{max} values were higher for females than for males. However, these differences can be accounted for by differences in body weight. The mean body weight for males subjects (83 kg) was approximately 30% greater than the mean body weight for female subjects (63.6 kg).

Study RP162

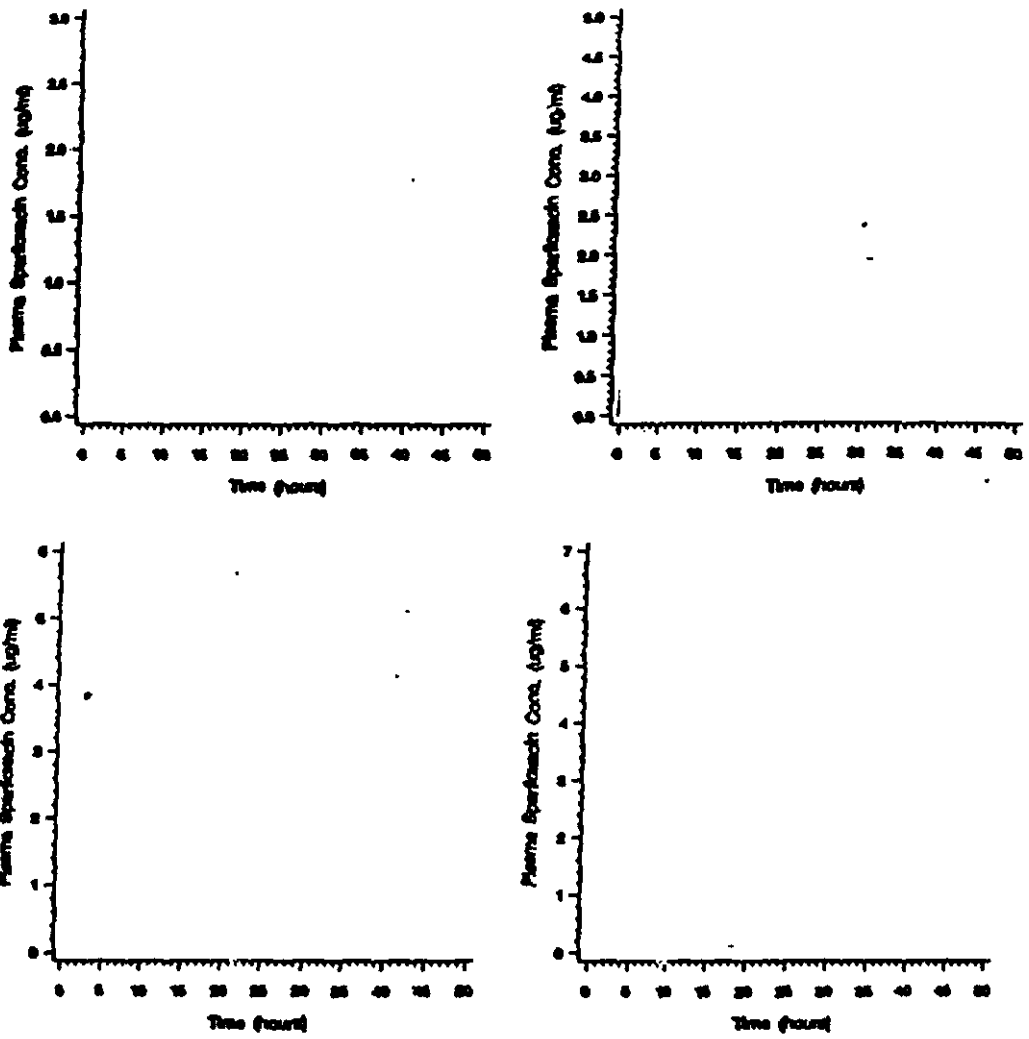


Figure 1. Individual plasma sparfloxacin concentrations following administration of a single oral 400 mg (top left; n=23), 800 mg (top right; n=23), 1200 mg (bottom left; n=22), and 1600 mg (bottom right; n=21) doses.

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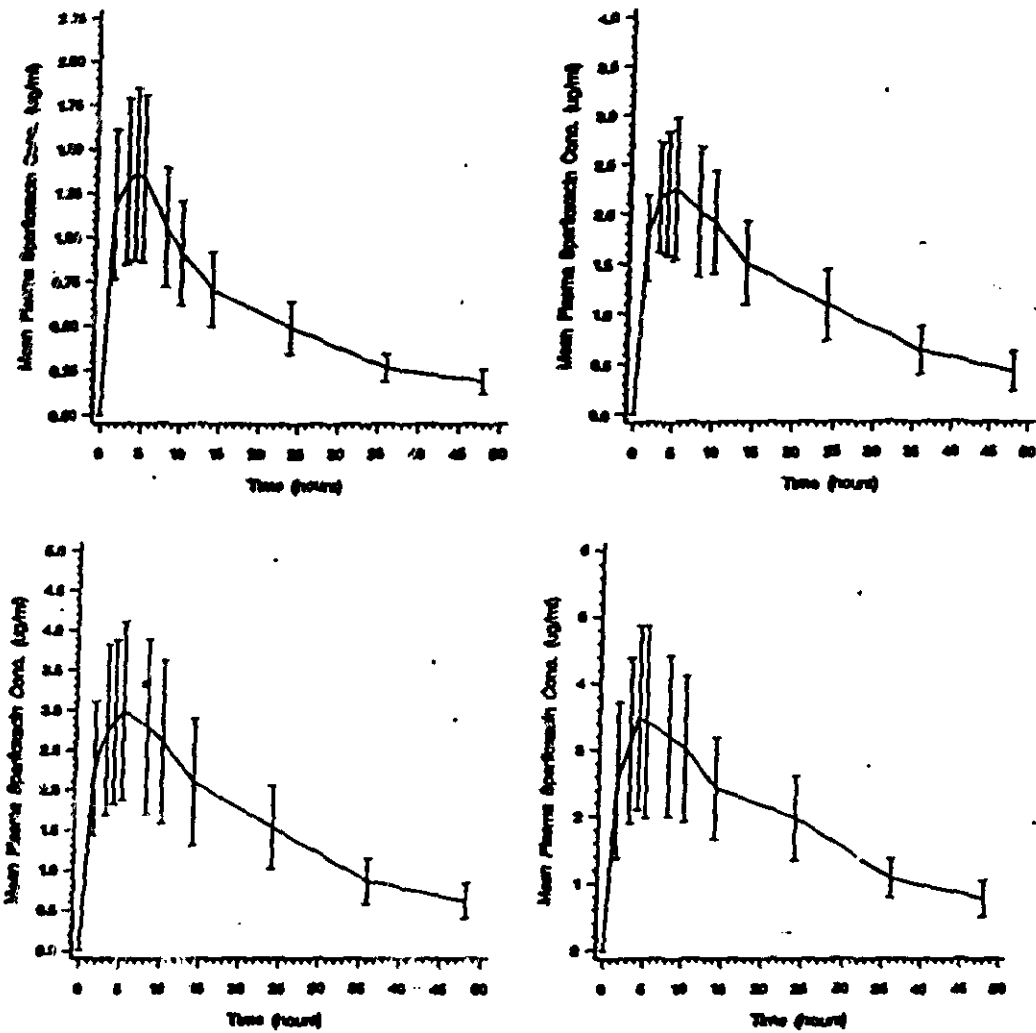


Figure 2. Mean plasma sparfloxacin concentrations following administration of a single oral 400 mg (top left; n=23), 800 mg (top right; n=23), 1200 mg (bottom left; n=22), and 1600 mg (bottom right; n=21) doses. Error Bars are ± 1 standard deviation.

Study RP64206-162.

Regression analysis were conducted for data submitted. The results are presented at the following

A. Regression analysis for the AUC data:

Linear Regression

$$\text{AUC} = 6.97 + (0.0701 * \text{Dose})$$

N = 4.00

R = 0.996 Rsqr = 0.992 Adj Rsqr = 0.988

Standard Error of Estimate = 4.0426

	Coefficient	Std. Error	t	P
Constant	6.9680	4.95119	1.41	0.2946
Col 1	0.0701	0.00452	15.51	0.0041

Analysis of Variance:

	DF	SS	MS	F	P
Regression	1	3929.1	3929.1	240.4	0.0041
Residual	2	32.7	16.3		
Total	3	3961.8	1320.6		

Normality Test: Passed (P = 0.2053)

Power of performed test with alpha = 0.0500: 0.8707

B. Regression analysis for Cmax data:

Linear Regression

$$C_{max} = 0.720 + (0.00196 * \text{Dose})$$

N = 4.00

R = 0.995 Rsqr = 0.991 Adj Rsqr = 0.986

Standard Error of Estimate = 0.1210

	Coefficient	Std. Error	t	P
Constant	0.72050	0.148192	4.86	0.0398
Col 1	0.00196	0.000135	14.49	0.0047

Analysis of Variance:

	DF	SS	MS	F	P
Regression	1	3.0733	3.0733	209.9	0.0047
Residual	2	0.0293	0.0146		
Total	3	3.1026	1.0342		

Normality Test: Passed (P = 0.2760)

Power of performed test with alpha = 0.0500: 0.8560

Results indicate that sparfloxacin dose-proportional increase for AUC, but less proportional increase for Cmax, up to 1600 mg dose.

TABULATED SUMMARY REPORT

Title of study (Phase):	The Oral Bioavailability of Sparfloxacin under Fed and Fasted Conditions, Protocol RP 64206X-157 (Phase I)
Investigator:	
Publication (reference):	None
Study period:	First Subject Treated: March 3, 1995 Last Subject Discharged: April 5, 1995
Study center:	
Objectives:	- To assess the effect of a high fat-meal on the oral absorption of sparfloxacin in healthy male volunteers. - To assess the effect of calcium containing foods (i.e. skim milk) on the oral absorption of sparfloxacin in healthy male volunteers.
Methodology:	This randomized, open-label three-way crossover study was conducted at a single study center. Treatments consisted of a single 200-mg oral, market-image sparfloxacin tablet following an overnight fast (Treatment A), with 8 ounces of skim milk (Treatment B), and with a standard high-fat breakfast excluding milk (Treatment C). Subjects were randomized into one of six treatment sequence groups, as follows: Sequence Group 1: B, A, C Sequence Group 2: A, C, B Sequence Group 3: C, B, A Sequence Group 4: B, C, A Sequence Group 5: A, B, C Sequence Group 6: C, A, B
Number of subjects:	24 enrolled, 23 completed all study procedures.
Diagnosis and criteria for entry:	Healthy, adult, nonsmoking, male volunteers between the ages of 18 and 45 years with normal screening physical and laboratory examinations, and electrocardiograms (ECGs) were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200-mg tablets, modified Nenagh process, manufactured by Rhône-Poulenc Rorer Oral Lot number: 241475 9411419
Duration of treatment:	Single dose in each of three crossover periods (minimum 10-day washout interval between study periods).
Reference therapy:	None
Safety measurements:	Vital signs, adverse events, physical examinations, 12-lead ECG, and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis).
Pharmacokinetics parameters:	Area under the plasma sparfloxacin concentration-time curve (AUC(0-∞)), maximum plasma concentration (C _{max}) and the time at which it occurred relative to the administered dose (T _{max}), and half-life (t _{1/2}).
Statistical methods:	An analysis of variance (ANOVA) was used to test for differences in the test means (Treatments B and C) for each pharmacokinetic parameter compared to the reference means (Treatment A) at an alpha level of 0.05. Ninety percent confidence intervals calculated from a two one-sided test were determined from natural logarithmically (ln) transformed data for AUC(0-∞) and C _{max} values. The Wilcoxon signed rank test was used to test for differences in T _{max} .
Results:	Safety and Tolerance: The proportion of subjects reporting adverse clinical experiences was highest while receiving sparfloxacin following an overnight fast, followed by equal reporting rates while receiving sparfloxacin with skim milk or a high-fat meal. Each adverse clinical experience was reported by one subject only, with the exception of two reports of headache. All of the adverse experiences were mild in intensity, and no subject discontinued due to an adverse clinical or laboratory experience.

TABULATED SUMMARY REPORT

	Pharmacokinetics: Mean sparfloxacin C_{max} and $AUC(0-\infty)$ values were similar among the three dosing regimens, suggesting that neither a concomitantly administered high-fat meal nor skim milk altered the extent of sparfloxacin absorption. However, the mean T_{max} value following a concomitantly administered high fat meal was 1.6 to 1.8 hours later than the values for the other two treatments, suggesting that a high fat meal may somewhat delay the onset of oral absorption (lag time). Similar $t_{1/2}$ values among the three dosing regimens indicated that elimination kinetics were not altered by concomitant administration with either a high-fat meal or skim milk.
Conclusions:	• Administration of a single 200 mg sparfloxacin oral dose either alone or accompanied by a high fat meal or skim milk is well tolerated. • Sparfloxacin absorption and elimination kinetics are unaffected by concomitant administration of calcium containing foods (i.e. skim milk) or a high-fat meal. The onset of sparfloxacin absorption is somewhat delayed by concomitant administration of a high-fat meal. • Sparfloxacin can be administered with or without food or calcium containing foods.

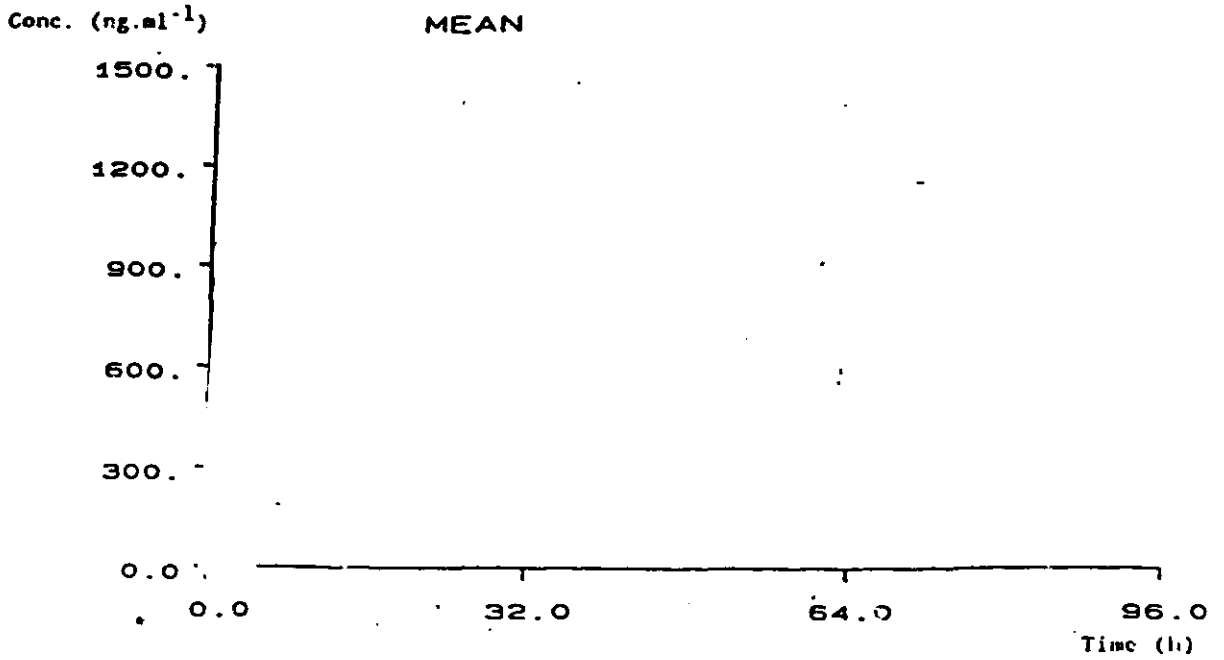
See Figure 3 for plots.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 33 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (phase I)	A phase I, open, crossover, randomised study on 10 healthy volunteers of food induced changes of sparfloxacin bioavailability after a 400 mg single oral administration	
Investigator:		
Study centre:		
Publication (reference):	None	
Study period (years):	1989-1990	
Objectives:	To assess the influence of food intake on the Pharmacokinetic of sparfloxacin. A secondary objective was the assessment of safety.	
Methodology:	Open, randomised, two-way crossover study.	
Number of subjects:	10	
Diagnosis and criteria for inclusion:	Healthy Caucasian male subjects aged 18-35 years. Body weight in accordance with the limits of the scale proposed by the Metropolitan Insurance Company. Non-smokers with normal eating habits. Not having participated in a study involving any drug within the preceding 3 months. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 400 mg as 4 film-coated tablets each containing 100 mg of sparfloxacin. Batch No. CB 3976	
Duration of treatment:	Single dose. Two administrations at a 7-day interval.	
Reference therapy	None	
Study procedures:	Administration of sparfloxacin alone in fasting subjects (treatment A) and administration with a standard meal (treatment B). Subjects were randomised into 2 groups of 5 corresponding to two treatment sequences (treatments separated by a 7-day washout period): - Treatment sequence A/B: treatment A in period 1 and treatment B in period 2 (5 subjects). - Treatment sequence B/A: treatment B in period 1 and treatment A in period 2 (5 subjects). After the administration of sparfloxacin the following samples were collected for the determination of sparfloxacin concentrations by HPLC assay: - Plasma: predose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose. - Urine: predose then during periods 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours postdose.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 33 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																																																				
Criteria for evaluation: Pharmacokinetics: Safety:	Determination of the following parameters: • Plasma: C_{max}, t_{max}, MRT, t_{lag}, t_{1/2}, AUC 0-t, AUC 0-∞ • Urine: Unchanged and total sparfloxacin amounts excreted (A_e), unchanged and total drug fractions of the dose excreted (f_e), renal clearance (Cl_r). Clinical evaluation, electrocardiogram, laboratory tests (at selection and one week after the last administration), adverse events recording.																																																					
Statistical methods:	Pharmacokinetic: Mean values ± SD. • Three-way ANOVA (treatment, subject and period) followed by calculation of the symmetrical 95% confidence interval limits according to Westlake and by the two one-sided t test according to Schürmann for the following parameters: C_{max} and AUC. • Three-way ANOVA for t_{1/2}, MRT, urinary excretion and renal clearance. • Wilcoxon's test for t_{max} and t_{lag}. Vital signs: Mean values ± SD and mean differences ± SD from baseline according to treatment sequence																																																					
Results - conclusions:	There was no dropout Pharmacokinetic results: All the individual data were pooled for statistical analysis after confirmation that there was neither carry-over effect nor period effect between treatment groups A and B. Plasma and urine pharmacokinetic: Mean values (SD) <table border="1" data-bbox="652 1169 1370 1507"> <thead> <tr> <th>PARAMETER</th> <th>FASTING (n = 10)</th> <th>STANDARD MEAL (n = 10)</th> <th>STATISTICS (symmetrical 95% confidence interval)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng·ml⁻¹)</td> <td>1476.8 (358.8)</td> <td>1461.1 (338.7)</td> <td>NS (1) (23.01%)</td> </tr> <tr> <td>t_{max} (h)</td> <td>4.70 (2.00)</td> <td>3.10 (1.60)</td> <td>NS (2)</td> </tr> <tr> <td>AUC 0-96h (μg·ml⁻¹·h)</td> <td>39.89 (9.88)</td> <td>39.05 (12.50)</td> <td>NS (1) (22.83%)</td> </tr> <tr> <td>AUC 0-∞ (μg·ml⁻¹·h)</td> <td>41.80 (11.12)</td> <td>40.80 (13.40)</td> <td>NS (1) (22.02%)</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>19.59 (3.61)</td> <td>20.9 (2.66)</td> <td>NS (1)</td> </tr> <tr> <td>MRT (h)</td> <td>28.70 (4.99)</td> <td>29.39 (3.25)</td> <td>NS (1)</td> </tr> <tr> <td>t_{lag} (h)</td> <td>0.00 (0.00)</td> <td>0.00 (0.00)</td> <td>-</td> </tr> <tr> <td>A_e (unchanged) (mg)</td> <td>35.402 (12.002)</td> <td>36.453 (9.859)</td> <td>NS (1)</td> </tr> <tr> <td>A_e (total) (mg)</td> <td>142.358 (27.673)</td> <td>145.038 (31.122)</td> <td>NS (1)</td> </tr> <tr> <td>f_e (unchanged) (%)</td> <td>8.9 (3.0)</td> <td>9.1 (2.5)</td> <td>-</td> </tr> <tr> <td>f_e (total) (%)</td> <td>35.6 (6.9)</td> <td>36.3 (7.8)</td> <td>-</td> </tr> <tr> <td>Cl_r (ml·min⁻¹)</td> <td>14.41 (4.31)</td> <td>15.50 (4.06)</td> <td>NS (1)</td> </tr> </tbody> </table> (1) 3-way ANOVA; (2) Wilcoxon's test		PARAMETER	FASTING (n = 10)	STANDARD MEAL (n = 10)	STATISTICS (symmetrical 95% confidence interval)	C _{max} (ng·ml ⁻¹)	1476.8 (358.8)	1461.1 (338.7)	NS (1) (23.01%)	t _{max} (h)	4.70 (2.00)	3.10 (1.60)	NS (2)	AUC 0-96h (μg·ml ⁻¹ ·h)	39.89 (9.88)	39.05 (12.50)	NS (1) (22.83%)	AUC 0-∞ (μg·ml ⁻¹ ·h)	41.80 (11.12)	40.80 (13.40)	NS (1) (22.02%)	t _{1/2} (h)	19.59 (3.61)	20.9 (2.66)	NS (1)	MRT (h)	28.70 (4.99)	29.39 (3.25)	NS (1)	t _{lag} (h)	0.00 (0.00)	0.00 (0.00)	-	A _e (unchanged) (mg)	35.402 (12.002)	36.453 (9.859)	NS (1)	A _e (total) (mg)	142.358 (27.673)	145.038 (31.122)	NS (1)	f _e (unchanged) (%)	8.9 (3.0)	9.1 (2.5)	-	f _e (total) (%)	35.6 (6.9)	36.3 (7.8)	-	Cl _r (ml·min ⁻¹)	14.41 (4.31)	15.50 (4.06)	NS (1)
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Results - conclusions: (continued)	Adverse experiences and safety profile • No adverse events reported. • No clinically significant changes in vital signs and ECG. • No clinically significant changes in laboratory test values. Conclusions: The concomitant ingestion of food did not significantly alter the pharmacokinetic of a single dose of 400 mg of sparfloxacin. The clinical and laboratory safety of the drug was excellent.	

FIGURE 1



RP-64206 plasma concentrations measured after a single 400 mg
RP-64206 oral administration :

— : in fasting subjects

o—o : with a standard breakfast

TABULATED SUMMARY REPORT

Title of study: (Phase)	The Effect of Staggered Dosing of Maalox® on the Oral Bioavailability of Sparfloxacin in Healthy Adult Male Volunteers, Protocol RP 64206X-154 (Phase I).
Investigators:	
Publication (reference):	Wilson J, Johnson RD, Caille G, Talbot G, Dorr MB, Heald D. The Effect of Staggered Dosing of Maalox® on the Oral Bioavailability of Sparfloxacin. Pharmaceutical Research 1994; 11(10):S-429.
Study period:	First subject treated: 11 September, 1993 Last subject discharged: 12 October, 1993
Study center:	
Objective:	To determine an optimal time for dosing antacids relative to sparfloxacin administration which would minimize antacid-induced reduction in sparfloxacin bioavailability.
Methodology:	The study was conducted as an open-label, single-dose, randomized, single-center, four-way crossover trial. Twenty subjects were randomly assigned to receive one of four treatment sequences of 1) sparfloxacin 400 mg alone, 2) Maalox® 2 hours before sparfloxacin, 3) Maalox® 2 hours after sparfloxacin, and 4) Maalox® 4 hours after sparfloxacin.
Number of subjects:	20 male subjects enrolled; all 20 subjects completed the study.
Diagnosis and criteria for entry:	Healthy male volunteers between the ages of 18 and 50 years with no clinical relevant laboratory or electrocardiogram (ECG) abnormalities or other disease were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 400 mg oral (2 x 200 mg tablets; lot number 9208221) plus Maalox® regular strength 30 mL (lot number 96017) given orally 2 hours prior, 2 hours after, and 4 hours after sparfloxacin.
Duration of treatment:	Subjects received a single dose of study drug in each of four study periods separated by a 1-week washout period. The total duration of study participation was 4 weeks.
Reference therapy: dose, route of administration, lot number:	Sparfloxacin 400 mg oral (2 x 200 mg tablets; lot number 9208221) alone.
Safety measurements:	Adverse clinical and laboratory experiences and changes in physical examination, vital signs, and ECG findings.
Pharmacokinetics parameters:	Maximum plasma sparfloxacin concentration (C _{max}), time to maximum plasma sparfloxacin concentration (T _{max}), terminal elimination rate constant (k _{term}), terminal half-life (t _{1/2}), and area under the plasma sparfloxacin concentration-time curve extrapolated to infinity (AUC(0-∞)).

TABULATED SUMMARY REPORT

Statistical methods:	An analysis of variance (ANOVA) for a four-way crossover design was used to test for differences in the test means for each biopharmaceutic parameter compared to the reference (sparfloxacin alone) means at an α level of 0.05. In addition, 90% confidence intervals (CI) were constructed for $AUC(0-\infty)$ and C_{max} values comparing test treatments with the reference treatment. The Wilcoxon signed rank test was used to test for the differences in T_{max} between the test treatments and the reference treatment.
Results:	<u>Safety and Tolerance:</u> Sparfloxacin was well tolerated when given alone and in combination with Maalox®. Three subjects reported a total of four adverse events during this study, one following each of the treatment regimens. None of the adverse events were considered serious and all were rated as mild in intensity. There were two reports of dyspepsia, one report of headache, and one episode of pharyngitis. No subject discontinued the study due to an adverse experience. Two subjects experienced adverse laboratory events (both elevated AST/SGOT values). No clinically relevant changes in physical examination, vital signs, or ECG findings occurred during the study. <u>Pharmacokinetics:</u> Maalox® administered 4 hours after sparfloxacin administration was the only regimen that did not cause a significant reduction in sparfloxacin absorption. CI for AUC and C_{max} were within the 80-120% limits. Administration of Maalox® 2 hours before and 2 hours after sparfloxacin caused a mean decrease in $AUC(0-\infty)$ of 23% and 17%, respectively. Corresponding decreases in mean C_{max} were 29% and 13%, respectively, and CI were outside of the 80-120% limits and did not include 100%. T_{max} and $T\%$ were similar across all four treatments, thus, the rates of absorption and elimination of sparfloxacin were unaffected by concomitant administration with Maalox®.
Conclusions:	• Sparfloxacin was well tolerated when given alone and in combination with Maalox®. • Maalox® did not affect the extent of oral absorption of sparfloxacin when given 4 hours after sparfloxacin administration. • Maalox® caused a statistically significant but modest decrease in the extent of sparfloxacin absorption when administered either 2 hours before or 2 hours after sparfloxacin administration. • Decreased sparfloxacin bioavailability may impact therapeutic efficacy; therefore, it is prudent to delay antacid dosing by at least 4 hours after sparfloxacin administration when both drugs are used concurrently.

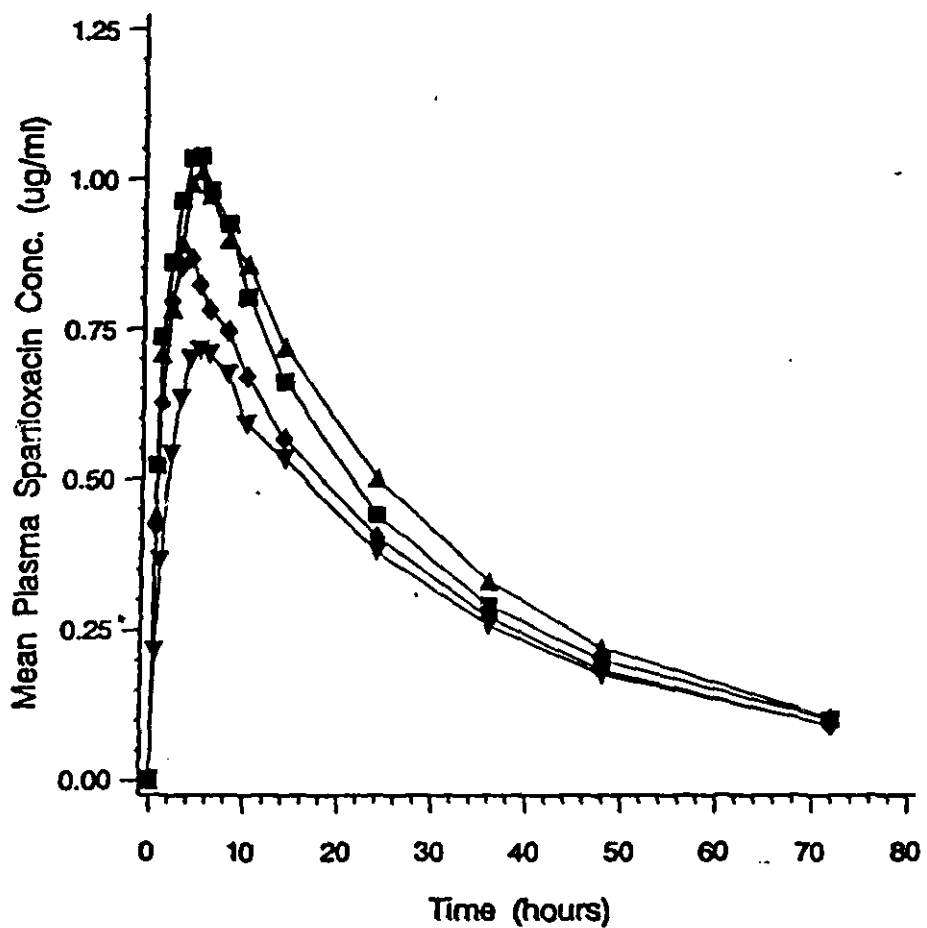


Figure 3. Mean plasma sparfloxacin concentrations following administration of sparfloxacin alone (▲), Maalox at two hours prior to sparfloxacin administration (▼), Maalox at two hours after sparfloxacin administration (◆), and Maalox at four hours after sparfloxacin administration (■).

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 41 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (phase I)	A phase I, open, crossover, randomised study on ten healthy volunteers, of the influence of antacid intake (2 tablets of Maalox® 400 mg) on the bioavailability of sparfloxacin after a 400 mg single oral administration	
Investigator:		
Study centre:		
Publication (reference):	MIGNOT A. et al., "Effect of aluminium hydroxide antacid on the Pharmacokinetic of the new quinolone RP 64206", 30th Interscience Conference on Antimicrobial Agents and Chemother (ICAAC), Atlanta, 21-24/10/1990, Abstract 1250.	
Study period (years):	1989 - 1990	
Objective:	To evaluate the possible modification of RP-64206 digestive absorption after antacid intake. A secondary objective was the assessment of safety.	
Methodology:	Open, randomised, two-way crossover study.	
Number of subjects:	10 subjects were planned, 12 were included (2 withdrawals)	
Diagnosis and criteria for inclusion:	Healthy male Caucasian subjects aged 18-35 years. Body weight in accordance with the limits of the scale proposed by the Metropolitan Insurance Company. Non-smokers with normal eating habits. Not having participated in a study involving any drug within the preceding 3 months. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 400 mg as 4 film-coated tablets each containing 100 mg of sparfloxacin. Batch No. CB 3976 Oral administration of 2 tablets of Maalox®, each containing aluminium hydroxide (400 mg) and magnesium hydroxide (400 mg). Batch No. 9090.	
Duration of treatment:	Single dose. Two administrations at 7-day interval.	
Reference therapy:	None	
Study procedure:	Administration of sparfloxacin alone (treatment A) or administration of sparfloxacin 30 minutes after the intake of aluminium and magnesium hydroxide (Maalox®) (treatment B).	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 41 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Study procedures: (continued)	Subjects were randomised into 2 groups of 5 corresponding to 2 treatment sequences (treatment separated by a 7-day washout period): - Treatment sequence A/B: treatment A in period 1 and treatment B in period 2. - Treatment sequence B/A: treatment B in period 1 and treatment A in period 2.	
Criteria of evaluation: Pharmacokinetics: Safety:	After the administration of sparfloxacin, the following samples were collected for the determination of sparfloxacin by HPLC assay: - Plasma: predose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose. - Urine: predose then during periods 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours postdose. Determination of the following parameters: - Plasma: C_{max}, t_{max}, MRT, t_{lag}, $t_{1/2}$, AUC 0-t, AUC 0-∞ - Urine: Unchanged and total sparfloxacin amounts excreted (A_e), unchanged and total drug fractions of the dose excreted (f_e), renal clearance (Cl_r). Clinical evaluation, electrocardiogram, laboratory tests (at selection and one week after the last administration), adverse events recording.	
Statistical methods:	Pharmacokinetics: Mean values ± SD. All the individual data were pooled for statistical analysis because there was neither carry-over effect nor period effect between treatment groups A and B. - C_{max}, AUC, $t_{1/2}$, MRT, A_e and Cl_r: 3-way ANOVA - t_{max} and t_{lag}: Wilcoxon's test - For $t_{1/2}$ and AUC, calculation of the 95% confidence interval limits according to Westlake and by two one-sided t tests according to Schuirmann. Vital signs: Mean values ± SD and mean differences ± SD from baseline according to treatment sequence.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 41 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results - conclusions:

Pharmacokinetic results:
10 subjects analysed: 2 subjects withdrew for personal reasons after the first administration of sparfloxacin.

Plasma and urine Pharmacokinetics: Mean values (SD)

	TREATMENT A 4 x 100 mg tablets without antacid intake (n = 10)	TREATMENT B 4 x 100 mg tablets with antacid intake (n = 10)	STATISTICS (Symmetrical 95% confidence interval)
C_{max} ($\mu\text{g}\cdot\text{mL}^{-1}$)	1405.6 (506.4)	736.6 (574.5)	$p < 0.01$ (1)
t_{max} (h)	3.60 (1.43)	5.10 (2.86)	NS (2)
AUC _{0-6h} ($\mu\text{g}\cdot\text{mL}^{-1}\cdot\text{h}$)	37.76 (13.92)	21.10 (14.75)	$p < 0.001$ (1) (59.36%)
AUC _{0-∞} ($\mu\text{g}\cdot\text{mL}^{-1}\cdot\text{h}$)	38.86 (16.04)	22.20 (15.83)	$p < 0.001$ (1) (58.89%)
$t_{1/2}$ (h)	20.63 (3.32)	20.85 (3.78)	NS (1) (14.20%)
MRT (h)	29.65 (5.57)	33.59 (6.71)	NS (1)
t_{lag} (h)	0.00 (0.00)	0.05 (0.16)	NS (2)
A_e (unchanged) (mg)	28.818 (18.838)	25.122 (18.728)	$p < 0.01$ (1)
A_e (total) (mg)	112.146 (34.180)	88.736 (31.490)	$p < 0.01$ (1)
f_e (unchanged) (%)	10.0 (4.7)	6.3 (4.8)	-
f_e (total) (%)	26.0 (8.8)	14.9 (7.8)	-
Renal clearance ($\text{mL}\cdot\text{min}^{-1}$)	16.31 (3.53)	16.41 (6.98)	NS (1)

(1) 3-way ANOVA; (2) Wilcoxon's test

Adverse experiences and safety profile
The 12 subjects included were analysed.

- No adverse event reported.
- Minor changes in clinical and biological parameters not clinically significant and not imputable to sparfloxacin.

Conclusions:
This study shows that antacid intake 30 minutes before sparfloxacin administration decreases the absorption of sparfloxacin by around 50%. The results are in agreement with those usually observed with the other quinolones. The clinical and laboratory safety of sparfloxacin was good.

COMPANY: EUROPE FINISHED PRODUCT:	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	Volume: 47 Page :	
Title of the study: (Phase I)	A double-blind, crossover, randomised study on twelve healthy volunteers of the linearity of kinetics of sparfloxacin given four times as a single oral dose ranging from 200 to 800 mg.	
Investigator:		
Study centre:		
Publication (reference):	None	
Study period (years):	1989-1990	
Objectives:	To study sparfloxacin plasma concentrations - dose relationship after single oral administration of 200, 400, 600 and 800 mg of sparfloxacin in twelve healthy volunteers. A secondary objective was the assessment of safety.	
Methodology:	Double-blind, randomised, four-way crossover study.	
Number of subjects:	12 (15 included: 3 drop-outs replaced)	
Diagnosis and criteria for inclusion:	Healthy male Caucasian subjects aged 18-35 years. Body weight within the limits of the scale of the Metropolitan Insurance Company. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 200 mg (2 sparfloxacin and 6 placebo tablets), 400 mg (4 sparfloxacin and 4 placebo tablets), 600 mg (6 sparfloxacin and 2 placebo tablets) or 800 mg (8 sparfloxacin tablets) sparfloxacin tablets as film-coated tablets each containing 100 mg of sparfloxacin. sparfloxacin (RP 64206) tablets batch No. CB 3976. Placebo tablets batch No. CB 4113 P.	
Duration of treatment:	Single dose, 4 administrations with a 1-week interval between intakes.	
Reference therapy	None.	
Study procedure	Each of the 12 subjects received 4 separate single doses of sparfloxacin, i.e. treatments A, B, C and D, in a randomised sequence, (12 sequences): - Treatment A: 2 sparfloxacin tablets (200 mg) with 6 placebo tablets - Treatment B: 4 sparfloxacin tablets (400 mg) with 4 placebo tablets - Treatment C: 6 sparfloxacin tablets (600 mg) with 2 placebo tablets - Treatment D: 8 sparfloxacin tablets (800 mg). Duration of 5 weeks for each subject including a 1-week run-in period followed by the 4 separate oral sparfloxacin administrations with a 7-day washout period between treatments and a 1-week final follow-up period.	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 47 Page :	(FOR NATIONAL AUTHORITY USE ONLY)

Study procedure (continued)

After the administration of each dose of sparfloxacin, the following samples were collected for the determination of sparfloxacin and its glucuroconjugate concentrations by HPLC assay with UV detection:

- Blood (predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours postdose).
- Urine (predose, 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96 and 96 to 120 hours postdose).
- Faeces (0 to 24, 24 to 48, 48 to 72, 72 to 96 and 96 to 120 hours).

Criteria of evaluation

Pharmacokinetics:

Determination of the following parameters:

- Plasma: C_{max}, t_{max}, t_{1/2}, AUC 0-120h, AUC 0-∞, MRT, plasma clearance.
- Urine: Urinary excretion of unchanged, total and conjugated sparfloxacin, renal clearance, metabolic ratio.

Safety:

Clinical examination, adverse events, ECG recording (at inclusion and at the end of study) and laboratory tests (at inclusion and a week after the last administration).

Statistical methods:

Pharmacokinetics: All the individual data were pooled for statistical analysis. Mean ± SD, min - max values, for all parameters, except t_{max}: median and range.

- Comparison of all the parameters by analysis of variance according to the General Linear Model procedure followed by multiple range test. C_{max} and AUCs normalized to the 400 mg dose.
- Linear regression *versus* dose for C_{max} and AUC
- Comparison of t_{max} by the Wilcoxon's test.

Vital signs: Mean ± SD, min - max values.

Results - conclusions:

Three subjects withdrew from the study for personal reasons, 4 days, 6 days and 11 days after first drug intake, respectively.

Pharmacokinetic results :

Plasma pharmacokinetics

PLASMA PARAMETERS (mean ± SD)	DOSE				No statistically significant difference among groups (mg)
	200 mg (n = 12)	400 mg (n = 12)	600 mg (n = 12)	800 mg (n = 12)	
t _{max} (h) (median)	4 (1-6)	5 (2-6)	5 (2-6)	5 (2-6)	200-400-600-800
C _{max} (ng/ml)	705 ± 158	1178 ± 282	1649 ± 582	1966 ± 620	1) 200-400 2) 400-600-800
Normalised C _{max} (ng/ml)*	1411	1178	1100	983	
t _{1/2} (h)	20.79 ± 3.62	18.17 ± 2.08	20.35 ± 2.88	19.98 ± 2.06	200-400-600-800
AUC 0-∞ (h.ng/ml)	18749 ± 2927	32732 ± 7232	45790 ± 9960	57453 ± 14774	1) 200-400 2) 400-600-800
Normalised AUC 0-∞ (h.ng/ml)*	37501	32733	30527	28726	
AUC 0-120 h (h.ng/ml)	18588 ± 1772	34235 ± 6275	44910 ± 10018	56349 ± 13854	1) 200-400-600 2) 400-600-800
MRT (h)	29.25 ± 4.43	26.99 ± 3.43	28.73 ± 5.44	29.32 ± 3.35	200-400-600-800
Clearance (l/h)	11.0 ± 2.4	12.8 ± 3.0	13.7 ± 3.4	14.8 ± 4.1	1) 200-400-600 2) 400-600-800

*: Normalised mean values to the 400 mg dose according to the General Linear Model Procedure with multiple range tests.

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Results - conclusions: (continued)

The pharmacokinetic analysis of conjugated sparfloxacin in plasma was done only for the 400 mg dose, in 6 subjects. The mean C_{max}, AUC 0-4h and AUC 0-∞ were 353 ng/ml, 5821 ng.h/ml and 6840 ng.h/ml, respectively. The mean t_{1/2} was 15.3 h and t_{max} ranges from 2 to 16h with a median of 5h.

Urinary excretion

URINARY PARAMETERS (mean ± SD)	DOSE				No statistically significant difference among groups (mg)
	200 mg (n = 12)	400 mg (n = 12)	600 mg (n = 12)	800 mg (n = 12)	
Unchanged sparfloxacin (% dose)	10.19 ± 2.43	9.53 ± 2.06	8.83 ± 2.07	8.50 ± 2.36	200-400-600-800
Unchanged sparfloxacin renal clearance (h)	1.120 ± 0.195	1.196 ± 0.160	1.186 ± 0.139	1.214 ± 0.223	200-400-600-800
Total sparfloxacin (% dose)	32.59 ± 4.93	30.87 ± 7.84	27.10 ± 5.99	25.44 ± 6.62	200-400-600-800
Conjugated sparfloxacin (% dose)	22.40 ± 4.48	21.34 ± 6.69	18.27 ± 4.23	16.94 ± 5.63	200-400-600-800
Metabolic ratio	2.33 ± 0.78	2.27 ± 0.63	2.09 ± 0.36	2.09 ± 0.75	200-400-600-800

Faecal excretion

Sparfloxacin concentrations in faeces were not taken into account because the analytical method probably did not extract the total amount of drug in faeces.

Adverse experiences and safety profile

- Clinical events: Moderate headache (1 subject) and asthenia (1 subject) of doubtful imputability.
- Clinical parameters: No clinically relevant abnormality.
- ECG recording: No clinically significant changes.
- Laboratory tests: No clinically significant changes.

Conclusions:

The linearity of the pharmacokinetics was acceptable from the linear regressions. However, at higher dose bioavailability tended to decrease. The lower bioavailability at higher doses appeared to be due to a decreased absorption of the drug.

The electrocardiographic, clinical and laboratory safety of sparfloxacin was good, with only transient headache and asthenia of mild-to-moderate intensity and of doubtful imputability reported by two subjects during a single treatment sequence in each case.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 46 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, open, noncomparative study of the pharmacokinetics in inflammatory fluid, plasma and urine and safety of sparfloxacin when administered as a single 400 mg oral dose to 6 healthy male volunteers.	
Investigator:		
Study centre:		
Publication (reference):	Johnson J.H., et al., "Pharmacokinetics and inflammatory fluid penetration of sparfloxacin" Antimicrobial Agents and Chemotherapy 1992; 36: 2444-2446.	
Study period (years):	1991	
Objectives:	To determine the pharmacokinetics of sparfloxacin in inflammatory fluid sampled from a chemically induced blister in healthy male volunteers and to compare the sparfloxacin concentrations in inflammatory fluid and blood. Secondly, to assess the safety of sparfloxacin in healthy male volunteers.	
Methodology:	open, noncomparative study.	
Number of subjects:	Six.	
Diagnosis and criteria for inclusion:	Healthy male subjects aged 18-45 years. Body weight within 10% of ideal range. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 400 mg as 4 film-coated tablets each containing 100 mg of sparfloxacin. CB 4654.	
Duration of treatment:	Single dose.	
Reference therapy	None.	
Study procedure	Blisters on forearms were induced by cantharides-impregnated plasters. After the administration of 400 mg of sparfloxacin, the following samples were collected for the determination of sparfloxacin concentrations by bioassay method: Inflammatory fluid (0.5, 1, 2, 3, 4, 6, 8, 12, 26 and 52 hours postdose). Blood (predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 26 and 52 hours post-dose) Urine (predose, 0 to 4, 4 to 8, 8 to 12, 12 to 26, 26 to 52 hours postdose).	
Criteria for evaluation: Safety:	Determination of the following parameters: inflammatory fluid: C _{max} , T _{max} , t _{1/2} , AUC _{0-∞} , AUC blister/AUC plasma Plasma: C _{max} , T _{max} , K _a , t _{1/2} , AUC _{0-∞} . Urine: Elimination over time and cumulated. Mean urine concentration Clinical examination (selection visit, day 3 and if necessary day 7), adverse events recording.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 46 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Statistical methods:	Pharmacokinetics: Mean ± SD, min - max values Vital signs: Mean ± SD, min - max values	

Results - conclusions:

There was no dropout.

Pharmacokinetic results:

Plasma and inflammatory fluid pharmacokinetics (all patients were analysed):

PARAMETER	PLASMA* (n=6)	INFLAMMATORY FLUID* (n=6)
C _{max} (µg/ml)	1.6 ± 0.3 (1.2 - 1.9)	1.3 ± 0.3 (1.0 - 1.7)
T _{max} (h)	2.7 ± 2.1 (0.5 - 6)	5.0 ± 1.7 (4 - 8)
K _a (h ⁻¹)	0.8 ± 0.7 (0.1 - 1.8)	ND
AUC _{0-∞} mg.h/l	32.3 ± 4.0 (27.6 - 38.5)	37.4 ± 6.3 (27.3 - 45.0)
t _{1/2 β} (h)	17.6 ± 2.0 (15.1 - 20.9)	19.7 ± 7.6 (12.2 - 32.6)
Inflammatory fluid AUC _{0-∞} / plasma AUC _{0-∞} ratio (%)	-	117 ± 21 (91 - 155)

* Mean values ± SD (range) ND: Not determined

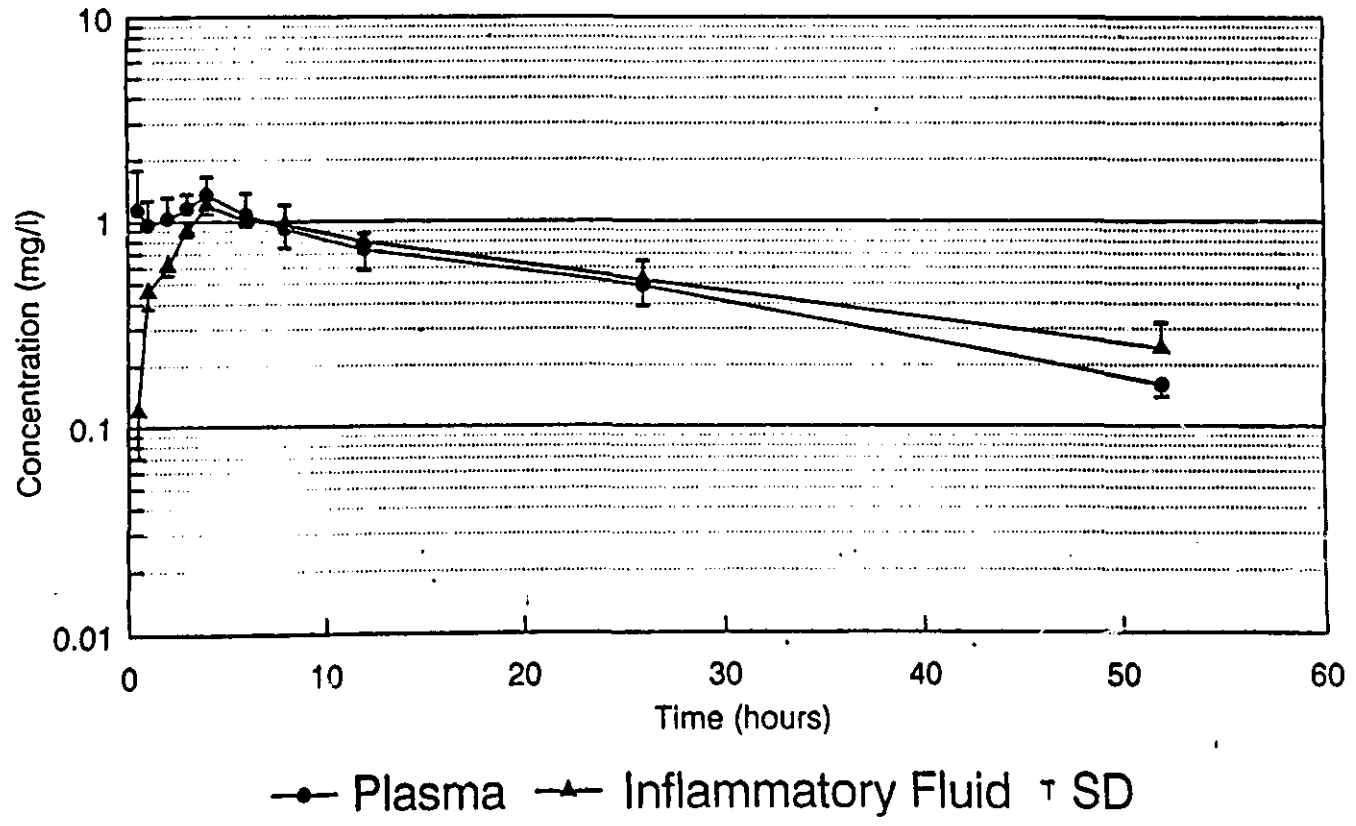
Urinary excretion

TIME PERIOD OF URINE COLLECTION	URINE RECOVERY mg*	MEAN URINARY CONCENTRATION µg/ml*
0 - 4 h	3.9 ± 1.3 (2.7 - 5.8)	25.4 ± 11.1 (15.9 - 43.6)
4 - 8 h	4.6 ± 1.5 (2.6 - 6.6)	20.2 ± 9.6 (11.1 - 34.2)
8 - 12 h	5.9 ± 2.0 (4.4 - 9.6)	10.8 ± 2.5 (6.8 - 14.7)
12 - 26 h	11.0 ± 2.1 (8.7 - 14.4)	11.7 ± 4.7 (5.4 - 19.9)
26 - 52 h	9.7 ± 2.9 (4.5 - 12.3)	5.2 ± 2.0 (2.9 - 7.9)
Total (0-52 h)	35.1 ± 6.9 (26.8 - 46.4)	-

* Mean values ± SD (range)

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 46 Page:	(FOR NATIONAL - AUTHORITY USE ONLY)
Adverse experiences and safety profile Clinical events probably related to sparfloxacin were observed in two subjects: one case of moderate phototoxicity (pruritus) of 5-days duration and one case of moderate dry skin and rash of 4-days duration. No other clinically significant abnormality at physical examination. Conclusions: The drug penetrated inflammatory fluid well with a mean peak concentration of 1.3 µg/ml seen at a mean time of 5 hour post dose. These concentrations exceeded the MIC_{90s} (minimum inhibitory concentration for 90% of strains) of most common bacterial pathogens, even 26 hours post dose (0.5 µg/ml). Mean peak plasma concentration (1.6 µg/ml) was slightly higher and obtained earlier (mean time of 2.7 hours) than in inflammatory fluid. The 400 mg single dose of sparfloxacin was well tolerated in this study, except for skin reactions observed in two subjects.		

Sparfloxacin volunteer study 400mg oral
Mean Plasma and Inflammatory Fluid levels



NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 50 Page :	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A phase I, open, noncomparative study of the pharmacokinetics, body fluid penetration, safety of a single oral dose of 400 mg sparfloxacin in 12 healthy volunteers.	
Investigators:		
Study centre:		
Publication (reference):	None	
Study period (years):	1991	
Objectives:	• To determine the body fluid penetration of sparfloxacin given as a single oral dose of 400 mg, by measurement of the concentrations of the drug in saliva, tears, sweat, nasal secretion, vaginal secretion, prostatic fluid and ejaculate. The plasma pharmacokinetics was determined at the same time. • Secondly, the safety of the drug was assessed.	
Methodology:	Open, noncomparative, single center study.	
Number of subjects:	15: 9 M and 6 F	
Diagnosis and criteria for inclusion:	Male and female healthy adults aged 19 to 45 years. Female subjects must use a reliable contraceptive mean (IUD, oral contraceptive, or surgically sterile). Body weight within 10% of ideal range. Written informed consent signed.	
Test product, dose, mode of administration, batch No.:	• Film-coated tablets each containing 100 mg of sparfloxacin, batch CB 4653: single dose of 400 mg (4 tablets) in the morning with a glass of water. • Iohexol (Omnipaque® -300): 5 ml i.v. by bolus injection (2534 mg) immediately before sparfloxacin intake.	
Duration of treatment:	Single dose	
Reference therapy:	None	
Criteria for evaluation:	Pharmacokinetics and body fluid concentrations • Sparfloxacin concentrations assayed by HPLC or: - 5 ml blood samples immediately before dosing and 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours thereafter. - Urine samples collected before dosing then during periods 0-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hours after dosing. - Saliva collection (performed over a period of exactly 1 minute) at the same times as outlined for plasma. - Nasal secretion (collected on 25 ± 5 mg preweighed cotton swab remaining in the right or left nostril for exactly 20 minutes): before dosing and 1, 2, 4, 8, 12, 16, 24, 36 and 48 hours thereafter.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A. OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Criteria for evaluation: (continued)	Volume: 50 Page:	
Safety:	- Tears (collected with small glass capillaries after stimulation of tears secretion): before dosing and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours thereafter. - Sweat (production stimulated by pilocarpine iontophoresis) collected before dosing and 1, 2, 4, 8, 12, 16, 24 and 36 h thereafter. - Prostatic fluid (obtained by digital massage of the prostate, collected into capillaries) collected 4 hours after drug intake (and injection of iohexol). - Ejaculate (obtained by the subject by masturbation) immediately after prostatic massage, and 12 hours after dosing (if possible) - Vaginal secretion (collected on a preweighed commercial tampon, placed by the subject in her vagina, and remaining there for 30 minutes), the evening before drug administration and at 2, 4, 12, 16, 24, 36 and 48 hours thereafter. - Determination of the pharmacokinetic parameters of unchanged sparfloxacin in plasma and urine: C_{max}, t_{max}, AUC 0-last (until last measurable sample), AUC 0-∞, $t_{1/2}$, MRT, Cl_T^* (total clearance), Cl_R^* (renal clearance), Cl_{NR} (nonrenal clearance), $Vd\beta$, Vd_{ss}^*, f_u (percent of the dose of sparfloxacin excreted in urine). - Determination of the pharmacokinetic parameters of conjugated sparfloxacin in plasma and urine: C_{max}, t_{max}, AUC 0-last, AUC 0-∞, $t_{1/2}$, Cl_T^*, f_u and $f_{u_{tot}}$ (total percent, i.e. unchanged and conjugated, of the dose of sparfloxacin excreted in urine). * These parameters were also expressed as corrected for body weight and for body surface area. - Determination of the pharmacokinetic parameters of unchanged sparfloxacin in body fluids: C_{max}, t_{max}, AUC 0-last, AUC 0-∞, $t_{1/2}$. - Evaluation of body fluid penetration of sparfloxacin expressed as the body fluid/plasma concentration ratio for unchanged sparfloxacin at scheduled time points and as the ratios of pharmacokinetic parameters for body fluids and plasma. Clinical evaluation, adverse events, vital signs and laboratory tests.	
Statistical methods:	- Pharmacokinetics and body fluid penetration: Descriptive statistics: Mean $\pm$ SD, min and max values - Vital signs and laboratory tests: Mean $\pm$ SD, min and max values, and mean difference $\pm$ SD from baseline at the end of the study	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (SPFX)(AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 50 Page :	(FOR NATIONAL AUTHORITY USE ONLY)

Results - conclusions:

Pharmacokinetic results:

- Plasma pharmacokinetics of unchanged and conjugated sparfloxacin

PHARMACOKINETIC PARAMETER	UNCHANGED DRUG (N = 12)	CONJUGATED DRUG (N = 12)
C _{max} (µg/ml)	1.55 ± 0.55	0.91 ± 0.32
t _{max} (h)	2.87 ± 2.10	2.09 ± 1.10
AUC 0-last (µg.h/ml)	31.4 ± 13.65	13.4 ± 4.65
AUC 0-∞ (µg.h/ml)	33.5 ± 13.27	15.1 ± 4.79
t _{1/2} (h)	15.6 ± 2.11	16.3 ± 4.57
MRT (h)	22.9 ± 3.67	-
Cl _r (ml/min)	233 ± 104.28	-
Cl _f (ml/min)	20.7 ± 6.61	184 ± 74.58
Cl _{TR} (ml/min)	212 ± 98.64	-
V _{dp} (l)	304 ± 109.16	-
V _{dss} (l)	308 ± 106.84	-
f _u (%)	9.56 ± 2.35	28.1 ± 6.81*
f _{u,ot} (%)	37.6 ± 7.55	-

* after correction for molecular weight

- Fluid pharmacokinetics and fluid/plasma C_{max} ratios: Mean ± SD (N)

	C _{max}	t _{max}	t _{1/2}	FLUID/PLASMA C _{max} RATIO
SALIVA	1.54 ± 0.73 (12)	2.12 ± 2.08 (12)	15.2 ± 3.89 (11)	0.970 ± 0.23(12)
TEAR	1.48 ± 1.33 (12)	1.95 ± 1.07 (12)	15.7 ± 2.73 (12)	0.982 ± 0.83(12)
SWEAT	1.03 ± 0.38 (12)	4.75 ± 1.09 (12)	16.4 ± 3.31 (12)	0.671 ± 0.09(12)
NASAL	6.84 ± 6.08 (12)	6.02 ± 2.78 (12)	16.7 ± 6.42 (10)	4.431 ± 3.62(12)
VAGINAL	10.4 ± 2.49 (4)	24.7 ± 8.30 (4)	29.0 ± 18.98(3)	5.143 ± 1.00(4)

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Results - conclusions: (continued)

Body fluid penetration of unchanged sparfloxacin

	Mean concentration (µg/ml)		Fluid/plasma ratio	
	at	h =	at	h =
SALIVA	0.25	h = 0.168 ± 0.12	0.25	h = 0.400 ± .25
	96	h = 0.044 ± 0.03	96	h = 0.890 ± 0.12
TEAR	1	h = 1.06 ± 0.42	1	h = 0.851 ± 0.20
	48	h = 0.177 ± 0.10	48	h = 0.957 ± 0.35
SWEAT	1	h = 0.646 ± 0.28	1	h = 0.520 ± 0.12
	36	h = 0.272 ± 0.20	36	h = 0.851 ± 0.32
NASAL	1	h = 3.28 ± 1.42	1	h = 2.222 ± 1.02
	48	h = 0.585 ± 0.42	12	h = 4.789 ± 2.51
VAGINAL	2	h = 0.696 ± 0.50	2	h = 0.399 ± 0.28
	48	h = 5.79 ± 3.67	48	h = 23.303 ± 5.46

- Ejaculate - Sperm - Prostatic fluid:
- Mean concentrations and ratio at 4 h and 12 h:

TIME AFTER ADMINISTRATION	EJACULATE		SPERM		PROSTATIC FLUID	
	N	µg/ml	N	µg/ml	N	µg/ml
4 h	9	1.60 ± 0.55	6	3.58 ± 1.23	6	2.21 ± 0.92
12 h	6	1.10 ± 0.27	5	3.73 ± 1.40	-	-*

TIME AFTER ADMINISTRATION	EJACULATE/PLASMA CONCENTRATION RATIO		SPERM/PLASMA CONCENTRATION RATIO		PROSTATIC FLUID/PLASMA CONCENTRATION RATIO	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
4 h	9	1.498 ± 0.38	6	3.393 ± 0.97	6	1.974 ± 0.79
12 h	6	1.724 ± 0.62	5	6.043 ± 2.83	-	-*

* No sample scheduled

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Results - conclusions: (continued)

Adverse experience and safety profile

- **Adverse events**
 - Reported in 9 subjects
 - 25 treatment possibly-related events:
 - Headache: 7 cases (2 severe, 3 moderate, 2 mild)
 - Diarrhea: 3 cases (1 moderate, 2 mild)
 - Nausea: 3 cases (1 moderate, 2 mild)
 - Flatulence: 3 cases (2 moderate, 1 mild)
 - Vomiting: 1 case (moderate)
 - Dizziness: 2 cases (mild)
 - Malaise: 1 case (moderate)
 - Chills: 1 case (moderate)
 - Pharyngitis: 1 case (moderate)
 - Urethritis: 1 case (moderate)
 - Photophobia: 1 case (moderate)
 - Scotomata: 1 case (mild)
- Vital signs: No clinically-significant changes.
- Laboratory tests: No clinically-significant changes.

Conclusions

After oral intake of a single dose of 400 mg, sparfloxacin was readily absorbed from the gastrointestinal tract. Maximal plasma concentration was observed after 3 hours. The pharmacokinetics of the drug were characterized by a long plasma half-life (15.6 hours), a high volume of distribution (300 l) and a low renal clearance (21 ml/min). Sparfloxacin is metabolized into a glucuronide conjugate. About 28% of the conjugated metabolite and 10% of the parent compound were excreted in urine. The penetration of sparfloxacin into body fluids was higher than that of other previously studied fluoroquinolones and was particularly high in nasal secretion and vaginal secretion. The MICs of relevant pathogens were exceeded in all fluids, in some cases up to 48 hours after drug intake. As regards safety, headache and gastrointestinal symptoms were the most frequently reported events. Although they may be, at least partially, attributed to sparfloxacin, these symptoms are commonly reported when a iodinated contrast medium such as iohexol is administered.

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 52 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																
Title of the study: (phase I)	A phase I open non-comparative multicenter study of the penetration into the tissues and fluids of the ENT sphere and safety of sparfloxacin administered orally as a single dose of 400 mg in 30 patients.																	
Investigators:																		
Study centres:																		
Publication (reference):	None																	
Studied period (years):	1991-1992																	
Objectives:	To determine the concentrations of sparfloxacin reached in the tissues and fluids of the ENT sphere after a single oral dose of sparfloxacin (200mg ^(a) or 400mg) with simultaneous evaluation of the plasma kinetics of the drug. ^(a) before amendment)																	
Methodology:	Multi-center, non-comparative, open study, two groups.																	
Number of subjects:	35 patients undergoing surgery of the ENT sphere were included. An amendment occurred to change the dose from 200 mg to 400 mg to provide a better prophylaxis; number of patients per group and per dose: <table border="1" data-bbox="641 1125 1264 1274" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>200 mg</th> <th>400 mg</th> <th>total</th> </tr> </thead> <tbody> <tr> <td>group A (chronic maxillary sinusitis)</td> <td>2</td> <td>9</td> <td>11</td> </tr> <tr> <td>group B (ENT sphere tumor)</td> <td>2</td> <td>22</td> <td>24</td> </tr> <tr> <td>total</td> <td>4</td> <td>31</td> <td>35</td> </tr> </tbody> </table>			200 mg	400 mg	total	group A (chronic maxillary sinusitis)	2	9	11	group B (ENT sphere tumor)	2	22	24	total	4	31	35
	200 mg	400 mg	total															
group A (chronic maxillary sinusitis)	2	9	11															
group B (ENT sphere tumor)	2	22	24															
total	4	31	35															
Diagnosis and criteria for inclusion:	Adult, male or female, over 18 years old; surgery of the ENT sphere prescribed due to chronic maxillary sinusitis or ENT sphere tumour; females either post-menopausal or surgically sterile, or using a reliable method of contraception (IUD; oral contraceptives); written informed consent.																	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 52 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Test product, dose, mode of administration, batch n°:	Oral sparfloxacin 2x100 mg tablets (first protocol version) or 4 x 100 mg tablets (amended protocol) administered as a single dose. CB 4654 and CB 4653	
Duration of treatment:	One day	
Reference Therapy:	None	
Study procedures:	Blood sampling: H0 before drug intake and one to three samples during surgery. Tissue and fluid sampling: one to ten samples during surgery, at various times.	
Criteria for evaluation: Safety: Pharmacokinetics:	Clinical evaluations (including laboratory tests), intercurrent events recording, at selection and at follow-up visit. Concentrations of sparfloxacin measured by HPLC assay in the following: plasma samples (5ml) taken before dosing (H0) and during surgery; sinus aspirate and sinus mucosa in group A; samples of the salivary glands, of oropharyngeal mucosa, tonsils, lymph nodes, bone, muscles, skin, thyroid, collected during surgery depending of the site of the tumor, in group B.	
Statistical methods:	Pharmacokinetics: Descriptive statistics were performed to evaluate the characteristic of the diffusion of sparfloxacin in plasma and ENT sphere tissues. Safety: Descriptive statistics were performed.	

Results - conclusions:

Evaluability is given in the following table (PK: pharmacokinetic analysis):

Evaluability	safety: Yes	safety: No
PK: Yes	31	
PK: No	3	1 ^(a)

^(a): no study medication intake

Pharmacokinetic results:

Plasma concentrations of sparfloxacin (400 mg dose):

period after dose:	number of samples	mean conc. (mg/l)	standard deviation
≤ to 2h	3	0.44	0.32
2h to 2h30	16	0.67	0.66
2h30 to 3h	6	0.81	0.24
3h to 4h	10	0.62	0.37
4h to 5h	5	0.62	0.38
> 5h	4	0.74	0.31

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Results - conclusions (continued):

Tissue concentrations (400 mg doses):

TISSUES	N	Mean corrected tissue concentrations (µg/g)	Concentration ranges (µg/g)
SINUS MUCOSA	8	5.81	
TONSILS	5	3.09	
THYROID	9	5.86	
OROPHARYNGEAL MUCOSA	9	6.56 (n=8)	
SKIN	11	5.54	
LYMPH NODES	9	1.49 (n=8)	
SALIVARY GLANDS	10	6.74	
CARTILAGE	4	1.83	
MUSCLE	17	3.06	
ADIPOSE TISSUE	14	0.59	

After an oral administration of 400 mg of sparfloxacin, the concentrations in the tissues studied - with the exception of the adipose tissue - were greater than 0.5 µg/g in 90% of the samples (n=98) for the period of 2 h to 6 h 45 min after sparfloxacin intake; sparfloxacin was not detectable in the sinus secretion.

The mean ratios of the tissue concentrations to the simultaneous plasma concentrations were greater than 2.86 for all the ENT sphere tissues studied, with the exception of the adipose tissue. The highest mean ratios were found in the sinus mucosa and salivary glands (approximately 9). They were virtually identical in the tonsils, thyroid, oropharyngeal mucosa, skin, muscle (approximately 5) and declined progressively in the cartilage, lymph nodes and adipose tissue (respective mean ratios of approximately 2.91, 2.86 and 0.73).

Safety

Three patients had clinically significant biochemical and haematologic abnormalities and 7 intercurrent events occurred (2 digestive symptoms, 2 events related to medical history, 1 hypoparathyroidism, 1 haemorrhage and 1 episod of arterial hypertension). They were not related to the study drug.

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 53 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (phase I)	A phase I, open, noncomparative, monocenter study of the penetration into the pulmonary tissues and safety of sparfloxacin administered orally as a single dose of 400 mg in 16 patients.	
Investigators:		
Study center:		
Publication (reference):	None	
Study period:	1991 - 1992	
Objectives:	To determine the distribution of sparfloxacin in pulmonary tissues after a single oral dose (400 mg). A secondary objective was the assessment of penetration into the tumor.	
Methodology:	Monocenter, non controlled, non comparative.	
Number of subjects:	16 patients planned; 15 patients included (8 patients in group A and 7 in group B)	
Diagnosis and criteria for inclusion:	Adult, male or female, over 18 years old. Surgery prescribed for bronchial or pulmonary tumor. Females must be either post-menopausal for at least 1 year (or surgically sterile, or using a reliable method of oral contraceptives). Written informed consent.	
Test product, dose, mode of administration, batch n°:	Administration of sparfloxacin at dose of 400 mg. Film-coated tablets each containing 100 mg of sparfloxacin. Batch n° CB 4654 was used.	
Duration of treatment:	Single dose.	
Reference Therapy:	None	
Study procedure:	Two groups of patients were constituted according to the time of blood and tissues sampling: group A from 2h to 6h postdose and group B from 12h to 24h postdose. After the administration of sparfloxacin, the following samples were collected: Blood samples: just before drug intake and during surgery at the time of ablation. Samples of pulmonary tissues and of mucus: healthy parenchyma, tumoral tissue, bronchial wall and pulmonary artery wall and mucus (mucus sampled by catheter from the main bronchus, inter-bronchial mucus proximal to the tumor, inter-bronchial mucus distal to the tumor) were to be collected during surgery.	
Criteria for evaluation: Pharmacokinetics	Determination of sparfloxacin concentrations in pulmonary tissues and blood samples by reversed phase HPLC assay with UV detection. Ratio between tissue to serum concentrations were calculated.	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 53 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Criteria for evaluation: (continued) Safety:	Clinical evaluation, vital signs, adverse events recording; ECG at inclusion; and 4 to 8 hours after dosing (only for patients of group B).	
Statistical methods:	Pharmacokinetics: Descriptive statistics were performed and student t-test was used to compare the serum and tissue concentrations and to analyse the ratio of tissue to serum concentrations. Safety: Descriptive statistics were performed.	

Results - conclusions:

There was no drop out.

Pharmacokinetic results:

GROUP A	N	Serum concentration mean $\pm$ sem (μ g/ml)	Tissue concentration mean $\pm$ sem (μ g/g)	Ratio of tissue to serum concentrations mean $\pm$ sem
Erythrocytes(RBC)	8	1,86 $\pm$ 0,33	2,00 $\pm$ 0,30	1,11 $\pm$ 0,04
Intrabronchial mucus proximal to the tumor	8	1,86 $\pm$ 0,33	3,49 $\pm$ 0,73	2,01 $\pm$ 0,46
Intrabronchial mucus distal to the tumor	8	1,86 $\pm$ 0,33	(1)4,92 $\pm$ 1,14	2,70 $\pm$ 0,65 (4)
Pulmonary parenchyma	8	1,86 $\pm$ 0,33	(3)10,03 $\pm$ 1,37	5,92 $\pm$ 0,91 (4)
Tumor tissue	8	1,86 $\pm$ 0,33	(3)7,16 $\pm$ 1,22	4,02 $\pm$ 0,51 (5)
Bronchus wall	8	1,86 $\pm$ 0,33	(2)4,87 $\pm$ 0,87	2,76 $\pm$ 0,44 (5)
Pulmonary artery wall	8	1,86 $\pm$ 0,33	(3)4,6 $\pm$ 0,53	2,69 $\pm$ 0,29(5)

Serum and tissue concentrations significantly different: (1) : $p < 0,05$, (2) : $p < 0,01$, (3) : $p < 0,001$

Concentration factor significantly different from 1: (4) : $p < 0,05$, (5) : $p < 0,01$

GROUP B	N	Serum concentration mean $\pm$ sem (μ g/ml)	Tissue concentration mean $\pm$ sem (μ g/g)	Ratio of tissue to serum concentrations mean $\pm$ sem
Erythrocytes(RBC)	7	1,02 $\pm$ 0,27	1,08 $\pm$ 0,26(6)	1,10 $\pm$ 0,08
Intrabronchial mucus proximal to the tumor	7	1,02 $\pm$ 0,27	1,93 $\pm$ 0,35	2,37 $\pm$ 0,47(4)
Intrabronchial mucus distal to the tumor	7	1,02 $\pm$ 0,27	(1)2,20 $\pm$ 0,33(6)	2,57 $\pm$ 0,58(4)
Pulmonary parenchyma	7	1,02 $\pm$ 0,27	(3)10,32 $\pm$ 1,60	15,77 $\pm$ 5,05(4)
Tumor tissue	7	1,02 $\pm$ 0,27	(2)3,84 $\pm$ 0,63(6)	5,02 $\pm$ 1,2(4)
Bronchus wall	7	1,02 $\pm$ 0,27	(3)3,79 $\pm$ 0,50	5,74 $\pm$ 1,45(4)
Pulmonary artery wall	7	1,02 $\pm$ 0,27	(3)3,43 $\pm$ 0,46	4,68 $\pm$ 1,03(4)

Concentrations and concentration factors significantly different in groups A and B: (6) : $p < 0,05$

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 53 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results - Conclusions
(continued)

After a 400 mg single oral dose of sparfloxacin, high concentrations were reached in all pulmonary tissues, whatever the removed tissue in both group A and B. The mean tissue to serum ratio ranged from 2.01 to 5.92.(group A) and 2.37 to 15.77 (group B). The highest mean ratio was found in the healthy parenchyma and the lowest in the mucus proximal to the tumor in both group.

Safety results:

10 intercurrent events occurred during the study period; they were not related to the study drug. One patient died 2 months after sparfloxacin intake because of a necrosis of a bronchial suture leading to a fistula.

Events	Subject number	Maximum severity	Relationship to treatment
ECG repolarization disorder		Moderate	Unrelated
Pre-delirium tremens		Moderate	Unrelated
Gastric pain		Moderate	Unrelated
Meteorism Gastric		Moderate	Unrelated
Sinusal tachycardia		Moderate	Unrelated
Intra - pleural haemorrhage		Moderate	Unrelated
Bronchial fistula		Severe	Unrelated
Surrenelectomy		Severe	Unrelated
Epigastralgia		Moderate	Unrelated
Gastralgia		Moderate	Unrelated

No clinically significant variations occurred in the vital signs measurements.

ECG: 3 patients had ECG at selection. One patient had ECG 4-8 hours after drug intake and the parameters were within normal limits.

Conclusions

This study showed a good penetration of sparfloxacin into the pulmonary tissues within 16 hours after drug administration. The clinical safety of sparfloxacin was good.

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TABLE 3: CONCENTRATION OF SPARFLOXACIN IN SERUM AND PULMONARY TISSUES ACCORDING TO THE TIME OF SAMPLING (GROUP A)

GROUP A PATIENT NUMBER	TIME AFTER DOSE: BLOOD	SERUM µg/ml	RBC µg/ml	TIME AFTER DOSE: TIBIAL	TRACHEAL MUCUS µg/ml	PROXIMAL MUCUS µg/ml	DISTAL MUCUS µg/ml	HEALTHY PARENCHYMA µg/g	TUMORAL TISSEU µg/g	BRONCHIAL WALL µg/g	PULMONARY ARTERY WALL µg/g
Mean ± sem	5h45 ± 0h07	1.86 ± 0.33	2.00 ± 0.30	7h31 ± 0h10	6.96 ± 2.63	3.49 ± 0.73	4.92 ± 1.14	10.03 ± 1.37	7.16 ± 1.22	4.87 ± 0.87	4.80 ± 0.53

TABLE 4: RATIO OF SPARFLOXACIN CONCENTRATION IN SERUM AND PULMONARY TISSUES (GROUP A)

GROUP A PATIENT NUMBER	RBC	TRACHEAL MUCUS	PROXIMAL MUCUS	DISTAL MUCUS	HEALTHY PARENCHYMA	TUMORAL TISSEU	BRONCHIAL WALL	PULMONARY ARTERY WALL
Mean ± sem	1.11 ± 0.04	3.69 ± 0.98	2.01 ± 0.48	2.70 ± 0.65	5.92 ± 0.91	4.02 ± 0.51	2.76 ± 0.44	2.69 ± 0.28

TABLE 5: CONCENTRATION OF SPARFLOXACIN IN SERUM AND PULMONARY TISSUES ACCORDING TO THE TIME OF SAMPLING (GROUP B)

GROUP B PATIENT NUMBER	TIME AFTER DOSE: BLOOD	SERUM µg/ml	RBC µg/ml	TIME AFTER DOSE: TISSE	TRACHEAL MUCUS µg/ml	PROXIMAL MUCUS µg/ml	DISTAL MUCUS µg/ml	HEALTHY PARENCHYMA µg/g	TUMORAL TISSE µg/g	BRONCHIAL WALL µg/g	PULMONARY ARTERY WALL µg/g
Mean ± sem	18h27 ± 1h40	1.02 ± 0.27	1.08 ± 0.26	17h48 ± 1h40	1.54 ± 0.39	1.33 ± 0.35	2.20 ± 0.33	10.32 ± 1.80	3.84 ± 0.83	3.79 ± 0.50	3.43 ± 0.46

TABLE 6: RATIO OF SPARFLOXACIN CONCENTRATION IN SERUM AND PULMONARY TISSUES (GROUP B)

GROUP B	RBC	TRACHEAL MUCUS	PROXIMAL MUCUS	DISTAL MUCUS	HEALTHY PARENCHYMA	TUMORAL TISSE	BRONCHIAL WALL	PULMONARY ARTERY WALL
Mean ± sem	1.10 ± 0.06	1.70 ± 0.30	2.37 ± 0.47	2.67 ± 0.58	15.77 ± 5.05	5.02 ± 1.20	5.74 ± 1.45	4.88 ± 1.03

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 49 Page :	(FOR NATIONAL AUTHORITY USE ONLY)																																	
Criteria for evaluation: Pharmacokinetics: Safety:	Determination of sparfloxacin concentrations in bronchial and serum samples by microbiological assay. Accumulation ratio with respect to serum. Clinical evaluation, vital signs, laboratory tests before and after treatment, clinical events.																																		
Statistical methods:	- Sparfloxacin concentrations: Mean value $\pm$ SD. Due to the small number of patients at each time point in the single dose study, results were pooled per sample site and per period and means expressed accordingly. - Vital signs: Mean values $\pm$ SD and mean differences $\pm$ SD from baseline for each treatment group.																																		
Results - conclusions:																																			
Sparfloxacin concentrations: (one patient of group B was withdrawn from the analysis because the patient failed to attend bronchoscopy).																																			
Single dose group (Mean $\pm$ SD)																																			
<table border="1"> <thead> <tr> <th>Period</th> <th>Serum (mg/l)</th> <th>Mucosa (mg/kg)</th> <th>Macrophages (mg/kg)</th> <th>ELF* (mg/l)</th> <th>time after dose (hour)</th> </tr> </thead> <tbody> <tr> <td>A1</td> <td>0.78 $\pm$ 1.01 (n=6)</td> <td>2.37 $\pm$ 2.67 (n=5)</td> <td>34.12 $\pm$ 39.16 (n=5)</td> <td>10.26 $\pm$ 15.22 (n=5)</td> <td>2.21 $\pm$ 0.64 (n=6)</td> </tr> <tr> <td>A2</td> <td>1.22 $\pm$ 0.44 (n=5)</td> <td>2.60 $\pm$ 0.78 (n=5)</td> <td>61.28 $\pm$ 31.17 (n=5)</td> <td>9.75 $\pm$ 5.71 (n=5)</td> <td>13.13 $\pm$ 1.17 (n=5)</td> </tr> <tr> <td>A3</td> <td>0.57 $\pm$ 0.18 (n=5)</td> <td>1.64 $\pm$ 0.49 (n=4)</td> <td>36.28 $\pm$ 10.90 (n=4)</td> <td>10.19 $\pm$ 4.45 (n=4)</td> <td>24.60 $\pm$ 0.82 (n=5)</td> </tr> <tr> <td>A4</td> <td>0.30 $\pm$ 0.19 (n=5)</td> <td>1.11 $\pm$ 0.56 (n=5)</td> <td>37.96 $\pm$ 45.05 (n=5)</td> <td>4.64 $\pm$ 3.84 (n=5)</td> <td>49.41 $\pm$ 0.63 (n=5)</td> </tr> </tbody> </table>	Period	Serum (mg/l)	Mucosa (mg/kg)	Macrophages (mg/kg)	ELF* (mg/l)	time after dose (hour)	A1	0.78 $\pm$ 1.01 (n=6)	2.37 $\pm$ 2.67 (n=5)	34.12 $\pm$ 39.16 (n=5)	10.26 $\pm$ 15.22 (n=5)	2.21 $\pm$ 0.64 (n=6)	A2	1.22 $\pm$ 0.44 (n=5)	2.60 $\pm$ 0.78 (n=5)	61.28 $\pm$ 31.17 (n=5)	9.75 $\pm$ 5.71 (n=5)	13.13 $\pm$ 1.17 (n=5)	A3	0.57 $\pm$ 0.18 (n=5)	1.64 $\pm$ 0.49 (n=4)	36.28 $\pm$ 10.90 (n=4)	10.19 $\pm$ 4.45 (n=4)	24.60 $\pm$ 0.82 (n=5)	A4	0.30 $\pm$ 0.19 (n=5)	1.11 $\pm$ 0.56 (n=5)	37.96 $\pm$ 45.05 (n=5)	4.64 $\pm$ 3.84 (n=5)	49.41 $\pm$ 0.63 (n=5)					
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Multiple dose group (2.9 to 4.9 hours after the last dose)																																			
<table border="1"> <thead> <tr> <th></th> <th>Serum (mg/l), n = 10</th> <th>Mucosa (mg/kg), n = 10</th> <th>Macrophages (mg/kg), n = 10</th> <th>ELF* (mg/l), n = 10</th> </tr> </thead> <tbody> <tr> <td>Mean $\pm$ SD</td> <td>1.2 $\pm$ 0.41</td> <td>4.40 $\pm$ 3.00</td> <td>63.70 $\pm$ 38.41</td> <td>15.00 $\pm$ 8.34</td> </tr> </tbody> </table>		Serum (mg/l), n = 10	Mucosa (mg/kg), n = 10	Macrophages (mg/kg), n = 10	ELF* (mg/l), n = 10	Mean $\pm$ SD	1.2 $\pm$ 0.41	4.40 $\pm$ 3.00	63.70 $\pm$ 38.41	15.00 $\pm$ 8.34																									
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* ELF: Epithelial lining fluid																																			

NAME OF COMPANY: RHONE D.P.C. EUROPE	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Sparfloxacin	Volume: 49	
NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	Page :	
Adverse experiences and safety profile: (All patients were included in the safety analysis). • Clinical event: Coughing in one patient not related to treatment. • Vital signs: No clinically significant changes in vital signs. • Laboratory tests: anaemia and high WBC counts in 2 patients; present before treatment = not related to treatment.		
Conclusions: Following single or multiple dosing, sparfloxacin concentrations in bronchial mucosa, epithelial lining fluid, alveolar macrophages, far exceeded those in serum. Sparfloxacin in bronchial and serum samples were clearly higher than MIC ₉₀ for common pulmonary pathogens (i.e. 0.25 µg/ml). No treatment-related clinical event was reported; the clinical and laboratory safety of sparfloxacin was good.		

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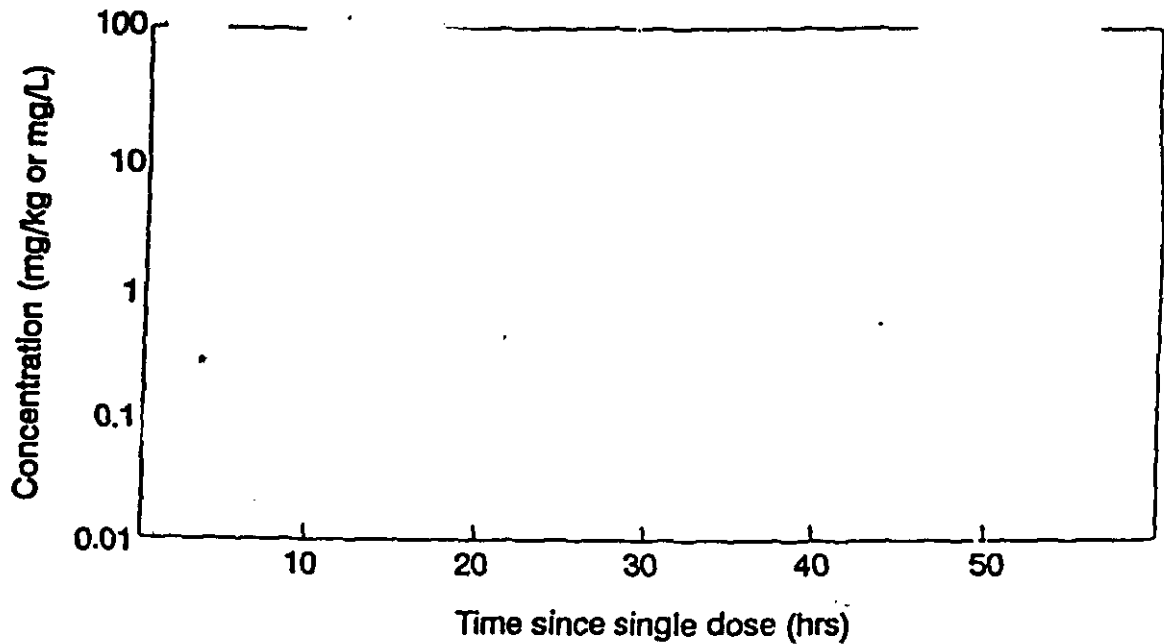


Figure 1: Sparfloxacin concentrations of in serum, bronchial mucosa, alveolar macrophages and epithelial lining fluid (ELF), following a 400 mg single oral dose.

- = serum concentration (mg/l)
- = mucosa concentration (mg/kg)
- ▲ = macrophage concentration (mg/kg)
- △ = ELF concentration (mg/l)

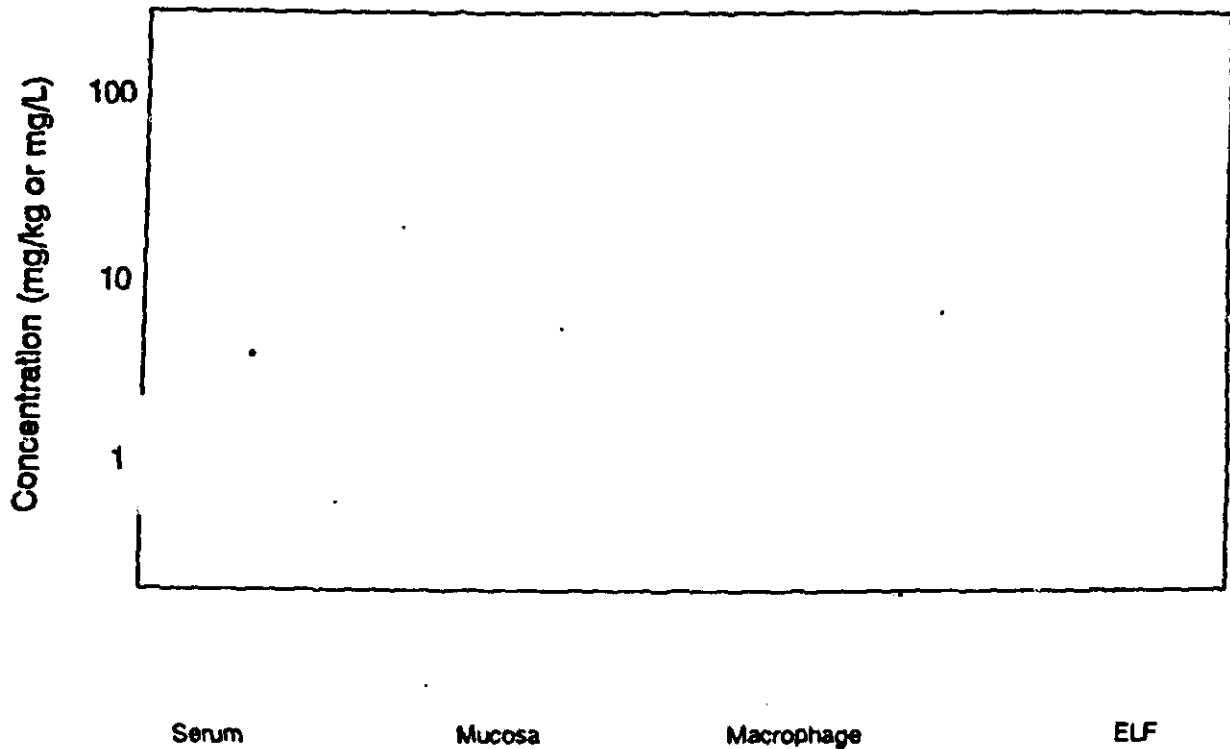


Figure 2: Sparfloxacin concentrations in serum, bronchial mucosa, alveolar macrophages and epithelial lining fluid (ELF), following multiple oral doses (400 mg o.d. D1, 200 mg o.d. D2 and D3).

- = serum concentration (mg/l)
- = mucosa concentration (mg/kg)
- ▲ = macrophage concentration (mg/kg)
- △ = ELF concentration (mg/l)

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A phase I, open, non-comparative, multicenter study of diffusion in pleural effusion and tolerance of sparfloxacin administered as a single 400 mg oral dose to 24 subjects.	
Coordinator :		
Investigators :		
Publication (reference)	None	
Study period (years):	1991 - 1992	
Objectives :	To study the concentrations achieved in pleural effusion and in plasma, and the clinical tolerance after a single oral 400 mg intake of sparfloxacin.	
Methodology:	Open, non-comparative, multicenter study, two groups of subjects randomized according to the time of sample with respect to sparfloxacin intake.	
Number of subjects:	Two groups will be randomly determined according to the time of sparfloxacin administration before pleural puncture. 24 adult volunteers with pleural effusion were planned (12 in each group). 31 were included.	
Diagnosis and criteria for inclusion:	Adult subjects male or female with reliable contraception or post-menopausal. Suspicion of pleural exsudative effusion. Written informed consent.	
Test product, dose: Mode of administration:	Oral single administration of 4 tablets of sparfloxacin 100 mg film coated tablets, on day 1. Group A: 4 hours $\pm$ 1 h before puncture; Group B: 20 hours $\pm$ 1 h before puncture.	
Batch n°:	Batch n°CB 4654	
Duration of treatment:	Single dose	
Reference therapy	None	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume : 54 Page :	(FOR NATIONAL AUTHORITY USE ONLY)																		
Study procedures: Pharmacokinetics Safety:	Samples were assayed by HPLC with U.V. detection - Blood samplings: Day 1: H0 (before sparfloxacin administration), H4 ± 1, or H20 ± 1 after sparfloxacin intake; - Pleural samplings: Day 1: H4 ± 1, or H20 ± 1; For each time group, following parameters were determined in plasma and pleural fluid. T_{mean} : mean time after dosing; C_{mean}: observed mean concentration; mean percentage of penetration (C_{pleural}/C_{plasma}). If further investigations were necessary for the management of the patients, some more samples of pleural tissue or pleural liquid were possible. - Clinical examination on selection visit, days 1, 3, and 7 if necessary. - adverse events recording at each visit.																			
Statistical methods:	- Pharmacokinetics: descriptive statistics - Safety: descriptive statistics.																			
Results - conclusions:	31 subjects were included in the study and analysed for the safety. (additional subjects were included to replace subjects that were not evaluable for pharmacokinetic analysis) Pharmacokinetics results: 25 subjects were analysed. After oral administration of 400 mg sparfloxacin, plasma concentrations decreased a two fold in the time delay from 4 hours (presumed T_{max}) till 20 hours post dose. Despite this decay in plasma concentrations, pleural fluid concentrations remained constant over time. They represented only 1/3 of the plasma concentrations at 4h post dose, but were close to plasma concentrations at 20h post dose (ratio 0.9). Mean plasma and pleural fluid concentrations (µg/ml) and ratio of pleural fluid to plasma concentration (± SD) <table border="1" data-bbox="612 1453 1321 1588"> <thead> <tr> <th colspan="3">4 ± 1 h post dose (n = 10)</th> <th colspan="3">20 h ± 1 h post dose (n = 11)</th> </tr> <tr> <th>Plasma</th> <th>Pleural liquid</th> <th>Ratio</th> <th>Plasma</th> <th>Pleural liquid</th> <th>Ratio</th> </tr> </thead> <tbody> <tr> <td>1.76 ± 0.65</td> <td>0.63 ± 0.39</td> <td>0.34 ± 0.12</td> <td>0.80 ± 0.27</td> <td>0.69 ± 0.29</td> <td>0.91 ± 0.30</td> </tr> </tbody> </table>		4 ± 1 h post dose (n = 10)			20 h ± 1 h post dose (n = 11)			Plasma	Pleural liquid	Ratio	Plasma	Pleural liquid	Ratio	1.76 ± 0.65	0.63 ± 0.39	0.34 ± 0.12	0.80 ± 0.27	0.69 ± 0.29	0.91 ± 0.30
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NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 54 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
	Safety: 18 adverse events were reported by the subjects during the study but they were not deemed as related to the study medication. Only episodes of moderate nausea with vomiting of possible imputability were reported by one subject (N°30) 3h after pleural puncture. Three subjects died respectively 15, 18, and 35 days after sparfloxacin intake, but these events were the progression of an underlying disease and were judged unrelated to the study medication by the investigators. One subject aged 79 years old died following aggravation of pleural adenocarcinoma, the second one aged 66 years old died of respiratory insufficiency due to the progression of his pulmonary cancer, and the third one aged 41 died of the terminale evolution of a non-Hodgkin's malignant lymphoma. No clinically significant changes were observed in clinical and haemodynamic parameters.	
	Conclusion: - The pleural concentration of sparfloxacin is 1/3 of plasma concentration after 4 hours and equal to plasma concentration after 20 hours. These concentration are superior to the MICs of most frequently isolated pathogens in community-acquired respiratory infections. - A single dose of 400 mg of sparfloxacin was generally well tolerated	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 55 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study (phase I)	A phase I, open non comparative study of ocular pharmacokinetics in aqueous humor and safety of sparfloxacin administered as a single 400 mg oral dose to 24 patients volunteers	
Investigators:		
Study centre:		
Publication (reference):	None	
Studied period (years):	1991	
Objectives:	To determine the concentration of sparfloxacin in aqueous humor after a single dose of 400 mg sparfloxacin and the ratio between humor and serum concentrations. Secondly, to assess the safety of sparfloxacin.	
Methodology:	Open, non-comparative, randomized study. 24 patients undergoing cataract surgery.	
Number of subjects:	24 planned, 31 enrolled, 3 dropouts from pharmacokinetic analysis	
Diagnosis and criteria for inclusion:	Patient volunteer, male or female, over 18 years old, undergoing cataract surgery; females of non child bearing potential; subjects giving written informed consent.	
Test product, dose, mode of administration, batch n°:	oral sparfloxacin 4 x 100 mg tablets administered as a single dose CB 4653	
Duration of treatment	One day	
Reference therapy, dose, mode of administration, batch n°:	None	
Study procedures:	Pharmacokinetics: concentration of sparfloxacin in aqueous humor and serum and ratio of aqueous humor to serum concentration. Blood sampling: H0 before drug intake and concomitant to aqueous humor sampling. Aqueous humor sampling: patients randomly allocated to one of the six sampling times: H2, H5, H8, H10, H12, H24 after drug intake. HPLC assay of serum and aqueous humor. Safety: clinical examination on days 1 and 7 and if necessary on the other days, adverse events recording.	
Statistical methods:	Descriptive statistics for pharmacokinetic parameters by group.	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 55 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results - conclusion

pharmacokinetic results:

Three patients were excluded from the pharmacokinetic analysis. Two had missing aqueous humor samples and the other one had a missing baseline blood sample.

Mean values and standard deviations per group:

Sampling time	n	Aqueous humor concentration (mg/l)	Serum concentration (mg/l)	Ratio of aqueous humor to serum (%)
H 2	5	0.127 (0.080)	1.228 (0.792)	16.3 (13.5)
H 5	5	0.212 (0.195)	1.012 (0.423)	18.9 (10.2)
H 8	4	0.248 (0.073)	1.201 (0.312)	21.2 (7.0)
H 10	5	0.387 (0.211)	1.404 (0.743)	26.7 (4.8)
H 12	4	0.356 (0.131)	1.230 (0.288)	28.4 (5.0)
H 24	5	0.404 (0.355)	0.465 (0.378)	115.2 (74.8)

The pharmacokinetic findings showed that an oral dose of 400mg sparfloxacin leads to reliable therapeutic concentrations in the aqueous humor within 8 to 10 hours after drug administration. The good penetration of sparfloxacin, persisting over 24 hours after dose is of particular interest (0.404 mg/l in aqueous humor versus 0.465 mg/l in serum). Regarding the rapid "turnover" of this biological fluid, the persistence of the product seems to be remarkable.

The penetration of sparfloxacin in aqueous humor exceeding MIC 90 levels, its persistence and its antibacteriological spectrum seem to qualify this agent for being an appropriate product at least in the maintenance treatment of endophthalmitis.

Safety:

No adverse events recorded; the clinical and biological safety of sparfloxacin was good.

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 56 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study:	A phase I, open, noncomparative study of intravitreal pharmacokinetics and safety of sparfloxacin administered as multiple oral dose to 6 patient volunteers.	
Investigators:		
Study centre:		
Publication (reference):	None.	
Study period (years):	1991 - 1992.	
Objectives:	To evaluate the concentration of sparfloxacin in vitreous and serum and the ratio of vitreous to serum concentrations after multiple dosing. To assess the safety of sparfloxacin.	
Methodology:	Open, noncomparative study.	
Number of subjects:	planned: 6; enrolled: 8.	
Diagnosis and criteria for inclusion:	Patient volunteer, male or female, over 18 years old, undergoing vitrectomy; females of non child bearing potential; written informed consent.	
Test product, dose, mode of administration, batch n°:	oral sparfloxacin 100 mg tablets administered as multiple dose (day 1: 4 tablets; day 2, day 3 and day 4: 2 tablets) CB 4653	
Duration of treatment:	Four days	
Reference therapy:	None	
Study procedures:	Pharmacokinetics: concentration of sparfloxacin in vitreous and serum; ratio of vitreous to serum concentrations. Blood sampling: - day 1: H0 before drug intake, - day 4: H0 before drug intake and 4 to 8 hours post dose (H4-8), concomitant to vitreous sampling. Vitreous sampling: - day 4: 4 to 8 hours post dose (H4-8) HPLC assay of serum and vitreous. Safety: Clinical examination including vital signs and biological profile at selection and D7; adverse event recording.	
Statistical methods:	Descriptive statistics for pharmacokinetic and safety parameters.	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 56 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results - conclusion:

Pharmacokinetic results:

Mean values and standard deviations at H4-8, day 4 (n=8)

Patient numbers	Vitreous sampling time after last dose	Mean serum concentration µg/ml H0 (day 4)	Mean serum concentration µg/ml H4-8 (day 4)	Mean vitreous concentration µg/ml H4-8 (day 4)	Mean ratio (%) of vitreous to serum concentrations H4-8 (day 4)
01	5h45min	ND	1.321	0.646	48.9
02	5h30min	ND	1.209	0.480	39.7
03	4h30min	0.787	1.836	0.651	35.5
04	5h30min	ND	1.484	0.800	53.9
05	7h35min	1.352	2.524	0.749	29.7
06	6h10min	0.728	0.821	0.500	60.9
07	4h40min	ND	3.635	2.060	56.7
08	8h00min	0.747	1.611	0.864	53.6
MEAN ± SD	6h09min	0.90 ± 0.13	1.81 ± 0.89	0.84 ± 0.51	47.4 ± 11.1

Safety:

One cardio-vascular adverse event was recorded (moderate thoracic pain and tachycardia), rated as not related to the study medication. No other adverse events were reported. No clinically significant changes related to the medication were found in any vital signs or laboratory values.

Conclusions:

A four days treatment (400 mg the first day and 200 mg the three following days) led to therapeutic concentrations in the vitreous.

Sparfloxacin clinical and biological safety appeared satisfactory.

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 49 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study (phase I)	A phase I, open, metabolism-balance and pharmacokinetics Study of ¹⁴ C sparfloxacin in 6 healthy male volunteers	
Investigators:		
Study centre:		
Publication (reference):	None	
Study period:	1991	
Objectives:	To carry out an excretion balance study of ¹⁴ C sparfloxacin and to investigate the pharmacokinetics of radiolabelled and parent compound.	
Methodology:	Open, one way study in 6 healthy male volunteers of an oral dose of 400 mg (50 μ Ci) of ¹⁴ C sparfloxacin.	
Number of subjects:	6	
Diagnosis and criteria for inclusion:	Male adult healthy volunteers between 18 to 40 years of age; body weight of within 10% of ideal range; Written informed consent	
Test product, dose, mode of administration, batch n°:	Oral sparfloxacin 3 x 100 mg tablets, batch number CB 4986; 100mg of sparfloxacin with 50 μ Ci of ¹⁴ C sparfloxacin (batch number CB 4987) in a carboxymethyl cellulose suspension.	
Duration of treatment	Single dose	
Reference therapy	None	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 49 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Study procedures:	Pharmacokinetics: Blood sampling pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours post-dose. Urine collection 0 to 4, 4 to 8, 8 to 12 and 12 to 24 hrs and each 24hrs up to 240 hours post-dose. Faeces collection each day for 10 days.	
Criteria for evaluation: Pharmacokinetics Safety	The total radioactivity in urine and faeces was determined and concentrations of unchanged and conjugated sparfloxacin in plasma and urine were assayed by HPLC. Pharmacokinetic parameters, blood and plasma: C _{max} , AUC, T _{1/2} , T _{max} , after a single oral dose. Assessments of blood/plasma and protein binding and urinary excretion. Physical examination including vital signs and biological profile, before treatment. Adverse events recording	
Statistical methods:	Continuous variables (C _{max} , AUC, T _{1/2}) were analysed using either the GLM procedure, followed by multiple range test, or univariate procedure. Wilcoxon's test was used for T _{max} . Descriptive statistics were used for patients demographic and biological data.	

Results (the 6 subjects included were analysed) : No adverse events was reported.

The pharmacokinetic results for total radioactivity were as follows :

Parameter	Mean ± SD	CV%	Plasma / blood ratio (mean ± SD)
C _{max} (ng/ml)			
plasma	3510 ± 1279	36.43	0.80 ± 0.13
blood	4280 ± 863	20.16	
T _{max} (h)			
plasma	0.75* : 0.5-1.0**		
blood	0.75* : 0.5-1.0**		
AUC 0-t (h.ng/ml)			
plasma	48248 ± 8566	17.15	0.70 ± 0.11
blood	69898 ± 14916	21.34	
AUC inf (h.ng/ml)			
plasma	50698 ± 8382	16.53	0.69 ± 0.11
blood	75238 ± 15944	21.19	
T _{1/2} (h)			
plasma	18.86 ± 1.14	6.02	
blood	20.24 ± 3.19	15.79	

* median

** range

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 49 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

The results of the pharmacokinetic analysis of unchanged sparfloxacin are shown below :

Parameter	Mean ± SD	CV%
C _{max} (ng/ml)	2587 ± 846	32.71
T _{max} (h)	0.75* ; 0.5-1.0**	
AUC 0-t (h.ng/ml)	39148 ± 7196	18.38
AUC Inf (h.ng/ml)	40846 ± 7142	17.49
T _{1/2} (h)	19.55 ± 1.27	6.49

* median

** range

Sparfloxacin and its metabolite do not concentrate in blood and cells.

Fast absorption of radiolabelled drug, T_{max} = 0.75 h.

In plasma there was little difference between the results obtained from assay of radioactivity and the specific HPLC assay for sparfloxacin.

Between 90.5 and 100.8% of the radiolabelled sparfloxacin was eliminated via the faeces and urine.

Conclusions

The overall recovery was excellent ranging from _____ % of the administered dose. Therefore, there was no retention of sparfloxacin in human body tissues.

Sparfloxacin was well tolerated.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 35 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, open, noncomparative study of biliary excretion and tolerance of sparfloxacin administered as a single 400 mg oral dose to 12 patients with biliary tract drainage.	
Investigators:		
Study centres:		
Publication (reference):	None	
Study period (years):	1992	
Objectives:	• To determine the biliary excretion of sparfloxacin and of its glucuronide conjugate in patients with biliary tract drainage. • To assess the safety of the drug.	
Methodology:	Bicentric, open, noncomparative, single dose study.	
Number of subjects:	12: 5 Males and 7 Females.	
Diagnosis and criteria for inclusion:	Patients aged 18-80 years of either sex; female must be of non-childbearing potential (surgically sterile, IUD or oral contraceptive). T tube drainage of biliary tract. Written or witnessed oral informed consent. Body weight in accordance with Metropolitan Life Insurance Actuary Tables ($\pm 20\%$ acceptable). This applies to AT 139 only.	
Test product, dose, mode of administration, batch No.:	Film-coated tablets each containing 100 mg of sparfloxacin, batch CB 4654. Single oral dose of 400 mg (4 tablets) in the morning with a glass of water.	
Duration of treatment:	Single dose.	
Reference therapy:	None.	
Study procedures	Collection of plasma, bile and urine samples from patients with bile drainage after drug intake. Unchanged sparfloxacin and sparfloxacin glucuronide concentrations measured by reversed-phase HPLC assay in:	
	• Plasma from blood samples immediately predrug and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 144 $\pm$ 24 hours postdrug. • Bile collected predrug and 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-16, 16-24, 24-36, 36-48 and 48-72 hours postdrug. • Urine collected predrug and 0-6, 6-12, 12-24, 24-48, 48-72 and 72-96 hours postdrug.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 35 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results- conclusions (continued)

PHARMACOKINETIC PARAMETER Mean ± SD	UNCHANGED SPARFLOXACIN (N = 11*)	SPARFLOXACIN GLUCURONIDE (N = 11*)
C _{max} (µg/ml)	1.56 ± 0.61	2.38 ± 1.32
t _{max} (h)	15.8 ± 15.28	14.5 ± 13.02
AUC 0-t _{last} (µg.h/ml)	46.9 ± 12.22	78.2 ± 38.68
AUC 0-∞ (µg.h/ml)	48.5 ± 11.58	81.0 ± 38.59
t _{1/2} (h)	21.3 ± 7.41	20.8 ± 6.02
MRT (h)	37.5 ± 18.40	-
Cl _r (ml/min)	145 ± 33.61	-
Cl _f (ml/min)	13.0 ± 3.47	65.5 ± 39.62
Cl _{rv} (ml/min)	132 ± 32.94	-
Cl _{bil} (ml/min)	2.77 ± 1.72	21.4 ± 16.65
V _{dp} (l)	272 ± 136.40	-
V _{dss} (l)	334 ± 218.93	-
f _u (% dose)	8.79 ± 3.08	39.4 ± 11.44
f _{u,bil} (% dose)	1.51 ± 1.00	11.5 ± 6.85
f _{u+bil} (% dose)	10.3 ± 3.15	50.9 ± 9.14
f _{tot} (% dose)	61.2 ± 11.13	

- * Patient (AT 111) was excluded from analysis, except for renal and biliary clearance (N = 12) because she was classified as a poor absorber due to postsurgical stenosis.

Adverse experience and safety profile:

- Increased liver enzymes and blood glucose possibly drug related in one patient.
- No clinically significant changes in vital signs.
- No clinically significant changes in ECG.

Conclusions:

Pharmacokinetic parameters showed a wide variability in patients with biliary drainage. Renal and biliary excretion of the drug accounted for 48% and 13% of the dose respectively resulting in a bioavailability of at least 61%. Plasma, urinary and biliary concentrations of unchanged sparfloxacin remained far in excess of MIC values for clinically relevant pathogens for periods up to 48 hours in plasma and bile and up to 96 hours in urine. The clinical and laboratory safety of sparfloxacin was good at a single dose of 400 mg.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 57 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, open, noncomparative study of biliary excretion and tolerance of sparfloxacin administered as a single 400 mg oral dose to 8 patients with biliary tract drainage.	
Investigators:		
Study centre:		
Publication (reference):	Pechinot A. et al. "Kinetics of biliary excretion of sparfloxacin in the human", 6th ECSMID, Seville, Spain, 28-31 March, 1993.	
Study period (years):	1992	
Objective:	To determine the biliary excretion of sparfloxacin and its glucuronide conjugate in patients with biliary drainage and to assess the safety of the drug after a single oral dose of 400 mg in these patients.	
Methodology:	Monocentric, open, noncomparative, single dose study.	
Number of subjects:	4: 3 male and 1 female.	
Diagnosis and criteria for inclusion:	Patients aged 18-80 years of either sex; female must be of non-childbearing potential. T tube drainage of biliary tract. Written informed consent. Body weight in accordance with Metropolitan Life Insurance Actuary Tables.	
Test product, dose, mode of administration, batch No.:	Film-coated tablets each containing 100 mg of sparfloxacin, batch CB 4654. Single dose of 400 mg (4 tablets) in the morning with a glass of water.	
Duration of treatment:	Single dose.	
Reference therapy:	None	
Study procedures:	Collection of serum, bile and urine samples in patients with bile drainage after drug intake. Sparfloxacin concentrations measured by HPLC assay on: • 5 ml blood samples immediately predrug and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 144 ± 24 hours postdrug • Bile collected predrug and 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-16, 16-24, 24-36, 36-48 and 48-72 hours postdrug. • Urine collected predrug and 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 hours postdrug.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 57 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Study procedures: (continued) Pharmacokinetics: Safety:	Determination of the following parameters: C _{max} , t _{max} , AUC 0-144, AUC 0-∞ and t _{1/2} in serum, A _{e,b} , f _{e,b} and Cl _b in bile and of A _{e,u} , f _{e,u} and Cl _u in urine. Clinical evaluation, adverse events, vital signs, 12-lead ECG recording and laboratory tests at selection and postdrug.	
Statistical methods:	Pharmacokinetic parameters: Mean ± SD. Vital signs and laboratory tests: Mean ± SD, min and max values at baseline, and mean differences ± SD from baseline on D2, D3, D4, D5, D7 ± 1.	

Summary - conclusions:

Note: Due to the difficulty in recruiting patients who would meet the inclusion/noninclusion criteria specified in the protocol, the sponsor decided to interrupt the study after the fourth patient.

Pharmacokinetic results

• Pharmacokinetic parameters

PARAMETERS	MEAN (N = 4) ± SD (RANGE)
SERUM	
C _{max} (µg/ml)	2.86 ± 1.71
t _{max} (h)	5
AUC 0-144 h (µg.h/ml ¹)	51.93 ± 14.65
AUC 0-∞ (µg.h/ml ¹)	52.74 ± 14.81
t _{1/2} (h)	21.2 ± 5.1
BILE	
A _{e,b} 0-72 h (mg)	11.95 ± 2.84
f _{e,b} (% dose)	2.99 ± 0.71
Cl _b (ml/h)	0.24 ± 0.04
URINE^a	
A _{e,u} (mg)	Not calculated
Cl _u (ml/h)	Not calculated
f _{e,u} (% dose)	Not calculated

a: Values in 2 patients only

b: First value for 0-96 h period; second value for 0-72 h period

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 57 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Summary - conclusions: (continued) • Plasma, bile and urine concentrations - Serum: • Concentration range of µg/ml one hour postdrug. • Maximal concentration range of µg/ml • Concentration range of µg/ml hours postdrug. - Bile: • Concentration range of µg/ml hour postdrug. • Maximum concentration range of µg/ml. • Concentration range of µg/ml in hour bile. - Urine: • Concentration range of µg/ml in hour urine. • Concentration range of µg/ml in hour urine. Safety results: - 15% increase in QTc probably related to the drug in one patient. - Low blood pressure (80-40 mmHg) in one patient 24 hours postdrug. - Increased heart rate (120 beats/min) in one patient 24 hours postdrug. - General decrease toward normal values of initially high WBC and neutrophil counts. Drug relationship of the blood pressure, heart rate and laboratory test observations was unknown. Conclusions: Following a single oral dose of 400 mg of sparfloxacin in 4 patients with biliary drainage, concentrations of the drug clearly above MIC values for susceptible pathogens were achieved in serum, bile and urine for postdrug periods of 48 hours (in serum) and 72 hours (in bile and urine). As regards safety, a reversible 15% increase in QTc value was observed in one patient with a low QTc baseline value but remained in the normal range (≤ 440 msec). Sparfloxacin clinical and laboratory safety appeared otherwise satisfactory.		

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 33 Page :	(FOR N USE ON
Title of the study: (Phase I)	A phase I, open, randomised, crossover sparfloxacin administered as a single 400 mg oral dose with Chlorammonic or Alcaphor to 12 healthy volunteers on crystalluria induction.	
Investigators:		
Study centre:		
Publication (reference):	None	
Study period (years):	1991	
Objectives:	• To assess an eventual effect of sparfloxacin on crystalluria induction. • To assess the safety of a 400 mg single dose of sparfloxacin.	
Methodology:	Design: Open, randomised, two-way crossover study.	
Number of subjects:	12 (13 included; 1 dropout)	
Diagnosis and criteria for inclusion:	Healthy male subjects aged 18-30 years. Body weight within 10% of ideal weight (Metropolitan Insurance Company Actuary Table). Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 400 mg as 4 film-coated tablets each containing 100 mg of sparfloxacin (RP 64206) at 8:00 a.m. Batch No. CB 4653 Oral administration of 6 tablets of Chlorammonic® (0.5 g of ammonium chloride per tablet) at 12:00 a.m. and 6 tablets at 8:00 p.m. : Batch No. 641. Oral administration of 30 ml (2 tablespoons) of Alcaphor® (trometamol 15.33 g/100 ml) at 12:00 a.m. and 30 ml at 8:00 p.m. Batch No. 03	
Duration of treatment:	Single dose of sparfloxacin. Two administrations at 15-day interval.	
Reference therapy:	None	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 33 Page :	(FOR NATIONAL AUTHORITY USE ONLY)
Study procedure:	Single oral administrations of sparfloxacin at 8:00 a.m. followed by administrations (12.00 a.m. and 8:00 p.m.) of either Chlorammonic® (treatment A) or Alcaphor® (treatment B) with each treatment separated by a 15-day washout period. Subjects were randomised into 2 groups of 6 corresponding to 2 treatment sequences: - Treatment sequence A/B: treatment A in period 1 and treatment B in period 2. - Treatment sequence B/A: treatment B in period 1 and treatment A in period 2. After treatment, urine was collected from 11:00 p.m. until 8:00 a.m. the next day.	
Criteria for evaluation Crystalluria: Excretion: Safety:	Determination of volume and pH of fresh urine. Assessment of crystalluria by light microscopy and IR spectrometry on fresh urine and urine stored at 4°C. Determination of calcium, phosphorus, uric acid, chloride, sodium, potassium, urea, creatinine, magnesium, citrate and oxalate urinary concentrations. Determination of unchanged and total sparfloxacin excretion in urine collected overnight (11:00 p.m.- 8:00 a.m.) Clinical evaluation (visits 1, 2, 4), adverse events, laboratory tests (visits 1, 4).	
Statistical methods:	Urinary excretion of sparfloxacin: Mean values $\pm$ SD were calculated after all the data were pooled. Vital signs: Mean values $\pm$ SD, minimum and maximum values and mean differences $\pm$ SD from baseline according to treatment sequence.	
Results - conclusions: One subject withdrew from the study for personal reasons after the first treatment (sparfloxacin + Alcaphor®). Assessment of crystalluria: - At ambient temperature - At baseline: No crystalluria. - After Chlorammonic®: Presence of crystals of dihydrated calcium oxalate in the urine of 4 subjects. - After Alcaphor®: Presence of crystals, mostly amorphous, calcium carbonate phosphate in the urine of 10 subjects. Presence of rare sparfloxacin crystals in the urine of 1 subject (urine pH = 6.5 at collection).		

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 33 Page :	(FOR NATIONAL AUTHORITY USE ONLY)

Results - conclusions:
(continued)

- At 4°C
- At baseline: Presence of crystals in the urine of most subjects.
- After Chlorammonic®: Presence of crystals in the urine of most subjects. Presence of rare sparfloxacin crystals in the urine of 1 subject (urine pH = 5.3 at collection).
- After Alcaphor®: Presence of crystals in the urine of all subjects.

Urinary excretion of sparfloxacin:

TREATMENT	UNCHANGED SPARFLOXACIN (N = 12)		TOTAL SPARFLOXACIN (N = 12)		% UNCHANGED SPARFLOXACIN
	Concentration (µg/ml)	Quantity (mg)	Concentration (µg/ml)	Quantity (mg)	
Sparfloxacin + Chlorammonic®					
Sparfloxacin + Alcaphor®					

Adverse experience and safety profile:

- After Alcaphor® treatment 2 cases of mild diarrhea possibly related to treatment.
- Minor changes in clinical and laboratory parameters not clinically significant and not related to treatment.

Conclusions:

Attempt was made to acidify the urine of 12 volunteers by treatment with Chlorammonic® and to alkalinize it by treatment with Alcaphor® in order to assess crystalluria following a single dose of 400 mg of sparfloxacin. Alcaphor® treatment resulted in alkaline urine (pH 7.1) in only two subjects whereas following Chlorammonic® urinary pH ranged from 5.0 to 5.8. Regardless of urine pH, rare sparfloxacin crystals were observed in the fresh urine of 1 subject but not after 48-72 h storage at 4°C and in the urine stored at 4°C but not in the fresh urine of another subject. The appearance of the sparfloxacin crystals in urine was therefore related to the conditions of storage rather than to a true crystalluria appearing within the urinary system. The clinical and laboratory safety of a single dose of 400 mg of sparfloxacin was good.

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 42 Page:	(FOR N/ USE ON
Title of the study (Phase I)	Double blind placebo-controlled phase I study of the tolerance of exposure to UV light and the pharmacokinetics of sparfloxacin administered as repeated doses for ten days in parallel groups of 8 healthy volunteers at doses 100, 200, 300, 400 mg once a day.	
Investigator:		
Study centre:		
Publication (reference): pharmacodynamics	R. GARRAFFO, Pharm D - 4 th International Symposium on new quinolones - Munich, August 1992; Abstract n° : 75	
Studied period (years):	1990	
Objectives: main objective secondary objectives	• to evaluate the tolerance to U.V.light exposure of various doses of sparfloxacin in repeated dosing. • To assess the clinical, biological and electrocardiological safety of differents regimens of sparfloxacin in caucasian healthy volunteers. • To determine the pharmacokinetic profile of sparfloxacin after loading dose and after repeated dosing. • To determine the kinetic of serum bactericidal efficacy of sparfloxacin.	
Methodology:	5 parallel groups, randomised, double-blind and placebo-controlled	
Number of subjects:	40 subjects were planned; 42 were included (2 withdrawals) .	
Diagnosis and criteria for inclusion:	Adult, male, healthy volunteers from 20 to 40 years old, fair-skinned and glabrous; subjects within a range of $\pm 15\%$ of the ideal body weight; written informed consent.	
Test product, dose, mode of administration, batch n°:	Once a day oral administration of film-coated tablets each containing 100 mg of sparfloxacin. 100 mg, 200 mg, 300 mg, 400 mg from Day 2 to Day 10 All subjects received an initial loading dose (double dose) on day 1 Batch CB 3976.	
Duration of treatment	Ten days (double dose on day 1 followed by 9 days of treatment).	
Reference therapy, dose, mode of administration, batch n°:	Matching placebo tablets. Same conditions of administration as test drug. Batch CB 4113 P	
Criteria for evaluation:	Tolerance to UV light exposure: Saidman photosensitivity test with UVA and UVB on days <u>4</u> , <u>4</u> and <u>10</u> . Control of response to test was done 24, 42 and 90 hours after exposure. In addition, erythema analysis was performed by digitization from color slides of the volunteers' patches to UVA irradiations on day 4. An hyperbolic model of erythema index change with increasing UVA irradiation was used. - clinical and haemodynamic evaluations: selection, days 1, 4, 10, 11 and 17. - ECG : selection, days 1 and 10 (before: H0, and 6 hours post dose: H6), 4 and 8 (H6), 11 and 17. An analysis of ECG by an independant expert was made after completion of the study.	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 42 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																														
Criteria for evaluation (cont'd):	- laboratory tests: selection, days 1, 4, 8, 11 and 17 - adverse events recording: every visit. - pharmacokinetics: Blood samples: D1: H0 - H1 - H2 - H3 - H4 - H6 - H8 - H12 - H24, Pe-1 - rough (H0, H6) on days 2, 3, 4, 8 D10: same as day 1 and H48 - H72 - H96 - H120. Urine samples: D1: H0, H0 - H6, H6 - H12, H12 - H24, D10: same as day 1 and, H24 - H48, H48 - H72, H72 - H96, H96 - H120, H120 - H144, H144 - H168. Determination of Cmax, Tmax, AUC 0-24H on days 1 and 10 Statistical analysis on data from Day 10 Kinetics of serum bactericidal effect: blood samples: Day 1: H0, H4, H8, H24 Kinetics of serum bactericidal activity were studied by assessing the bactericidal activity of serially diluted sera sampled 4, 8 and 24 hours after receiving the loading doses (200, 400, 600, and 800 mg). The number of surviving bacteria were counted after 0, 1, 3, 5, and 24 hours in the various sera.																															
Statistical methods:	Analysis of variance for UVA Minimum Erythral Dose. Logistic regression for spontaneous adverse reactions. Descriptive statistics for other safety parameters (including ECG) ANOVA and Wilcoxon test for pharmacokinetics																															
Results - conclusions:	42 subjects were included and completed study. Two withdrawals occurred during treatment (1 in the placebo group, for personal reasons, the other in the 400/200 mg group, for violation of selection criteria). All subjects are kept in the analysis for available data. Kinetic of serum bactericidal effect was studied in 30 subjects (5 groups of 6 subjects). 1) U.V.A / Irradiation: Saidman test: Photosensitivity reactions, with U.V.A only, were clearly observed in volunteers receiving active treatment, as shown by the calculation of Minimum Erythral Dose (MED). (UVB: no photosensitivity) <table border="1" data-bbox="649 1447 1344 1626"> <thead> <tr> <th>Mean ± SD (J cm⁻²)</th> <th>N</th> <th>Day -4</th> <th>Day 4</th> <th>Day 10</th> </tr> </thead> <tbody> <tr> <td>Placebo group</td> <td>9</td> <td>NM</td> <td>NM</td> <td>49.2 (n=1)*</td> </tr> <tr> <td>200/100 mg</td> <td>8</td> <td>NM</td> <td>15.48±5.87 (n=5)*</td> <td>17.38±7.59</td> </tr> <tr> <td>400/200 mg</td> <td>9</td> <td>NM</td> <td>11.05±4.02</td> <td>10.59±2.40 (n=8)*</td> </tr> <tr> <td>600/300 mg</td> <td>8</td> <td>NM</td> <td>10.38±3.20</td> <td>9.00±3.16</td> </tr> <tr> <td>800/400 mg</td> <td>8</td> <td>NM</td> <td>8.04±3.74</td> <td>6.57±3.80</td> </tr> </tbody> </table> NM: no MED was measurable (no clear erythema) *: mean was calculated only with "n" cases (other cases were NM)		Mean ± SD (J cm ⁻²)	N	Day -4	Day 4	Day 10	Placebo group	9	NM	NM	49.2 (n=1)*	200/100 mg	8	NM	15.48±5.87 (n=5)*	17.38±7.59	400/200 mg	9	NM	11.05±4.02	10.59±2.40 (n=8)*	600/300 mg	8	NM	10.38±3.20	9.00±3.16	800/400 mg	8	NM	8.04±3.74	6.57±3.80
Mean ± SD (J cm ⁻²)	N	Day -4	Day 4	Day 10																												
Placebo group	9	NM	NM	49.2 (n=1)*																												
200/100 mg	8	NM	15.48±5.87 (n=5)*	17.38±7.59																												
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NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 42 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																																														
2) Erythema, paresthesia: Local spontaneous photosensitivity reactions (erythema, pigmentation, desquamation) occurred with a clear dose - effect relationship.																																																
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Results of the hyperbolic model were similar to the clinical observation. Paresthesias (pruritus, tingling, feeling of warmth) were observed, with a direct relationship between symptoms and dose, and a good correlation with erythema. No modification of vital signs were observed in any group. Laboratory safety was good: a moderate increase in transaminases was observed, which disappeared spontaneously during continued treatment in one case receiving 600/300 mg of active product. Electrocardiographic monitoring showed an increase in QTc duration on the ECG 6 hours post-dose on D1, in the 600/ 300 and 800/400 mg groups.																																																

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The mean increases were 6.56% and 7.71% (QTc Bazett) respectively. This effect was still present on the ECG performed at H6 on D4 and D8, but decreased over 24 hours as observed on D10, H0 but recured on D10, H6. The QTc values returned towards baseline within 24 hours after the end of the treatment (D11). The maximum QTc value observed was 423 msec, which is still within normal limits. Other parameters (PR, QRS) were not modified.																																																																																																																																		

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Other clinical events occurred in all groups, especially headaches with the same frequency in all groups, and digestive symptoms. Their frequency or severity was not related to the dose.

Treatment group	Events	Subjects and number of episodes ()	Maximum severity	Relationship to treatment
Placebo	Headache Fatigue Epistaxis Dyspepsia Dermatitis eyelid	14 (3), 17 (2), 36 (2) 17, 31, 36 36 (3) 8 6	Severe Moderate Mild Mild Mild	possible possible possible possible None
200/100	Headache Fatigue After taste, paraesthesia Diarrhea Herpes	2(2) 2 2, 35, 40, 11 9 35	Moderate Mild Moderate Severe Moderate	possible possible possible possible possible
400/200	Headache Fatigue After taste Nausea Meteorism Vasovagal reaction Epistaxis Photopsis Rhinitis Lumbago	1, 12(3), 26, 34 12, 26 (2) 26 (3) 41 (2) 24 (2) 24 37 7 12 19	Severe Moderate Moderate Mild Mild Severe Mild Mild Moderate Moderate	possible possible possible possible possible None possible possible None None
600/300	Headache Fatigue After taste Diarrhea Constipation Dyspepsia Dysphagia Pain epigastric Pain (jaw, tooth) Pain muscle Pain Coughing Intellect impaired Ear buzzing Adenopathy Rhinitis and pharyngitis Hemstoma (puncture site)	5(2), 18(4), 30, 33(3) 8 5 23 18 23 8 5 30 (2) 33 8 8 36 6 5 8 36	Severe Mild Mild Moderate Moderate Moderate Mild Mild Moderate Mild Mild Mild Mild Mild Mild Mild Moderate	possible None Probable None None None None possible None None None possible possible possible possible None None
800/400	Headache Fatigue After taste Diarrhea Nausea Polyuria and polydipsia Adenopathy Rhinitis	13(2), 27(3), 32, 39 10, 39 27 39 13 (2) 39 16 27	Severe Mild Mild Mild Moderate Moderate Moderate Mild	possible possible possible None possible possible None None

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Conclusion: the photosensitivity reactions were dose dependent, and remain mild at 400/200 mg/day. General clinical and laboratory tolerance were good.

The increase in the Qtc values was also dose dependant, and observed in the 600/300 and 800/400 mg/day groups. However all values remained within the normal range (highest value observed: 423 ms).

Pharmacokinetic: Results showed that there was no significant difference between days 1 and 10 for C_{max}, t_{max} or AUC 0-24h values, for the 200/100 mg, 600/300 mg and 800/400 mg dosage regimens. In contrast, for the 400/200 mg dose regimen, C_{max} and t_{max} were not statistically different, but AUC 0-24h was significantly higher on day 1 than on day 10.

		Mean (SD)	200/100 mg	400/200 mg	600/300 mg	800/400 mg
Day 1	after loading dose	C _{max} (ng/ml)	817 (229)	1 688 (473)	1 950 (449)	2 401 (610)
		t _{max} (h)	4.25 (2.82)	3.13 (0.83)	5.88 (2.53)	5.5 (3.12)
		AUC _{0-24h} (ng/ml/h)	2 638 (3 220)	24 687 (5 775)	33 681 (7 098)	41 587 (11 462)
Day 10	after repeated dosing	C _{max} (ng/ml)	723 (110)	1 358 (369)	2 074 (487)	2 874 (597)
		t _{max} (h)	3.25 (1.98)	3.5 (2.14)	5.5 (2.27)	3.75 (1.39)
		AUC _{0-24h} (ng/ml/h)	11 038 (1 115)	20 410 (4 585)	34 571 (7 271)	45 329 (13 826)

Sparfloxacin half-life was unchanged for the 4 dosage regimens (means between 17.82 and 22.29 h).

Urinary excretion of free (unchanged) and total (+ glucuronide metabolite) sparfloxacin calculated on Day 10 was about 8% and 30% respectively for all dose regimens.

C_{max} and AUC were dose related, increasing proportionately with increasing sparfloxacin doses. Sparfloxacin kinetics after repeated administration are linear.

Serum bactericidal activity.

Against *E. coli*, sparfloxacin activity was "concentration dependant" the lowest effective concentration was 0.015 µg/ml, less than one tenth of the trough plasma concentration obtained with the 200/100 mg regimen. The maximal bactericidal effect was calculated and gave 1.2 µg/ml obtained with the 400/200 mg regimen.

Against Gram positive organisms, sparfloxacin activity was "time dependant". The lowest effective dose against *Staphylococcus aureus* was calculated to be 0.089 µg/ml and was reached with the 200/100 mg regimen which gives bactericidal serum concentration for 24 hours. The lowest effective dose against *Streptococcus pneumoniae* (penicillin susceptible) was 0.45 µg/ml and was reached by the 400/200 mg regimen which gives bactericidal serum concentration for 24 hours. The penicillin resistant strain was as susceptible to sparfloxacin as the penicillin susceptible strains.

SYNOPSIS

TITLE A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, RISING, MULTIPLE-DOSE, SAFETY AND PHARMACOKINETIC STUDY OF ORAL SPARFLOXACIN (CI-978) IN HEALTHY SUBJECTS (PROTOCOL 978-1)

CLINICAL INVESTIGATORSCI-978 ANALYST

OBJECTIVE To determine the tolerance and pharmacokinetic characteristics of sparfloxacin tablets following administration of a loading dose and multiple (QD) doses to healthy subjects

STUDY DESIGN This was a randomized, double-blind, placebo-controlled, 2-week, rising, multiple-dose study.

DRUG TREATMENT Three groups of 10 subjects each were randomly assigned to multiple-dose treatment with either 100, 200, or 300 mg QD sparfloxacin or placebo on a sequential, rising-dose schedule. All doses were administered once daily for 2 weeks, with an initial loading dose of twice the subsequent doses. Eight subjects per group received sparfloxacin and 2 subjects per group received placebo.

PATIENT CHARACTERISTICS AND DISPOSITION A total of 30 healthy, fair-skinned Caucasian men, ranging in age from 18 to 47 years, participated in this study. Twenty-nine subjects completed the study; 1 subject withdrew because of an adverse event.

PHARMACOKINETICS Single-Dose Pharmacokinetics Sparfloxacin was slowly absorbed following administration of 200-, 400-, and 600-mg oral loading doses. Mean t_{max} values increased from 4.7 to 9.1 hours over this dose range. Mean C_{max} and AUC(0-24) values increased with increasing dose following 200- to 400-mg doses (0.59 to 0.76 $\mu\text{g}/\text{mL}$ and 9.9 to 12.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively); mean values following 600-mg doses (0.78 $\mu\text{g}/\text{mL}$ and 13.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively) were similar to those following 400-mg doses. Mean elimination $t_{1/2}$ values were similar following 200- and 400-mg doses (20.0 and 20.9 hours) and increased to 32.8 hours following the 600-mg dose. Longer $t_{1/2}$ and later t_{max} values are suggestive of prolonged absorption following the 600-mg dose.

Multiple-Dose Pharmacokinetics Sparfloxacin was slowly absorbed during administration of 100-, 200-, and 300-mg doses QD. Mean t_{max} values were approximately 4 hours over this dose range. Mean C_{max} , C_{min} , and AUC(0-24) values increased proportionally with dose: mean C_{max} values were 0.56, 0.70, and 1.34 $\mu\text{g}/\text{mL}$; C_{min} values were 0.22, 0.31, and

0.63 $\mu\text{g}/\text{mL}$; and $\text{AUC}(0-24)$ values were 8.5, 11.3, and 23.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ following administration of once-daily 100-, 200-, and 300-mg doses, respectively. Elimination $t_{1/2}$ values following administration of 100- to 300-mg doses QD were similar and averaged approximately 22 hours.

Steady-state plasma sparfloxacin concentrations during 100- and 200-mg daily maintenance dosing were similar to plasma concentrations following 200- and 400-mg loading doses, respectively. Steady-state plasma concentrations during 300-mg daily maintenance dosing were higher than those following a 600-mg loading dose because of slower absorption of the 600-mg dose.

The mean percentage of dose excreted in urine as total (unconjugated plus conjugated) sparfloxacin varied considerably and decreased with increasing dose. Mean values following 100, 200, and 300 mg QD were 33%, 26%, and 19%, respectively.

SAFETY Overall, 2 of 6 subjects (33%) receiving placebo experienced 6 adverse events, and 17 of 24 subjects (71%) receiving sparfloxacin experienced 45 adverse events. Sparfloxacin doses through 200 mg QD for 14 days were well tolerated. The most frequently reported adverse events for sparfloxacin-treated subjects were phototoxic rash (29%), headache (21%), dizziness (13%), and nausea (13%). None of the subjects receiving 100 or 200 mg sparfloxacin for 14 days had phototoxic reactions. Mild to moderate phototoxicity was observed in all subjects following sparfloxacin doses of 300 mg QD for 14 days. Of these 8 subjects with phototoxic reactions, 7 subjects had rash which began on Day 12 or 13 of treatment, and 1 subject had generalized pruritus and withdrew from the study on Day 7. One subject treated with 300 mg sparfloxacin had decreased visual acuity, considered a natural progression of myopia and not related to drug administration. Mean cardiac QTc intervals increased 2% to 3% during treatment with 200 mg, and 4% to 8% during treatment with 300 mg sparfloxacin; no effect was noted at a sparfloxacin dose of 100 mg QD or following treatment with placebo. There were no clinically significant changes in vital signs, electroencephalograms, or clinical laboratory measurements.

CONCLUSIONS Sparfloxacin is slowly absorbed. Following single doses up to 400 mg, and multiple daily doses up to 300 mg, mean t_{max} values are approximately 4 to 5 hours, mean C_{max} values range between 0.6 and 1.3 $\mu\text{g}/\text{mL}$, and elimination $t_{1/2}$ values average approximately 20 to 22 hours. Sparfloxacin doses up to 200 mg QD for 14 days are well tolerated. Mild to moderate phototoxicity and mild QTc prolongation are observed following administration of 300 mg QD sparfloxacin for 14 days.

Tabulated Summary Report

Title of study (Phase):	Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose, Parallel Group Study of the Pharmacodynamic Effect of Sparfloxacin Given as 100, 200 or 400 mg Daily (Following a Double-Loading Dose on Day 1) on the Electrocardiograms of Healthy Adult Male Volunteers, Protocol RP 64206X-153 (Phase I).
Investigator:	
Publication (reference):	None.
Study Period:	First Subject Treated: 8 February, 1993 Last Subject Discharged: 21 March, 1993
Study Center:	
Objectives:	The objectives of the study were to: 1) determine whether sparfloxacin dosages of 200/100 mg, 400/200 mg and 800/400 mg are associated with an increase in QTc compared to placebo; 2) define the relationship, if any, between the change in QTc and plasma sparfloxacin pharmacokinetics at three dosage levels in healthy male volunteers; 3) determine the electrocardiographic (ECG) safety of an 800/400-mg dosage regimen; and 4) determine the time course of reversibility of QTc changes following discontinuation of sparfloxacin.
Methodology:	This study was conducted as a randomized, double-blinded, parallel group, multiple-dose study conducted at a single site. Subjects were randomly assigned to one of four treatment groups: Treatment 1: "placebo" (placebo sparfloxacin: eight tablets p.o. Day 1; four tablets p.o. QD Days 2-4). Treatment 2: "sparfloxacin 200/100" (sparfloxacin 200 mg p.o. Day 1; 100 mg QD Days 2-4 plus placebo sparfloxacin six tablets p.o. Day 1 and three tablets p.o. QD Days 2-4). Treatment 3: "sparfloxacin 400/200" (sparfloxacin 400 mg p.o. Day 1; 200 mg p.o. plus placebo sparfloxacin four tablets p.o. Day 1 and two tablets p.o. QD Days 2-4). Treatment 4: "sparfloxacin 800/400" (sparfloxacin 800 mg p.o. Day 1; 400 mg p.o. QD Days 2-4).
Number of subjects:	90 subjects randomized; 88 completed all study procedures.
Diagnosis and criteria for entry:	Healthy adult male volunteers with normal screening physical and laboratory examinations, ECGs, and 24-hour Holters were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 100 mg tablets, manufactured by [redacted] at doses specified above; oral; (lot number 9204834).
Duration of treatment:	4 days.
Reference therapy: dose, route of administration, lot number:	Sparfloxacin placebo, manufactured by [redacted]; oral; (lot number 9204883).
Safety measurements:	Electrocardiograms (mean and maximum QTc at 3, 4 and 5 hours following the sparfloxacin dose on Dosing Days 1 and 4, compared to baseline QTc obtained 0.5 hour before the first dose) and Holter monitoring. The QTc was calculated by the methods of Bazett ("QTc-b"), Fridericia ("QTc-f") and Sagie ("QTc-s"). The relationship of QTc to sparfloxacin pharmacokinetics was examined by comparison of the absolute QTc and change in QTc to plasma drug concentrations. In addition, adverse events, physical examinations, vital signs, and clinical laboratory determinations were assessed.
Pharmacokinetics parameters:	Maximum plasma concentration (Cmax) and time at which it occurred relative to the administered dose (Tmax), half-life (t1/2), and area under the plasma sparfloxacin concentration-time curve (AUC(0-24)).
Statistical methods:	One-way analysis of variance (ANOVA) model with sparfloxacin group versus placebo. One-sided t-tests were used.

Tabulated Summary Report

Results	Safety and Tolerance: Thirty-seven clinical adverse experiences (AEs) occurred during this study, of which 31 occurred during study drug administration. None was considered serious or rated as severe in intensity. No subject discontinued the study due to an AE. The majority of AEs occurring during therapy occurred in the body as a whole (nine subjects), followed by the digestive system (six subjects) and nervous system (four subjects). ECG and Holter Measurements: At steady-state, the sparfloxacin 200/100, 400/200, and 800/400 regimens produced placebo-adjusted increases in the mean QTc from baseline of 7, 12 and 26 msec, respectively. Overall results were similar using Bazett's, Fridericia's, or Sagie's formulas. However, subjects in all treatment groups showed an increase in heart rate at 1.5 hours following sparfloxacin dosing, perhaps related to consumption of breakfast. Of the three formulas, Fridericia's formula appeared to correct most accurately for observed changes in heart rate. Holter monitoring and telemetry showed no torsades de pointes or other forms of ventricular tachyarrhythmia. Maximum plasma sparfloxacin concentrations were 6-16% lower at steady-state than after the loading dose, which was reflected in slightly lower QTc on Day 4 vs. 1. Change in QTc demonstrated a direct relationship to plasma concentrations. Pharmacokinetics: Mean Cmax values at steady-state were 6 to 16% lower than values obtained following a double-loading dose. Mean AUC(0-24) values increased with dose, although the increase was slightly smaller than the dose increase.
Conclusions	• At steady-state, the sparfloxacin 200/100, 400/200, and 800/400 regimens produced placebo-adjusted increases from baseline in the mean QTc of 7, 12, and 26 msec, respectively. • A direct relationship was observed between the change in QTc from baseline and plasma sparfloxacin concentration. • Holter monitoring and telemetry revealed no findings of concern in subjects treated with sparfloxacin as compared to those receiving placebo. • QTc returned to baseline at 48 hours following the last dose.

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Title of the study: (phase I)	Double blind placebo controlled study of the tolerance and pharmacokinetic of sparfloxacin given in repeated doses for 14 days in parallel groups of 8 healthy volunteers, at doses of 400 mg once a day or 200 mg bid.	
Investigators:		
Study centre:		
Publication (reference)	None	
Study period (years):	1989	
Objectives:	To assess on a Caucasian population of young healthy volunteers the general tolerance of a repeated dosing of 400 mg of sparfloxacin, given either as a single dose, or as 200 mg BID. The secondary objective was to determine the pharmacokinetic parameters after single oral administration and after 2 weeks of repeated dosing.	
Methodology:	Parallel groups, randomised double blind and placebo controlled study, planned with 3 groups of 8 volunteers Subjects were included by blocks of 12 (ie.: 4 subjects per treatment group)	
Number of subjects:	24 healthy volunteers were planned; 12 were included (early study discontinuation due to photosensitivity).	
Diagnosis and criteria for inclusion:	Male healthy volunteers of 20 to 40 years old, within $\pm 15\%$ of ideal weight, written informed consent.	
Test product, dose, mode of administration, batch n°:	Oral administration of film-coated tablets each containing 100 mg of sparfloxacin. 400 mg OD or 200 mg BID or placebo. - Initial single dose (Day 1) followed 1 week wash-out (Day 2 to 7). - 2 weeks of repeated dosing (day 8 to 21). Batch n°CB 3976	
Duration of treatment:	15 days (first single dose, one week wash-out and two weeks treatment with repeated dose from day 8 to day 21).	
Reference therapy: dose, mode of administration, batch n°:	Matching placebo tablets Same dosing schedule as the sparfloxacin tablets. Batch n° CB 4113 P	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Criteria for evaluation: Pharmacokinetics	Volume: 26 Page: - Blood samples: After first and last dose (day 1 and day 21): H0, H0.5, H1, H2, H3, H4, H5, H6, H8, H12, H24, H48, H72, H96. During repeated dosing at H0 and H6 on days 8, 9, 11, 13, 15, 19. - Urine samples: On day 1 and day 21 during the following periods: H0-H4, H4-H8, H8-H12, H12-24, H24-H48, H48-H72, H72-H96 and H96-H120 (only after day 21).	
Safety	- Clinical examination: at selection visit and on days 1, 8, 13, 19, 21, 22, 28, - Ophthalmological examination: prior to first dosing and after the last dose. - Non directive questioning for side effects: on day 1 and 21, H0 and every 2 hours for 12 hours, and on days 2, 3, 8 (H0, H6), 9 (H0, H6), 10 (H0, H6), 11 (H0, H6), 13 (H0, H6), 15, 17, 19 (H0, H6), 21, 22, 23, 26, 28. - Vital signs: at selection, on day 1 and 21 (H0, H2, H4, H6, H8) and on days 8, 13, 19, 28. - ECG monitoring: at selection visit and on day 1 and day 8 (H0 and H6), on days 2, 9, 10, 11, 13, 15, 19, 21 (H6), on day 22 and day 28 - Laboratory safety: complete biological assessments (blood and urine tests) were performed at selection and on days 1, 8, 13, 19, 21, 23 ^(*) , 26 ^(*) , and 28 ^(*) if previous abnormalities - hepatic function tests: on days 2, 9, 10, 11, 15, and 17.	
Statistical methods:	Pharmacokinetics: Due to early discontinuation of the study leading to limited sample size, only descriptive statistics, i.e. mean $\pm$ standard deviation, median, minimal and maximal values. Safety: descriptive statistics, i.e. mean $\pm$ standard deviation, median, minimal and maximal values.	
Summary - conclusions:	A high incidence of photosensitivity reactions was observed after repeated dosing with 400 mg of sparfloxacin (200 mg BID or 400 mg OD). These reactions consisted of paresthesia of mild to moderate intensity and erythema of moderate to severe intensity (see table below). This led to early discontinuation of the study after the first group of 12 subjects (treatment was interrupted for 4 subjects, n ^{OS} : 1, 7, 8, 12, and suspended for subject n ^O 4).	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 26 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Treatment group	Events	subjects numbers (number of episodes)	Maximum severity	Relationship to treatment
Placebo	Diarrhea Sensation of hunger Epigastralgia Hypogastric pain Headache Occipital trauma Hematoma subcutaneous		Mild Mild Moderate Mild Mild Mild	Possible Possible Possible Possible Possible None None
200 mg BID	Nausea Headache Dysesthesia of hands, pain under cold water, sensation of cold hands Tingling (face, hands) Pruritus forearms Erythema Pain Achille tendon		Moderate Moderate Moderate Moderate Moderate	Possible Possible Certain Certain Possible
400 mg OD	Diarrhea Dysesthesia, Tingling, Pruritus Erythema, sunburn Desquamation Cold, Cough Talgia submaxilar Heavy legs		Mild Moderate Severe Mild Moderate Severe Moderate	Possible Probable Probable Probable Possible Possible Possible

* = treatment interrupted
= treatment suspended

Apart from these reactions of photosensitivity the clinical tolerance was similar in all groups. Vital signs monitoring did not reveal any difference between the two groups receiving sparfloxacin and the placebo group.

The biological tolerance was unremarkable throughout the study with only one clinically significant high abnormal value (haptoglobin) recorded 7 days after the end of the treatment in the 400 mg OD group.

A modification was observed in the ECG recorded during the study. This concerns the QTc interval, other parameters (PR, QRS, QRS axis) remaining stable (see table).

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)																																																					
Volume: 26 Page:																																																							
Pharmacokinetic results:	EVOLUTION OF QTc VALUES (MS) DURING THE STUDY																																																						
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A slight increase in duration of the QTc interval (about 5% in the 400 mg OD group and 3 % in the 200 mg BID group) was observed after the single dose (day 1, H6), and was sustained during repeated dosing (day 13,H6) in the 2 groups receiving sparfloxacin. QTc values returned to baseline at the end of the study (day 20). The maximum QTc value observed was 449 ms.																																																							
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MEAN (SD) SPARFLOXACIN PLASMA PHARMACOKINETIC PARAMETERS, CALCULATED AFTER SINGLE ORAL ADMINISTRATION OF SPARFLOXACIN 400 MG OR 200 MG (DAY 1)																																																							
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Results were in agreement with those obtained in the first study (AT 101). Available data from peak and trough samples suggest that the steady-state was obtained after 3 to 5 days of repeated dosing.																																																							

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 28 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, double-blind, placebo-controlled, crossover tolerability and pharmacokinetic study of sparfloxacin administered as a single oral dose (100 mg rising to 600 mg) to healthy elderly volunteers	
Investigators:		
Study centre:		
Publication (reference):	None	
Study period (years):	1989	
Objectives:	• To study the clinical and biological tolerability of increasing single oral doses of sparfloxacin, compared to placebo. • To carry out a preliminary pharmacokinetic study of sparfloxacin after administration of single oral dose to elderly people.	
Methodology:	Double-blind, single dose, randomised, crossover, placebo-controlled study	
Number of subjects:	8.	
Diagnosis and criteria for inclusion:	Male or female Caucasian subjects ≥ 70 years; weight within $\pm 15\%$ of 1983 Metropolitan Life Insurance Actuary Tables. Medical history without major pathology All physical examination parameters without sign of clinically-relevant pathology. Computerized 12-lead ECG without sign of pathology. No clinically-relevant observations in laboratory tests. Written informed consent signed.	
Test product, dose, mode of administration, batch No.:	Administration of film-coated tablets each containing 100 mg of sparfloxacin. D1: single oral dose of 100 mg, 200 mg, 400 mg or 600 mg in the morning. Batch CB 3976.	
Duration of treatment:	4 single doses (placebo included) separated by 1-week interval.	
Reference therapy:	Matching placebo tablets. Same conditions of administration as test drug. Batch CB 4113 P	
Study procedures:	Subjects were randomised to receive in groups of two, 3 of the 4 single oral doses of 100, 200, 400 or 600 mg of sparfloxacin or a placebo in 4 treatment periods at intervals of 1 week according to the following treatment sequences: - 100-200-400-placebo: 2 subjects - Placebo-200-400-600: 2 subjects - 100-placebo-400-600: 2 subjects - 100-200-placebo-600: 2 subjects	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RF 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 28 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Criteria for evaluation:	Safety study: • Clinical examination: At selection, predrug on D1, then on D2, D3 postdrug, for each treatment period, and on D8 of the last treatment period. • Blood pressure and heart rate: At selection, predrug on D1 then 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hours postdrug and on D8 of last period. • 12-lead ECG: At selection, predrug and 6 h postdrug on D1, then on D2, D3 postdrug and on D8 of last period. • Laboratory tests (haematology, biochemistry, urinalysis): At selection, predrug on D1 then on D2 and D3, and on D8 of last period. • Adverse events: By questionnaire on D1, D2, D3 and D8. Pharmacokinetic study: • Blood samples: Predrug then 4, 6, 8, 12, 24, 36, 48 and 72 h postdrug: C_{max}, t_{max}, t_{1/2}, MRT, AUC 0-72 h, AUC 0-∞. • Urine collection: -12-0 h predrug then 0-12 h, 12-24 h, 24-48 h and 48-72 h postdrug: Cl_r and A_e.	
Statistical methods:	Safety parameters: • Vital signs: Mean values ± SD at baseline and mean ± SD differences from baseline at each scheduled time point for the 2 subjects of each treatment sequence. • ECG intervals: Mean ± SD at each scheduled time point for the 2 subjects of each treatment sequence. Pharmacokinetic parameters: All individual values were pooled and expressed as mean ± SD for each dose level (N = 6). • Analysis of variance according to General Linear Model Procedure on C_{max}, AUC 0-72 h, AUC 0-∞ normalized to 200 mg dose and on t_{1/2} and renal clearance. • Regression analysis on C_{max} and AUC 0-∞ versus dose.	
Results - Conclusions: Safety results The eight patients were included safety analysis. • Treatment-related adverse events: - Anorexia: 2 cases (1 mild and 1 moderate) possibly related (one on placebo). - Headache: 1 case., 2 episodes (mild, same patient) probably related. - Dizziness: 2 cases (mild) possibly related. - Vision anomaly: 1 case (mild) possibly related. - Photosensitivity: 2 cases (1 moderate, 1 severe) probably related. • Vital signs: No clinically significant variations of SBP, DBP, HR and RR. • Electrocardiogram: No treatment-related rhythm or conduction disorder. Slight increases in QTc were observed after 400 and 600 mg of sparfloxacin, (5.49 and 7.68 % respectively). Up to 400 mg, all QTc values remained within normal range. • Laboratory tests: No clinically significant variations attributable to sparfloxacin.		

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 28 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results - Conclusions (continued)

Pharmacokinetic results:

(The results from eight patients were analysed; the means do not include the 2 values from placebo treatment).

- Pharmacokinetic parameters (Mean $\pm$ SD, N = 6)

PHARMACOKINETIC PARAMETER	DOSE (mg)			
	100	200	400	600
t _{max} (h)*	4 (4)	4 (4-8)	4 (4-8)	4 (4-8)
C _{max} (ng/ml)	309 $\pm$ 77	690 $\pm$ 155	1346 $\pm$ 317	1705 $\pm$ 344
t _{1/2} (h)	18.96 $\pm$ 2.12	19.22 $\pm$ 0.64	18.78 $\pm$ 2.01	18.85 $\pm$ 1.11
AUC 0- ∞ (ng.h/ml)	8812 $\pm$ 1091	18519 $\pm$ 2934	35153 $\pm$ 5939	47534 $\pm$ 5903
AUC 0-72 h (ng.h/ml)	8141 $\pm$ 1024	17576 $\pm$ 2769	32581 $\pm$ 5863	43904 $\pm$ 5241
MRT (h)	31.33 $\pm$ 2.91	32.20 $\pm$ 1.91	30.20 $\pm$ 4.85	32.02 $\pm$ 2.31
Cl (l/h)	11.50 $\pm$ 1.48	11.00 $\pm$ 1.58	11.66 $\pm$ 2.08	12.76 $\pm$ 1.39
Cl _r (l/h)	1.29 $\pm$ 0.42	1.07 $\pm$ 0.39	0.95 $\pm$ 0.28	1.06 $\pm$ 0.26
A _e (% dose)	10.3 $\pm$ 3.5	9.2 $\pm$ 3.8	7.6 $\pm$ 2.0	7.7 $\pm$ 1.08

- * Median range

Mean plasma concentrations ($\pm$ SD, N = 6) of unchanged sparfloxacin 24 h after 100 mg: 146 $\pm$ 22 ng/ml; 200 mg: 347 $\pm$ 97 ng/ml; 400 mg: 593 $\pm$ 147 ng/ml; 600 mg: 750 $\pm$ 119 ng/ml.

- Urinary concentrations (expressed in μ g/ml) of unchanged sparfloxacin (Mean $\pm$ SD; N = 6)

DOSE (mg)	TIME OF COLLECTION			
	0-12 h	12-24 h	24-48 h	48-72 h
100	5.91 $\pm$ 2.96	3.16 $\pm$ 0.43	1.79 $\pm$ 0.61	0.73 $\pm$ 0.24
200	10.80 $\pm$ 5.62	6.43 $\pm$ 4.27	3.31 $\pm$ 0.94	1.19 $\pm$ 0.59
400	14.71 $\pm$ 5.23	7.58 $\pm$ 1.50	5.78 $\pm$ 1.43	3.18 $\pm$ 0.76
600	26.19 $\pm$ 7.00	15.15 $\pm$ 4.16	8.65 $\pm$ 3.06	4.90 $\pm$ 2.39

Conclusions:

Sparfloxacin at single doses of 100, 200, and 400 mg was well tolerated in elderly subjects. However, 2 cases of phototoxicity with the 600 mg dose suggested that during and following treatment with this antibiotic, exposure to sunlight should be avoided, as with other fluoroquinolones. The pharmacokinetics of sparfloxacin were linear. Plasma concentrations at 24 hours compared favorably with the MIC values for susceptible pathogens. Urinary excretion of unchanged sparfloxacin over 72 hours was of the order of 10% of the dose. Urinary concentrations far exceeded MIC values for susceptible pathogens.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 30 Page :	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (phase I)	A phase I pharmacokinetic and tolerability study on sparfloxacin (AT 4140) during repeated oral dosing of 200 mg once a day for 7 days in 10 healthy elderly male and female volunteers	
Investigators:		
Study centre:		
Publication (reference):	G. Montay et al.: "Pharmacokinetics of sparfloxacin after repeated administration in healthy elderly volunteers" 31th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Chicago, 1991, Abstract: 593	
Study period (years):	1990	
Objectives:	To evaluate the pharmacokinetics and tolerability during repeated dosing of sparfloxacin in healthy elderly male and female volunteers.	
Methodology:	Multiple dose, double-blind, randomized, two-way crossover, placebo-controlled study.	
Number of subjects:	10 planned: (11 included, 1 withdrawal after 3 days for problem with venous sampling.)	
Diagnosis and criteria for inclusion:	Male or female Caucasian subjects $\geq$ 66 years; weight within $\pm$ 15% of 1983 Metropolitan Life Insurance Actuary Tables. Without history of major pathology. All physical examination parameters without sign of clinically-relevant pathology. 12-lead ECG without sign of pathology. No clinically-relevant abnormalities on laboratory tests. Written informed consent signed.	
Test product, dose, mode of administration, batch No.:	Oral administration of film-coated tablets each containing 100 mg of sparfloxacin (S). Day 1: single dose of 400 mg (4 tablets) in the morning then.. Day 2 through Day 7: 200 mg (2 tablets) O.D. orally in the morning. Batch CB 3976	
Duration of treatment:	Two 7-day periods separated by at least 1 week wash-out.	
Reference therapy:	Film-coated placebo tablets (P). Same dosing schedule as for the sparfloxacin tablets. Batch CB 4113 P	
Study procedures:	Subjects were randomized into 2 groups of 5 corresponding to 2 treatment sequences (treatment separated by a 7-day interval): - Treatment sequence S/P: Treatment S in period 1 and treatment P in period 2. - Treatment sequence P/S: Treatment P in period 1 and treatment S in period 2.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 30 Page :	(FOR NATIONAL AUTHORITY USE ONLY)
Study procedures: Pharmacokinetics: Safety:	• On D1 (400 mg or P): blood samples pre-dose then 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 h post-dose; urine collection over 2 h pre-dose then 0-4, 4-8, 8-12, 12-24 h post-dose. • During D2-D7 (200 mg or P O.D.): blood samples pre-dose and 6 h post-dose on D2, D3, D4, D5, D6 and starting on D7, blood samples pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 48, 72, 96 and 120 h post-dose; urine collection starting on D7: over 2 h pre-dose then 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 h post-dose. • Clinical examination at selection, pre-dose on D1 and on D8, and D12. • Adverse events: from D1 to D7 pre-dose and at 12 h post-dose, then daily from D8 through D12 (with questionnaire "How do you feel?"). • Blood pressure, heart rate and temperature at selection, pre-dose and 6 h post-dose on D1, pre-dose on D2, D3, D4, D5, D6, pre-dose and 6 h post-dose on D7, then on D8, D9, D10, D11, D12. • 12-lead ECG: at selection, pre-dose and 6 h post-dose on D1, 2 h post-dose on D4, and on D8 and D12. • Laboratory tests (haematology, blood chemistry, urinalysis) at selection, pre-dose on D1, D2 and D4 and on D8 and D12. Plasma pharmacokinetic parameters: • On D1: C_{max}, t_{max}, AUC 0-24. • On D2-D6: C_{min} and C 6 h. • D7: C_{max} t_{max}, AUC 0-24, AUC 0-∞, t_{1/2}, MRT, Cl, observed accumulation ratio AUC 0-24 (D7) x 2/AUC 0-24 (D1) and theoretical accumulation ratio 1/1-e^{-k_t}. Urinary excretion: • On D1: Free and total drug. • On D7-D12: Free and total drug, Cl_r and metabolic ratio.	
Statistical methods:	Pharmacokinetics: Analysis of variance according to General Linear Model procedure (GLM). All the individual data (10 subjects) were pooled for statistical analysis (mean values ± SD). • C_{min} and C 6 h: GLM followed by Scheffe's test. • C_{max}, C_{min}, AUC, t_{1/2}, t_{max} and Cl_r from elderly subjects compared to same parameters in young subjects. • C_{max}, AUC normalized to weight, MRT and t_{1/2} : Between sex comparison using GLM (t test). Vital signs and laboratory tests: Mean values ± SD and mean differences ± SD from baseline according to treatment sequence at the different time points. 12-lead ECG: Mean values ± SD at the different time points for the two treatment sequences.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volumes: 30 Page :	(FOR NATIONAL AUTHORITY USE ONLY)																																																																								
Results - Conclusions :	Pharmacokinetic results: - Plasma pharmacokinetic parameters after D1 and D7 (N = 10) <table border="1" data-bbox="643 566 1332 858"> <thead> <tr> <th>PARAMETERS</th> <th>D1</th> <th>D7</th> </tr> </thead> <tbody> <tr> <td>t_{max}^(a) (h)</td> <td>3 (2-4)</td> <td>3 (1-8)</td> </tr> <tr> <td>C_{max} (ng/ml)</td> <td>1689 ± 556</td> <td>1303 ± 226</td> </tr> <tr> <td>AUC 0-24 h (ng·h/ml)</td> <td>22724 ± 6678</td> <td>17686 ± 2927</td> </tr> <tr> <td>AUC _∞ (ng·h/ml)</td> <td>-</td> <td>30499 ± 6651</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>-</td> <td>19.66 ± 4.29</td> </tr> <tr> <td>Cl (l/h)</td> <td>-</td> <td>11.6 ± 1.9</td> </tr> <tr> <td>MRT (h)</td> <td>-</td> <td>28.24 ± 6.36</td> </tr> <tr> <td>Observed accumulation ratio</td> <td>-</td> <td>1.63 ± 0.36</td> </tr> <tr> <td>Theoretical accumulation ratio</td> <td>-</td> <td>1.79 ± 0.26</td> </tr> </tbody> </table> ^a: Median value (range) Note: There was no significant difference between male and female subjects when analyzed separately for C_{max} and AUC 0-24 h (normalized to the mean weight of subjects), t_{1/2} and MRT values. - C_{min} and C_{6 h} from D2 through D7 (N = 10). <table border="1" data-bbox="634 1043 1324 1252"> <thead> <tr> <th>DAY</th> <th>C_{min} (ng/ml)</th> <th>C_{6 h} (ng/ml)</th> </tr> </thead> <tbody> <tr> <td>D2</td> <td></td> <td></td> </tr> <tr> <td>D3</td> <td></td> <td></td> </tr> <tr> <td>D4</td> <td></td> <td></td> </tr> <tr> <td>D5</td> <td></td> <td></td> </tr> <tr> <td>D6</td> <td></td> <td></td> </tr> <tr> <td>D7</td> <td></td> <td></td> </tr> </tbody> </table> [*] Significantly different from D2 value (p ≤ 0.01) The steady state was reached after the second administration. - Comparison between elderly subjects and young subjects at steady state <table border="1" data-bbox="628 1407 1321 1640"> <thead> <tr> <th>PARAMETERS</th> <th>ELDERLY SUBJECTS (n = 10)</th> <th>YOUNG SUBJECTS[*] (n = 8)</th> </tr> </thead> <tbody> <tr> <td>t_{max}^(a) (h)</td> <td>3.0 (1-8)</td> <td>3.5 (1-8)</td> </tr> <tr> <td>C_{max} (ng/ml)</td> <td>1303 ± 226</td> <td>1359 ± 369</td> </tr> <tr> <td>C_{min} (ng/ml)</td> <td>425 ± 102</td> <td>566 ± 198</td> </tr> <tr> <td>AUC 0-24 h (ng·h/ml)</td> <td>17686 ± 2927</td> <td>20410 ± 4585</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>19.9 ± 4.3</td> <td>20.2 ± 1.9</td> </tr> <tr> <td>Cl_r (l/h)</td> <td>1.28 ± 0.30</td> <td>0.84 ± 0.19</td> </tr> </tbody> </table> ^a: Median value (range) [*]: Young subjects from study AT 119 (6) There is no significant difference between elderly and young subjects.		PARAMETERS	D1	D7	t _{max} ^(a) (h)	3 (2-4)	3 (1-8)	C _{max} (ng/ml)	1689 ± 556	1303 ± 226	AUC 0-24 h (ng·h/ml)	22724 ± 6678	17686 ± 2927	AUC _∞ (ng·h/ml)	-	30499 ± 6651	t _{1/2} (h)	-	19.66 ± 4.29	Cl (l/h)	-	11.6 ± 1.9	MRT (h)	-	28.24 ± 6.36	Observed accumulation ratio	-	1.63 ± 0.36	Theoretical accumulation ratio	-	1.79 ± 0.26	DAY	C _{min} (ng/ml)	C _{6 h} (ng/ml)	D2			D3			D4			D5			D6			D7			PARAMETERS	ELDERLY SUBJECTS (n = 10)	YOUNG SUBJECTS [*] (n = 8)	t _{max} ^(a) (h)	3.0 (1-8)	3.5 (1-8)	C _{max} (ng/ml)	1303 ± 226	1359 ± 369	C _{min} (ng/ml)	425 ± 102	566 ± 198	AUC 0-24 h (ng·h/ml)	17686 ± 2927	20410 ± 4585	t _{1/2} (h)	19.9 ± 4.3	20.2 ± 1.9	Cl _r (l/h)	1.28 ± 0.30	0.84 ± 0.19
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Results - Conclusions: (continued)	• Urinary excretion <u>24 h excretion of sparfloxacin:</u> Free drug: 19.97 ± 5.63 mg (± SD) = 5% of the dose Total drug: 86.83 ± 17.35 mg (± SD) = 21.7% of the dose <u>0-120 h excretion of sparfloxacin after 7-day treatment:</u> Free drug: 35.89 ± 6.31 mg (± SD) Clr free drug: 1.28 ± 0.30 l/h (± SD) Total drug: 133.83 ± 18.12 mg (± SD) Conjugated drug: 97.95 ± 20.10 mg (± SD) Conjugated/free drug: 2.79 ± 0.86 (± SD) Adverse experience and safety profile • Adverse events: - On sparfloxacin: Adverse events were reported in 11 subjects, possibly related to treatment in 7 subjects: somnolence (mild): 2 subjects; diarrhea (mild): 5 subjects; flatulence (mild): 2 subjects; headache (mild): 1 subject. - Washout period following sparfloxacin: Adverse events were reported in 3 subjects. One case of moderate photosensitivity (erythema) was probably related to sparfloxacin (the drug following last sparfloxacin intake). - On placebo: Adverse events were reported in 8 subjects. Treatment possibly related adverse events were reported in 6 subjects: Photosensitivity (pruritus): 1 subject (the case occurred 37 days after the first intake of sparfloxacin); nausea: 1 subject; taste perversion: 1 subject; diarrhea: 2 subjects; somnolence: 2 subjects; abdominal pain: 1 subject, headache: 1 subject. • Vital signs: No clinically-significant changes. • ECG: - Some abnormalities were observed that were either present at selection or appeared during treatment (sparfloxacin or placebo or both). None of these abnormalities was deemed clinically significant or related to the study treatment.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 30 Page :	(FOR NATIONAL AUTHORITY USE ONLY)																																	
Results - Conclusions: (continued)	-increased QTc were observed after sparfloxacin intake, but disappearing generally within 24 hours post-dose: <table border="1" data-bbox="659 562 1358 890"> <thead> <tr> <th rowspan="3"></th> <th colspan="4">QTc relative variation (% between day 1 H0 and day 1 H6)</th> </tr> <tr> <th colspan="2">Group P/S</th> <th colspan="2">Group S/P</th> </tr> <tr> <th>Period 1 (placebo)</th> <th>Period 2 (sparflo.)</th> <th>Period 1 (sparflo.)</th> <th>Period 2 (placebo)</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>5</td> <td>5</td> <td>5</td> <td>5</td> </tr> <tr> <td>MEAN</td> <td>-0.09</td> <td>2.13</td> <td>6.31</td> <td>3.49</td> </tr> <tr> <td>MIN</td> <td>-4.83</td> <td>-2.25</td> <td>-0.26</td> <td>-1.37</td> </tr> <tr> <td>MAX</td> <td>7.65</td> <td>8.62</td> <td>19.28</td> <td>10.80</td> </tr> </tbody> </table> • Laboratory tests: Clinically-nonsignificant variations in laboratory test results. Conclusions: Steady-state concentrations of sparfloxacin were achieved on D2 after administration of a 400 mg loading dose followed by 200 mg O.D. dosage regimen. Kinetics were not different in male and female subjects. Kinetics of sparfloxacin in healthy elderly subjects are similar to those achieved in young subjects. An increase in QTc was observed after sparfloxacin intake; this effect disappeared generally within 24 hours after dosing. The dose regimen was well tolerated in 5 male subjects and 4 female subjects and moderately tolerated in one female subject due to phototoxicity.			QTc relative variation (% between day 1 H0 and day 1 H6)				Group P/S		Group S/P		Period 1 (placebo)	Period 2 (sparflo.)	Period 1 (sparflo.)	Period 2 (placebo)	N	5	5	5	5	MEAN	-0.09	2.13	6.31	3.49	MIN	-4.83	-2.25	-0.26	-1.37	MAX	7.65	8.62	19.28	10.80
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Title of the study: (Phase I)	A phase I open non comparative study of pharmacokinetics and tolerance of sparfloxacin administered as a single oral dose to cirrhotic and/or cholestatic volunteers	
Investigators:		
Study centre:		
Publication (reference):	none	
Study period :	1992	
Objectives:	To study the pharmacokinetics and clinical tolerability of sparfloxacin in subjects with cirrhosis and/or cholestasis	
Methodology:	Open, one way study in 12 non-cholestatic liver patients of an oral dose of 400 mg sparfloxacin.	
Number of subjects:	First part of the study : 12 non-cholestatic liver patients with a Pugh score of 6 to 12 were included	
Diagnosis and criteria for inclusion:	Adult subjects 20 to 80; male or female if not of childbearing potential; Subjects with histologically proven cirrhosis; Written informed consent.	
Test product, dose, mode of administration, batch No.:	400mg : 4 x 100mg tablets, Oral Batch C85136	
Duration of treatment:	Single dose	
Reference therapy	none	
Study Procedures	Blood sampling : Day 1 (H0 before sparfloxacin), H2, H3, H4, H6, H8, H10), Day 2 (H24), Day 5 (H96) Day 6 (H120). Urine sampling : Day 1 (H0 before drug intake) (H24 - H48)	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 40 Page :	(FOR NATIONAL AUTHORITY USE ONLY)

Criteria for evaluation: Pharmacokinetics: Safety:	The following pharmacokinetic parameters were determined: • Plasma: C_{max}, t_{max}, AUC 0-t, t_{1/2}, AUC ∞, oral plasma clearance, MRT, Metabolic Index • Urine: The quantity excreted unchanged (U) and metabolised (U_m), fraction of drug excreted unchanged (f_e), renal clearance of unchanged and metabolised drug (Cl_r), Metabolic Index. Clinical examination during screening and on day 6, including vital signs (supine blood pressure and heart rate). Recording of adverse events. Laboratory tests during screening and on day 6. ECG pre-dose, 6hr and 24hr post dose

Statistical methods:	Descriptive for all safety parameters; Students t-test for the pharmacokinetic data. Regression analysis of pharmacokinetic parameters against selected biological parameters.

Results The pharmacokinetic parameters as mean values (SD) are summarised in the following table:

Parameter	Mean ± SD Cirrhotic subjects	Mean ± SD Healthy Volunteers (AT115)	Significance
Plasma C _{max} (mg/l)	1.6 ± .5	1.8 ± 0.7	NS
Plasma T _{max} (h)	5.1 ± 2.1	1 to 6	NS
Plasma AUC ∞ (h.mg/l)	47 ± 18	53 ± 12	NS
Plasma t _{1/2}	22.3 ± 5.4	25 ± 4	NS
Cl (ml/min)	163 ± 72	131 ± 31	NS
U (%dose)	8.8 ± 4.8	13.1 ± 2.3	P<0.05
U _m (%dose)	45 ± 22	24 ± 6	P<0.05
Renal Clearance (ml/min)	14 ± 9	17 ± 2	NS
Urinary Metabolic Ratio	4.7 ± 1.4	1.9 ± 0.7	P<0.01

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NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 40 Page :	(FOR NATIONAL AUTHORITY USE ONLY)
There were no statistically significant differences between the plasma pharmacokinetic parameters of unchanged sparfloxacin in subjects with mild to moderate liver failure when compared with a group of healthy volunteers analyzed under the same conditions. The renal clearance of sparfloxacin was also unchanged. Plasma concentrations of conjugated sparfloxacin and the renal excretion of conjugated sparfloxacin were significantly increased in subjects with mild to moderate liver failure. Regression analysis revealed that there was no correlation between the severity of cirrhosis as measured by the Pugh score and the pharmacokinetics of sparfloxacin. As regards safety: • No adverse events were reported • No clinically significant changes were found in any ECG nor laboratory test values.		
Conclusions: There were no statistically significant differences between the pharmacokinetic behaviour of unchanged sparfloxacin in cirrhotic subject and healthy subjects. The biological and clinical safety of the product was good. Therefore, there is no reason to modify the dosing regimen for cirrhotic patients with a Pugh score of 12 or less.		

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Title of the study: (Phase I)	A Phase I, open, noncomparative study of pharmacokinetics and tolerance of sparfloxacin administered as a single 400 mg oral dose to 12 patients with chronic renal failure.	
Investigator:		
Study centre:		
Publication (reference):	J.P. FILLASTRE et al. "Pharmacokinetics of sparfloxacin in patients with renal impairment", 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, (ICAAC), October 11-14, 1992, Anaheim, Abstract 749.	
Study period (years):	1991-1992	
Objectives:	To determine the pharmacokinetics of sparfloxacin in patients with a range of renal function from 2 to 30 ml/min/1.73 m ² for creatinine clearance. To assess the safety of a single oral dose of 400 mg of sparfloxacin in patients with renal failure.	
Methodology:	Single centre, open, noncomparative study.	
Number of subjects:	14 (17 included; but 3 subjects were excluded from pharmacokinetic analysis for protocol deviations).	
Diagnosis and criteria for inclusion:	Patients of either sex aged 18-70 years with renal failure: Group I: Renal clearance $\leq$ 30 ml/min/1.73 m ² and $>$ 10 ml/min/1.73 m ² . Group II: Renal clearance $\leq$ 10 ml/min/1.73 m ² and $>$ 2 ml/min/1.73 m ² . Stable renal function over the preceding 6 months and stable antihypertensive medication over the preceding 2 months. Body weight in accordance with Metropolitan Life Insurance Actuary Tables. Negative hepatitis B surface antigen and HIV antigen. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 400 mg as 4 film-coated tablets each containing 100 mg of sparfloxacin. Batch No. CB 4385.	
Duration of treatment:	Single dose.	
Reference therapy	None.	
Study procedures:	After single administration of 400 mg of sparfloxacin, the following samples were collected for determination of unchanged and conjugated sparfloxacin by HPLC assay: Blood (predose, 1, 2, 3, 4, 6, 8, 12, 24, 34, 48, 72, 96 and 144 $\pm$ 24 hours postdose). Urine (predose, 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 hours postdose and 24-hour urine the day before D7).	

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Criteria for evaluation Pharmacokinetics: Safety:	Determination of the following parameters: - Plasma: C _{max} , t _{max} , AUC 0-∞, t _{1/2} , Cl _r for unchanged and conjugated (glucuronide) sparfloxacin; Cl _p and Cl _r for unchanged sparfloxacin. - Urine: Recovery of unchanged and conjugated sparfloxacin. Vital signs at selection, D1, D2, D3, D4, D5, D7; ECG recording at selection and on D1, post-dose (D2 and D7 if previously abnormal); clinical events recording each day.	
Statistical methods:	Pharmacokinetics: Mean ± SD (median and range for t _{max}). Comparison of the two groups to a reference group of 6 healthy subjects from another study (AT121). GLM procedure followed by Tukey's test or Wilcoxon's test. Vital signs: Mean differences ± SD from baseline.	

Conclusions:

Pharmacokinetic results:

14 patients were analysed. (3 subjects were not included in the pharmacokinetic analysis for violation of selection criteria: Nos and some parameters could not be calculated on the whole group)

Plasma pharmacokinetics of unchanged sparfloxacin (mean ± SD)

GROUP	C _{max} (ng/ml)	t _{max} ^a (h)	AUC 0-∞ (ng.h/ml)	Cl _p (h)	Cl _r (h)	t _{1/2} (h)
Group I (n = 7)	1426 ± 645	4 (1-8)	44240 ± 19173	10.6 ± 4.5	10.2 ± 4.3	34.9 ± 9.2*
Group II (n = 7)	1313 ± 436	4 (4-8)	49367 ± 11101	8.5 ± 1.9*	8.2 ± 1.9	36.5 ± 13.4*
Healthy subjects (n = 6)	1094 ± 234	5 (3-6)	31458 ± 5874	13.1 ± 2.5	11.8 ± 2.5	19.1 ± 2.5

- ^a Median value (range)
- * Significantly different from healthy subjects
- ** from study AT121

Plasma pharmacokinetics of sparfloxacin glucuronide (mean ± SD)

GROUP	C _{max} (ng/ml)	t _{max} (h)	AUC 0-∞ (ng.h/ml)	t _{1/2} (h)
Group I (n = 7)	678 ± 180	6 (2-24)	25462 ± 7165§	23.7 ± 3.9§
Group II (n = 7)	981 ± 590	12 (4-24)	64943 ± 36957E	35.0 ± 8.5E
Healthy subjects (n = 6)	353 ± 128	5 (2-16)	6840 ± 4284	15.3 ± 3.8

- § n = 5, E n = 6 (AUC 0-∞ and t_{1/2} not calculated for some subjects)
- All Group II data are significantly different from healthy subjects data (group III) except for t_{max}. AUC and t_{1/2} are significantly different between groups I and II

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Urinary excretion of unchanged sparfloxacin and sparfloxacin glucuronide (mean ± SD)

% DOSE	GROUP I	GROUP II	HEALTHY SUBJECTS
Unchanged sparfloxacin	4.0 ± 1.9*	3.2 ± 0.9*	9.7 ± 2.3
Glucuronide	9.8 ± 4.3*	8.4 ± 4.7*	18.6 ± 3.9

* Significantly different from healthy subjects

Safety: all patients were considered in the safety analysis.

- No variations in vital signs attributable to sparfloxacin.
 - Two patients with clinical events:
 - One patient (No. [redacted] group II) with severe increase in creatinemia on day 2 of the study and moderate attack of gout.
 - One patient (No. [redacted] group II) had reappearance of hypertension of moderate intensity upon discontinuation of treatment (appeared at baseline).
- None of these effects were imputable to sparfloxacin.

Conclusion:

Marked impairment of the elimination of unchanged and conjugated sparfloxacin suggesting dose adjustment of the drug in patients with renal failure (the daily dosage regimen for patients with $Cl_{cr} < 30$ ml/mn should be reduced by half: 200 mg followed by 100 mg daily dose). The 400 mg single dose of sparfloxacin was well tolerated in these patients.

TABULATED SUMMARY REPORT

Title of study (Phase):	Phase I, Open, Noncomparative, Multiple-Dose Study of Sparfloxacin Pharmacokinetics in Patient Volunteers with Chronic Renal Insufficiency and Healthy Volunteers, Protocol RP 64206X-159 (Phase I)
Investigator:	
Publication (reference):	None
Study period:	First Subject Treated: May 9, 1994 Last Subject Discharged: November 22, 1994
Study center:	
Objectives:	- To assess sparfloxacin pharmacokinetics in patients with chronic renal insufficiency. - To assess the effect of a loading dose followed by multiple sparfloxacin doses on the QTc interval and to assess the pharmacokinetics of sparfloxacin glucuronide in this special patient population.
Methodology:	This was a Phase I, open-label, multiple-dose study of the steady-state pharmacokinetics of sparfloxacin in male and female patient volunteers with chronic renal insufficiency. Subjects were stratified at baseline according to observed creatinine clearance (CrCl) into one of the following groups (eight subjects each): Groups 1a and 1b (Control Groups): CrCl ≥ 50 mL/min/1.73 m² Group 2: CrCl = 30-49 mL/min/1.73 m² Group 3: CrCl = 10-29 mL/min/1.73 m² Each control subject was age-, weight-, and sex-matched to a subject with renal insufficiency and could serve as a match in each of Groups 2 and 3 if appropriate. Subjects in all groups received a 400-mg loading dose of sparfloxacin on Day 1. Groups 1 and 2 then received 200 mg QD for 9 days, and Group 3 received 200 mg on Days 3, 5, 7, and 9. Repeat CrCl determination on Day 9 (Group 3) or Day 10 (Groups 1 and 2) was used to assess potential changes in each subject's renal function.
Number of subjects:	32 enrolled (15 males and 17 females), 30 completed all study procedures
Diagnosis and criteria for entry:	Adult male or female (nonpregnant/nonlactating) volunteers ≥ 18 years of age, with normal screening physical and laboratory examinations and electrocardiograms (ECGs) as well as measured CrCl with above and stable renal function, were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200 mg tablets, manufactured by Parke-Davis Groups 1 and 2: 400 mg oral loading dose Day 1, 200 mg once daily Group 3: 400 mg oral loading dose Day 1, 200 mg once daily Lot number: 9212494
Duration of treatment:	Ten days in Groups 1 and 2; 5 days of dosing over a 9-day period
Reference therapy: dose, route of administration, lot number:	None.
Safety measurements:	Repeat CrCl, vital signs, adverse clinical experience examinations, 12-lead ECG, and clinical laboratory evaluation (chemistry, and urinalysis).
Pharmacokinetics parameters:	Plasma and urine concentrations of unchanged sparfloxacin and sparfloxacin glucuronide. The maximum steady-state plasma concentrations (C _{max,ss}) for sparfloxacin and sparfloxacin glucuronide and the time at which they occurred (T _{max,ss}), elimination rate constant (k _{term}), harmonic mean terminal elimination half-life (t _{1/2}), area under the steady-state plasma sparfloxacin and plasma sparfloxacin glucuronide concentration-time profile over a dosing interval (τ) (AUC _{(0-\tau),ss}), average steady-state concentrations (C _{ave,ss}) for sparfloxacin and sparfloxacin glucuronide, and steady-state renal clearance (CL _{r,ss}) for sparfloxacin

TABULATED SUMMARY REPORT

	and sparfloxacin glucuronide.
Statistical methods:	Steady-state sparfloxacin and sparfloxacin glucuronide pharmacokinetic parameters in plasma and urine were analyzed by multiple stepwise regression using the PROC GLM procedure within SAS, with regression of pharmacokinetic parameters against body weight, gender, and CrCl.
Results:	Safety and Tolerance: Sparfloxacin was well tolerated across the three study groups, with an overall AE reporting rate of 19% (6 of 32 subjects). No severe or serious clinical or laboratory adverse experiences were reported for any study group. One subject was prematurely discontinued from the study due to an AE (moderate anaphylactoid reaction with a probable relationship to study drug in a subject with moderate renal insufficiency). The only other AE with a possible relationship to study drug was a mild prolongation of the QT interval also reported for a subject with moderate renal insufficiency. Analysis of QTc interval data indicated that the effect of sparfloxacin on the QTc was similar among subjects with normal renal function and subjects with mild or moderate renal insufficiency. Pharmacokinetics: Results of this multiple-dose study show that the plasma sparfloxacin concentration-time profile for subjects with moderate renal insufficiency following a 48-hour dosing interval was similar to that for subjects having normal renal function who were dosed at a 24-hour dosing interval. Mean plasma sparfloxacin concentrations were approximately two to three times higher in mildly renally impaired subjects as compared to subjects with normal renal function receiving the same dose. The concentrations of sparfloxacin glucuronide in plasma generally increased with decreasing renal function. Renal clearance and AUC were shown to be dependent on creatinine clearance.
Conclusions:	• Sparfloxacin was well tolerated by subjects with normal renal function and by subjects with mild renal insufficiency when administered at a 24-hour dosing interval, and by subjects with moderate renal insufficiency when administered at a 48-hour dosing interval. • The effect of sparfloxacin on the QTc was similar among subjects with normal renal function and subjects with mild or moderate renal insufficiency (CrCl 10-49). • An every-alternate-day (48-hour dosing interval) dosing regimen following a double loading dose on Day 1 is recommended for patients with moderate renal insufficiency (CrCl 10-29 mL/min) and may be appropriate for patients with mild renal insufficiency (CrCl 30-49 mL/min).

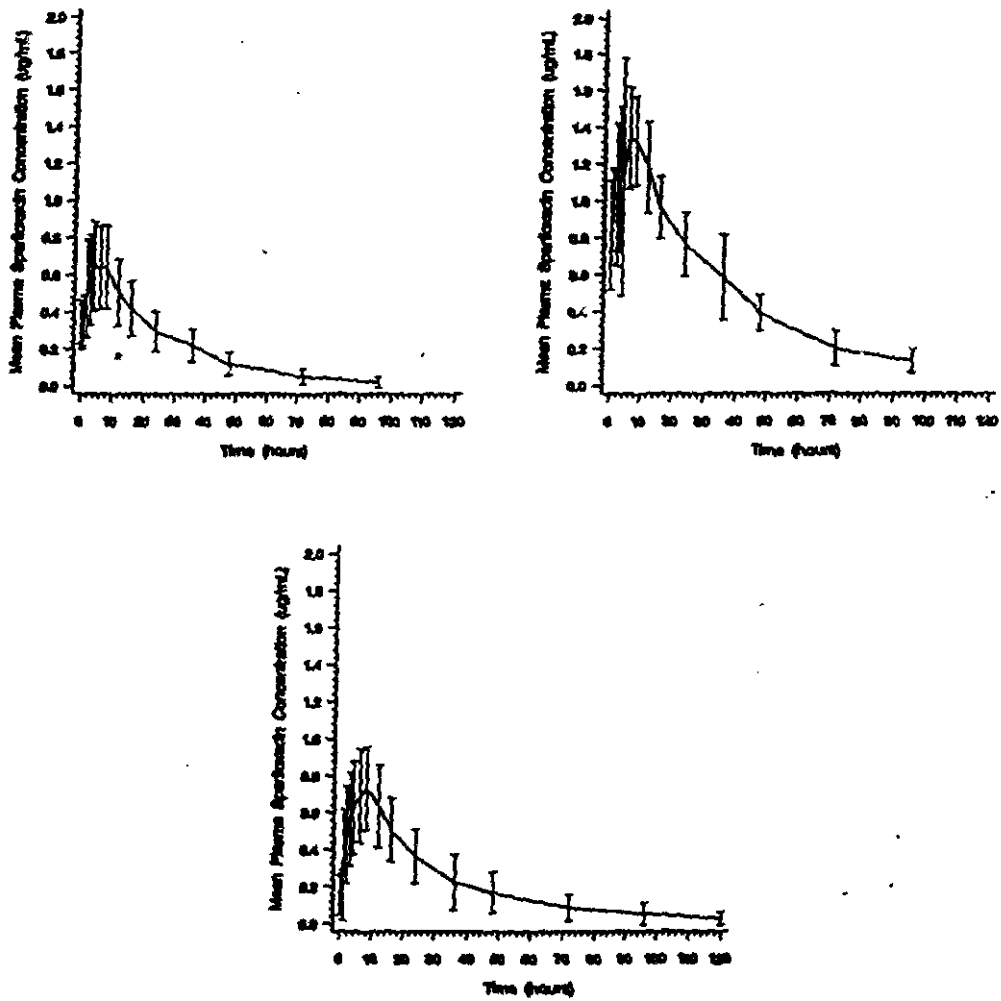


Figure 2. Mean plasma sparfloxacin concentrations for subjects with normal renal function (top left), mild renal insufficiency (top right), and moderate renal insufficiency (bottom center) following the last multiple oral dose administration (200 mg) of sparfloxacin. Subjects were excluded for previously stated reasons. Error bars are ± 1 standard deviation.

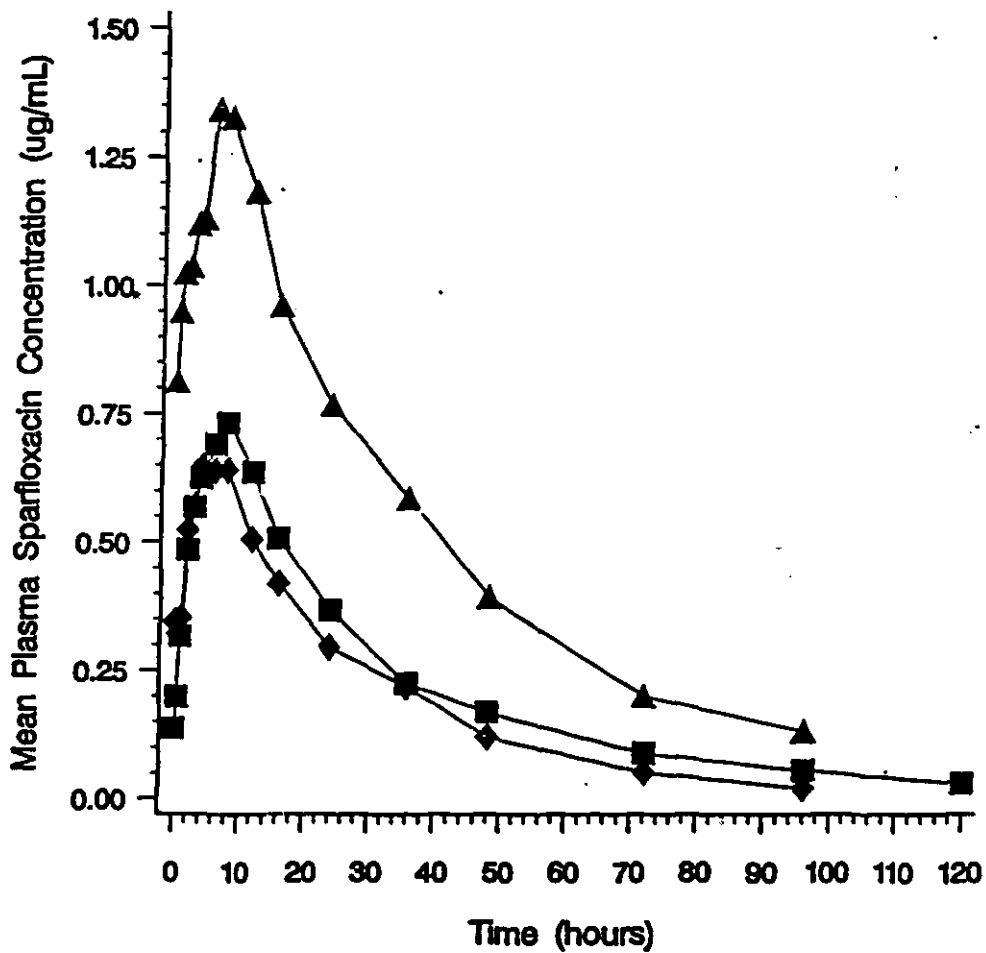


Figure 3. Mean plasma sparfloxacin concentrations for subjects with normal renal function (◆), mild renal insufficiency (▲), and moderate renal insufficiency (■) following the last multiple oral dose (200 mg) administration of sparfloxacin. Subjects #160, 163, and 165 were excluded for previously stated reasons.

Table 2. Mean (%CV) Plasma Sparfloxacin Concentrations After the Last Multiple 200 mg Oral Dose for Subjects with Normal Renal Function, Mild Renal Insufficiency, and Moderate Renal Insufficiency^a.

Time	Mean Steady-State Plasma Sparfloxacin Concentrations ($\mu\text{g/ml}$)		
	Normal Renal Function ($\text{Cl}_{\text{cr}} \geq 50 \text{ ml/min}$) ^b (n=12) ^c	Mild Renal Insufficiency ($30 \leq \text{Cl}_{\text{cr}} \leq 49 \text{ ml/min}$) ^b (n=7) ^d	Moderate Renal Insufficiency ($10 \leq \text{Cl}_{\text{cr}} \leq 29 \text{ ml/min}$) ^b (n=8)
0.0	0.346 (34.1)	0.812 (36.5)	0.137 (83.4)
0.5	0.321 (37.8)	0.949 (23.7)	0.198 (45.9)
1	0.353 (39.4)	1.024 (13.6)	0.317 (94.6)
2	0.523 (50.2)	1.037 (37.3)	0.484 (54.2)
3	0.571 (42.6)	1.120 (35.1)	0.567 (44.8)
4	0.647 (37.6)	1.132 (57.0)	0.626 (40.3)
6	0.639 (35.0)	1.343 (20.7)	0.690 (36.6)
8	0.641 (35.2)	1.328 (18.3)	0.723 (30.8)
12	0.506 (35.4)	1.183 (20.9)	0.637 (35.0)
16	0.420 (35.4)	0.961 (17.5)	0.508 (34.1)
24	0.295 (36.3)	0.767 (22.6)	0.367 (39.8)
36	0.218 (40.7)	0.586 (40.0)	0.225 (67.2)
48	0.121 (51.4)	0.393 (24.8)	0.169 (65.3)
72	0.052 (83.5)	0.201 (46.7)	0.089 (80.6)
96	0.020 (138)	0.132 (48.0)	0.055 (111)
120	— ^b	— ^b	0.030 (125)

^a Steady-state concentrations over a dosing interval are represented by mean values up to 24 hours (normal and mild renal insufficiency) or up to 48 hours (moderate renal insufficiency).

^b Pharmacokinetic blood sampling occurred until 96 hours post-dose for Groups 1 and 2.

^c Excluding Healthy Subjects who did not appear to be at steady-state.

^d Excluding Mildly Renally Impaired Subject who did not appear to be at steady-state and had questionable study medication compliance.

The intersubject variability of plasma concentrations at each time point as assessed by the %CV of the steady-state plasma sparfloxacin concentrations tended to be higher for subjects with moderate renal insufficiency. Intersubject variability of the other two groups were generally consistent with previous reports.

Steady-state plasma sparfloxacin pharmacokinetic parameters with descriptive statistics are included in Appendix D. Mean (%CV) steady-state plasma sparfloxacin pharmacokinetic parameters are summarized in Table 3.

Table 3. Mean (%CV) Steady-State Plasma Sparfloxacin Pharmacokinetic Parameters for Subjects with Normal Renal Function, Mild Renal Insufficiency, and Moderate Renal Insufficiency.

Parameter	Normal Renal Function ($Cl_{cr} \geq 50$ ml/min) ^a (n=12) ^{d,f}	Mild Renal Insufficiency ($30 \leq Cl_{cr} \leq 49$ ml/min) ^a (n=7) ^{e,f}	Moderate Renal Insufficiency ($10 \leq Cl_{cr} \leq 29$ ml/min) ^{a,f} (n=8)
$AUC_{0-\tau}^{ss}$ ($\mu\text{g/ml}\cdot\text{hr}$)	11.502 (32.2) ^b	25.397 (19.5) ^b	19.2 (35.2) ^c
C_{ave}^{ss} ($\mu\text{g/ml}$)	0.479 (32.2) ^b	1.06 (19.5) ^b	0.40 (35.2) ^c
C_{max}^{ss} ($\mu\text{g/ml}$)	0.750 (29.3) ^b	1.46 (17.2) ^b	0.800 (27.8) ^c
T_{max}^{ss} (hr)	5.9 (47.0)	4.9 (38.4)	6.3 (35.0)
k_{elim} (hr^{-1})	0.037 (34.4)	0.025 (32.6)	0.034 (53.9)
$t_{1/2}$ (hr)	18.7	27.7	20.4

^a Normalized to a body surface area of 1.73 m².

^b $\tau = 24$ hours.

^c $\tau = 48$ hours.

^d Excluding Healthy Subjects: who did not appear to be at steady-state.

^e Excluding Mildly Renally Impaired Subject who did not appear to be at steady-state and had questionable study medication compliance.

^f Represents mean values up to 24 hours (normal and mild renal insufficiency) or up to 48 hours (moderate renal insufficiency).

In general, mean C_{max}^{ss} , $AUC_{0-\tau}^{ss}$, and C_{ave}^{ss} values were higher for subjects with mild renal insufficiency than for subjects with normal renal function receiving the same dosage regimen. This observation is consistent with results obtained from a previous single dose renal insufficiency study (AT-108) where $AUC_{0-\tau}^{ss}$ values increased with a decrease in renal function, probably due to the slower apparent elimination rate in renally impaired patients.

For subjects with moderate renal insufficiency, the 48-hour dosing interval generally produced plasma sparfloxacin concentration-time profiles and mean C_{max}^{ss} and C_{ave}^{ss} values that were consistent with profiles in subjects with normal renal function following the standard 24-hour dosing interval. A 48-hour dosing interval may also be more appropriate for subjects with mild renal insufficiency if it is desirable to produce a plasma concentration-time profile more similar to that observed for the moderate renal insufficiency group

3.2.2 Urine Sparfloxacin Pharmacokinetics

Appendix E contains a summary of unchanged urine sparfloxacin concentrations and collected volumes over 0-24, 24-48, 48-72, 72-96, and 96-120 hour intervals for each subject. The amount of sparfloxacin excreted and cumulative amount of sparfloxacin excreted with descriptive statistics are also listed in Appendix E. Urine sparfloxacin pharmacokinetic parameters (fraction of unchanged drug excreted, steady-state renal clearance, and k_{term}) are included in Appendix E.

Appendix F contains individual sparfloxacin cumulative urinary excretion versus time plots over the appropriate sampling-time interval. Mean cumulative urinary excretion profiles of sparfloxacin for all three groups excluding Subjects #160, 163, and 165 are illustrated in Figure 4. Mean (%CV) steady-state urine sparfloxacin pharmacokinetic parameters are listed in Table 4.

Table 4. Mean (%CV) Steady-State Urine Sparfloxacin Pharmacokinetic Parameters for Subjects with Normal Renal Function, Mild Renal Insufficiency, and Moderate Renal Insufficiency.

Parameter	Normal Renal Function ($Cl_{cr} \geq 50$ ml/min) ^a (n=12) ^{b,e}	Mild Renal Insufficiency ($30 \leq Cl_{cr} < 50$ ml/min) ^a (n=7) ^{c,e}	Moderate Renal Insufficiency ($10 \leq Cl_{cr} < 30$ ml/min) ^a (n=7) ^{d,e}
% Excreted	8.3 (35.3)	9.2 (29.8)	4.0 (55.4)
Cl_r (L/hr)	1.50 (32.4)	0.74 (31.9)	0.42 (38.1)
k_{term} (hr ⁻¹)	0.040 (39.9)	0.025 (23.2)	0.035 (40.3)
$t_{1/2}$ (hr)	17.3	27.7	19.8

^a Normalized to a body surface area of 1.73 m².

^b Excluding Healthy Subjects who did not appear to be at steady-state.

^c Excluding Mildly Renally Impaired Subject who did not appear to be at steady-state and had questionable compliance.

^d Excluding Moderately Renally Impaired Subject who had a poorly defined elimination phase.

^e Represents mean values up to 24 hours (normal and mild renal insufficiency) or up to 48 hours (moderate renal insufficiency).

Subjects having moderate renal insufficiency excreted less sparfloxacin than subjects having normal renal function and mild renal insufficiency.

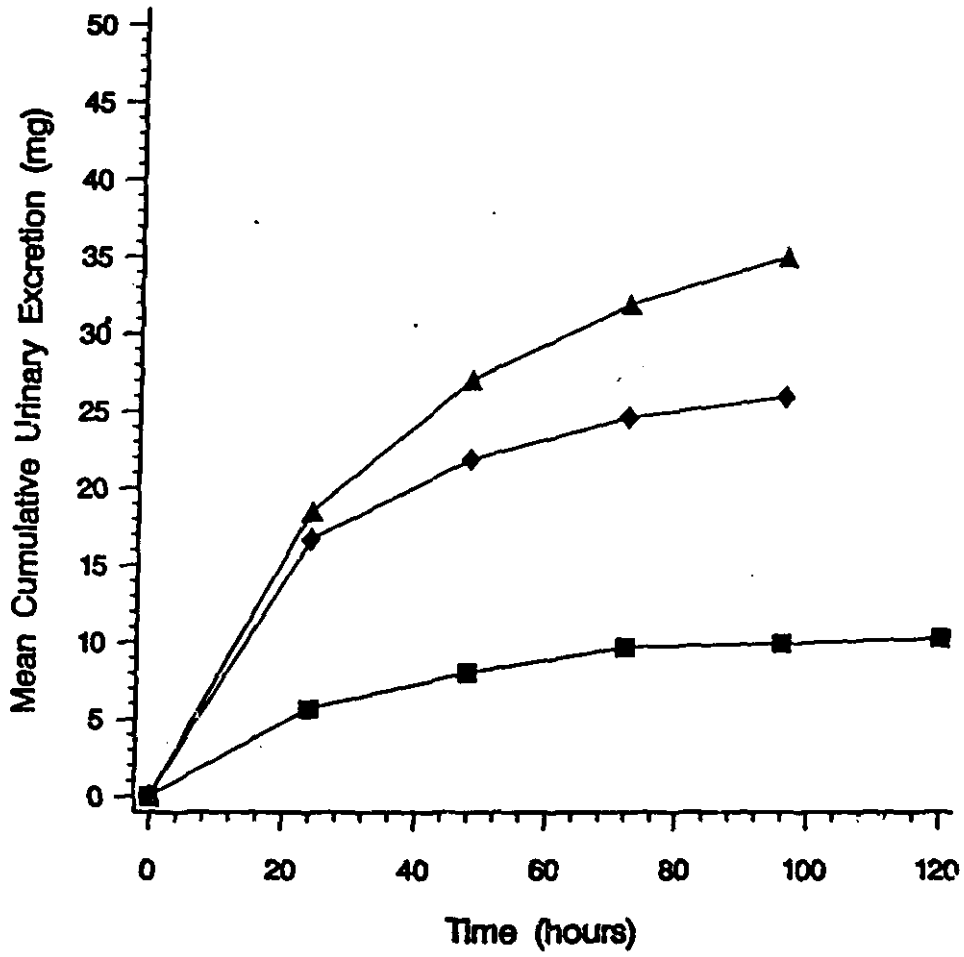


Figure 4. Mean cumulative urinary excretion of sparfloxacin for subjects with normal renal function (◆), mild renal insufficiency (▲), and moderate renal insufficiency (■) following the last multiple dose oral administration (200 mg) of sparfloxacin. Excluding Subjects

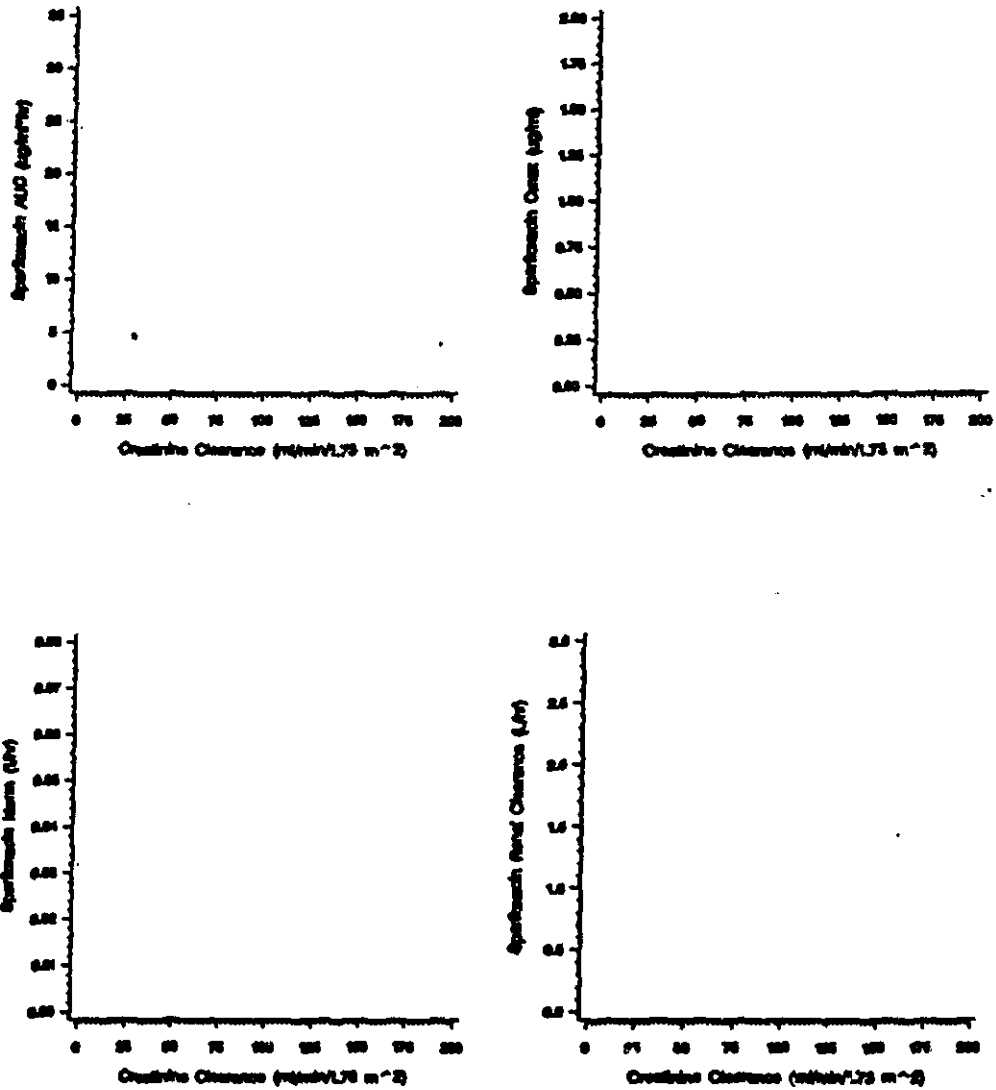


Figure 5. Scatter plots for steady-state sparfloxacin pharmacokinetic parameters $AUC_{0-\infty}^{ss}$, CL_r , C_{max}^{ss} , and k_{term} versus creatinine clearance. Excluding Subjects

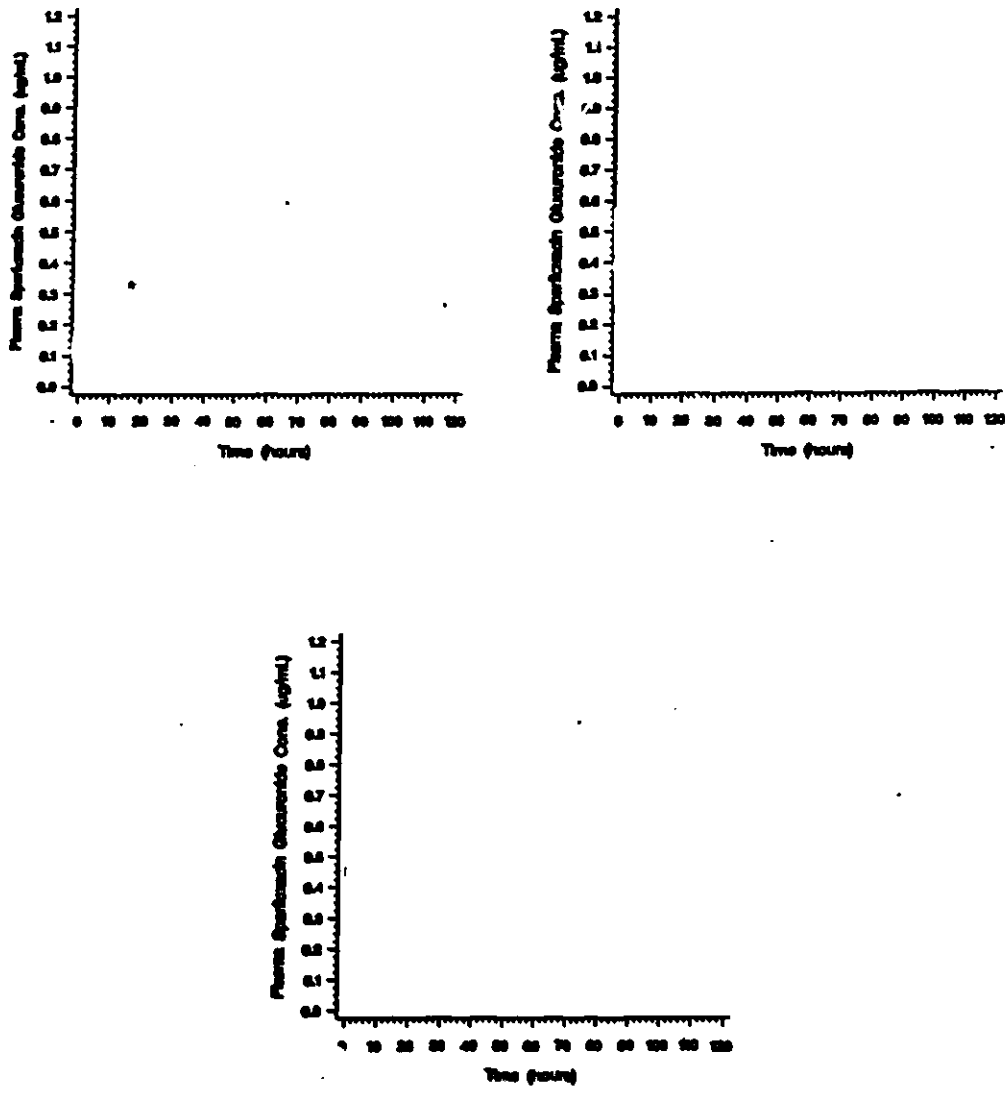


Figure 6. Individual plasma sparfloxacin glucuronide concentrations for subjects with normal renal function (top left), mild renal insufficiency (top right), and moderate renal insufficiency (bottom center) following the last multiple oral dose administration (200 mg) of sparfloxacin.

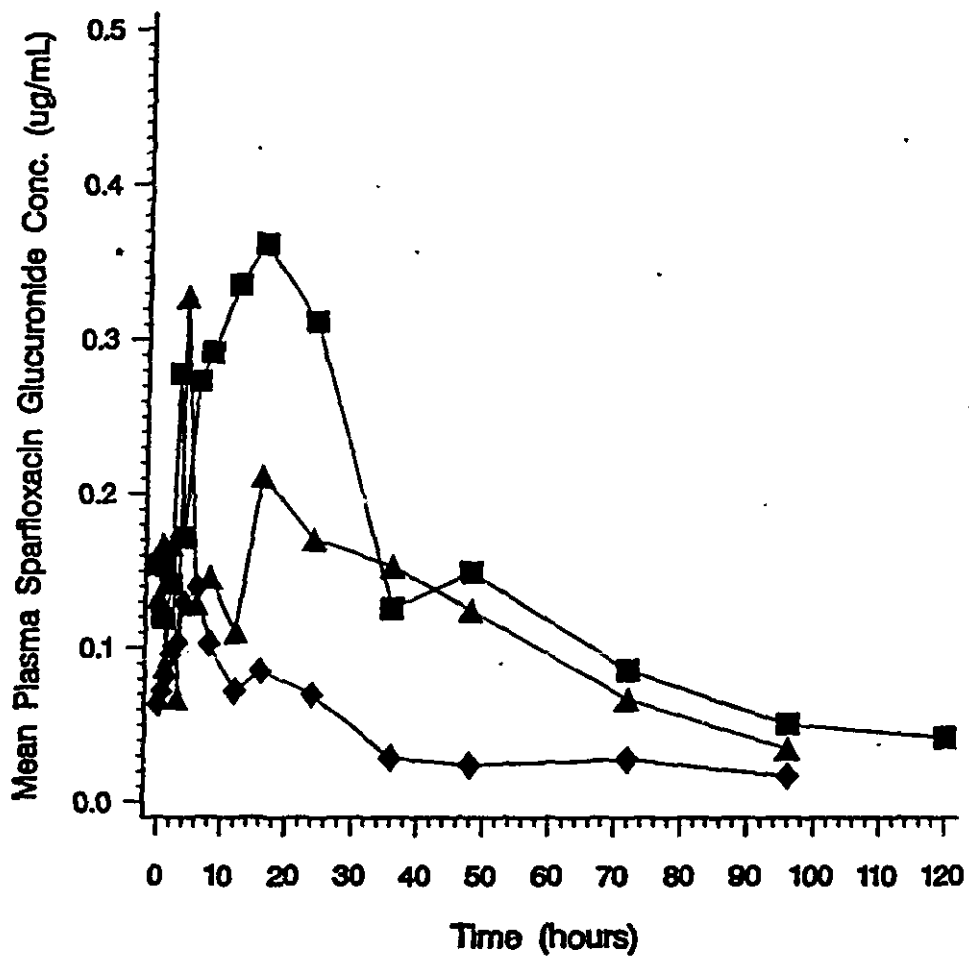


Figure 8. Mean plasma sparfloxacin glucuronide concentrations for subjects having normal renal function (◆), mild renal insufficiency (▲), and moderate renal insufficiency (■) following the last multiple dose administration (200 mg) of sparfloxacin. Subjects were excluded for previously described reasons.

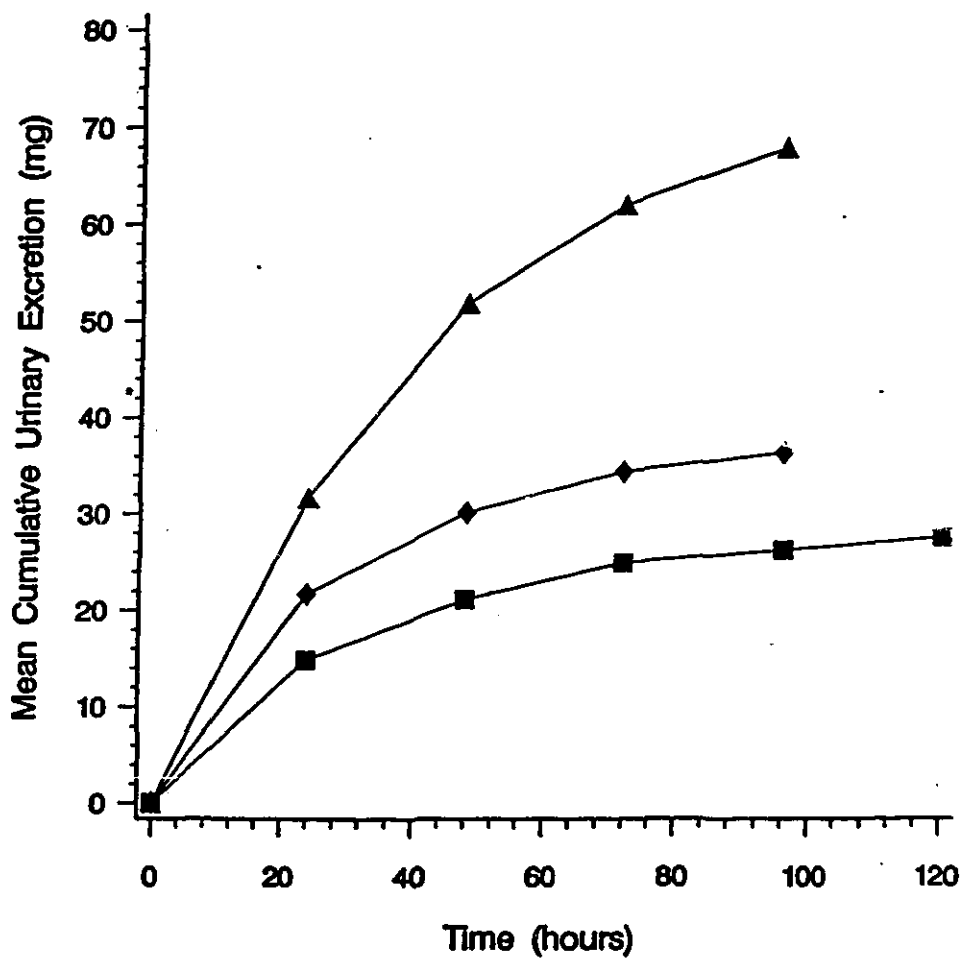


Figure 10. Mean cumulative urinary excretion of sparflouxacin glucuronide for subjects with normal renal function (◆), mild renal insufficiency (▲), and moderate renal insufficiency (■) following multiple dose oral administration (200 mg) of sparflouxacin. Excluding Subjects

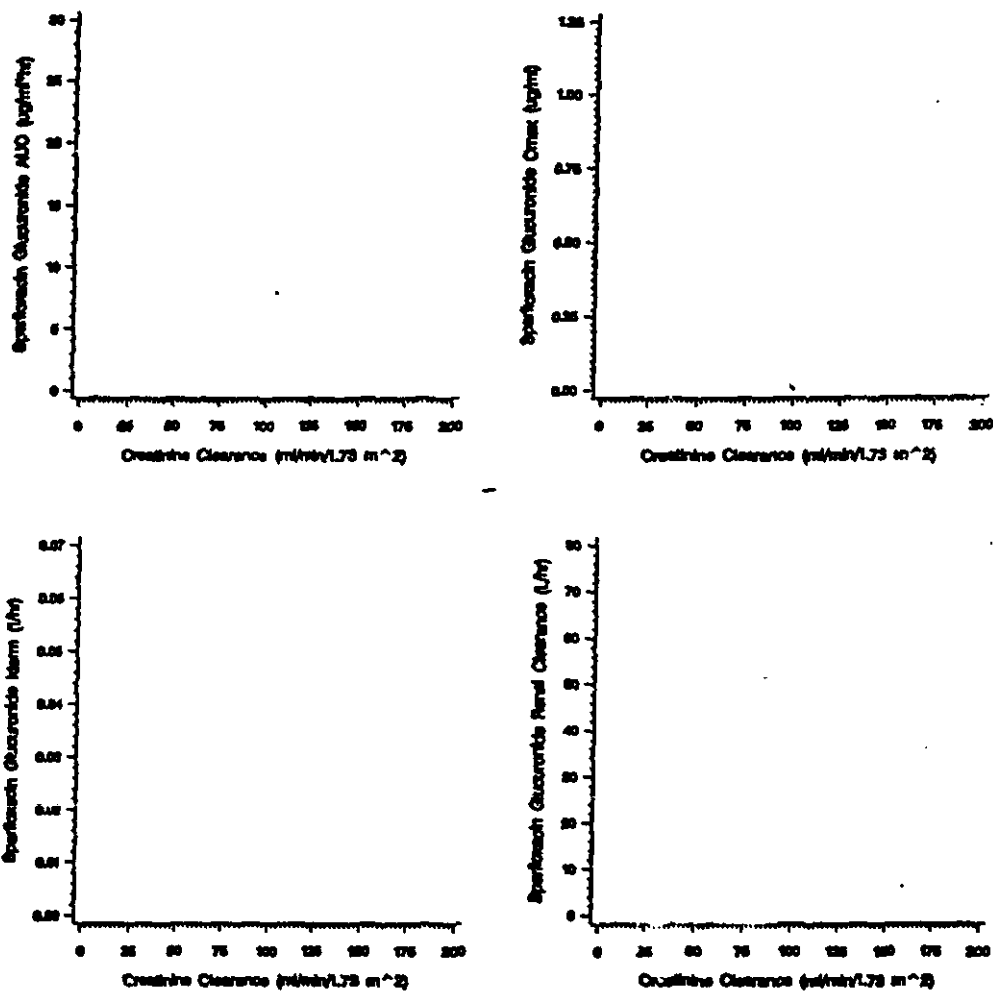


Figure 11. Scatter plots for steady-state sparfloracin glucuronide pharmacokinetic parameters $AUC_{0-\infty}^{ss}$, CL_T^{ss} , C_{max}^{ss} , and k_{term} versus creatinine clearance. Excluding Subjects

Tabulated Summary Report	
Title of study: (Phase)	A Phase I, Sequential, Multiple-Dose Pharmacokinetic Study of the Effect of Sparfloxacin on the Pharmacokinetics of Theophylline in Healthy Adult Male and Female Volunteers, Protocol RP 64206X-156 (Phase I).
Investigator:	
Publication (reference):	None.
Study period:	First subject treated: 8 March, 1994 Last subject treated: 16 March, 1994
Study center:	
Objectives:	To assess the effect of multiple oral sparfloxacin doses on steady-state theophylline pharmacokinetics in healthy adult nonsmoking male and female volunteers. A secondary objective was to assess a potential pharmacodynamic interaction of the two drugs in combination on the QT interval.
Methodology:	The study was conducted as an open-label, sequential, multiple-dose, single-center trial. Twenty subjects (10 male and 10 female) received oral theophylline every 8 hours during each of two treatment periods, lasting 4 days each. During Period 1 (Days 1-4), subjects received theophylline alone; during Period 2 (Days 5-8), subjects received theophylline concomitantly with sparfloxacin (400 mg loading dose on Day 5 followed by 200 mg on Days 6-8).
Number of subjects:	20 enrolled (10 males, 10 females); nineteen completed all study procedures (9 males, 10 females).
Diagnosis and criteria for entry:	Healthy nonsmoking male or female (not of childbearing potential) volunteers between the ages of 18 and 65 years with normal body weight and no clinically relevant laboratory or electrocardiographic (ECG) abnormalities or other disease were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 200 and 400 mg oral (1 x 200 mg tablet and 2 x 200 mg tablets; lot number 9208221, manufactured by Parke-Davis). Slo-Phyllin® 100 mg theophylline tablets (dose individualized per subject based on single-dose theophylline clearance determined during screening; lot number 9311922, manufactured by Rhône-Poulenc Rorer Pharmaceuticals).
Duration of treatment:	Subjects received theophylline every 8 hours for 8 days, Days 1-8; concomitant sparfloxacin was administered for 4 days, Days 5-8.
Reference therapy: dose, route of administration, lot number:	Theophylline alone (see above).
Safety measurements:	Adverse clinical and laboratory experiences and changes in physical examination, vital sign, and ECG findings.
Pharmacokinetic parameters:	Steady-state theophylline pharmacokinetic parameters included: maximum plasma theophylline concentration (C _{max}), time to reach the maximum plasma theophylline concentration (T _{max}), area under the plasma theophylline concentration-time profile over the 8-hour dosing interval (AUC(0-8)), and apparent oral theophylline clearance (CL _{ss/T}).
Statistical methods:	An analysis of variance (ANOVA) was used to test for differences in the test means (theophylline alone and theophylline plus sparfloxacin) for each pharmacokinetic parameter at an α level of 0.05.

Tabulated Summary Report

Results:	Safety and Tolerability: Concomitant administration of sparfloxacin and theophylline was generally well tolerated, although tolerance of theophylline alone during Period 1 was poor. Sixteen subjects reported adverse events while receiving theophylline alone, and five subjects reported adverse events while receiving sparfloxacin plus theophylline. The most frequently reported adverse events were headache (8 subjects), nausea (5 subjects), vomiting (5 subjects) and somnolence (4 subjects). None of the events were considered serious; one subject reported severe nausea and vomiting while receiving theophylline alone. One subject was discontinued from the study by the investigator due to adverse experiences (abdominal pain, vomiting, and somnolence reported on Day 2 of receiving theophylline alone). No subject had a serious adverse laboratory event. No clinically relevant changes in physical examination, blood pressure or ECG findings occurred during the study. Seven subjects experienced increases in heart rate on Days 2 or 3 while receiving theophylline alone. Pharmacokinetics: Concomitant sparfloxacin administration did not affect the steady-state pharmacokinetics of theophylline in healthy nonsmoking males and females. Mean theophylline concentration-time profiles were essentially superimposable for the two treatments. No gender effects were observed for pharmacokinetic parameters except for mean steady-state $CL_{ss/f}$, which was higher in males than in females during both study periods.
Conclusions:	• Concomitant administration of sparfloxacin and theophylline was generally well tolerated. • Sparfloxacin did not affect the steady-state pharmacokinetics of theophylline. • No changes in theophylline dosing are necessary during coadministration of sparfloxacin and theophylline.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (Ri² 84206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 38 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (phase I)	A phase I open study of the tolerance and the pharmacokinetic and pharmacodynamic interactions between digoxin, at plasma steady-state, and a single oral 400 mg dose of sparfloxacin administered to 10 healthy volunteers	
Investigators: Co-investigators:		
Study centre:		
Publication (reference)	Rodolphe GARRAFFO, Pharm D, M.D. 4th international symposium on new quinolones - Munich - August 1992	
Study period (years):	1990 - 1991	
Objectives:	To assess the possible effect of concd single dose administration on pharmacodynamics of digoxin.	
Methodology:	10 volunteers receiving a steady state given a single dose of sparfloxacin or treatment. Pharmacokinetic profiles of digoxin, or sparfloxacin intake): blood sampling pre 24, 36, 48 hours post-dose; residual plas 3, 11, 12. Pharmacokinetic profile of sparfloxacin times were the same as for digoxin wlt hours post-dose	
Number of subjects:	12 subjects were included	
Diagnosis and criteria for inclusion:	Male healthy volunteers of 20 to 40 years old, body weight of within 15% of ideal range, written informed consent.	
Test product, dose, mode of administration, batch n°:	Oral sparfloxacin 4 x100 mg tablets, batch n°CB 3976	
Duration of treatment:	Single dose	
Reference therapy: dose, mode of administration, batch n°:	Digoxin Nativelle (0,25 mg/day) orally administered once daily for a 10 days period. Batches n°964 and 959	
Criteria for evaluation:	Safety: clinical and biochemical evaluations at selection, D1 (except for biology) and D11, adverse events recording. Pharmacokinetic parameters: Cmax, AUC, T1/2, T max	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 38 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																																
criteria for evaluation: (continued)	Pharmacodynamics parameters: heart rate, corrected QT (Bazett) duration, PR and QRS durations. These parameters were determined with: - 12 leads ECG recording while digoxin alone, - high amplification (signal averaged) ECG recording (H0 and H6) and ambulatory electrocardiography (Marquette system) recording (25 hours) the day of concomitant administration of both drugs (day 9).																																	
Statistical methods:	Pharmacokinetics: Calculations were done by non compartmental methods by mean of the software. Student's paired t-test and Westlake analysis were performed to evaluate the differences between pharmacokinetic parameters of digoxin with and without coadministration of sparfloxacin. Pharmacodynamics: descriptive Safety: descriptive																																	
Results - conclusions: 12 subjects were included in the safety analysis and 10 in the pharmacokinetic and pharmacodynamic analysis (because of 2 withdraws). Pharmacokinetic results: • <u>Digoxin pharmacokinetics:</u> Digoxin Cmax and Tmax determined at steady-state are not statistically different after sparfloxacin intake. On the other hand, the AUC0-12h is significantly increased (p=0.03) after sparfloxacin intake (within ± 11.58% of the AUC before). The combination with sparfloxacin can not be considered as responsible of a significant pharmacokinetic interaction (p=0.05) if the profile's equivalence is accepted within the range of ± 15%. Anyway, 0.25 mg/day of digoxin can be considered as a low dosage, and a careful therapeutic monitoring when associated to sparfloxacin could be recommended due to the very small therapeutic index. • <u>Sparfloxacin pharmacokinetics:</u> the data obtained are largely in agreement with the previous published data. Digoxin should not modify sparfloxacin pharmacokinetics in human. <table border="1" data-bbox="373 1397 1251 1608"> <thead> <tr> <th rowspan="2">Mean (SD**)</th> <th colspan="2">plasma digoxin</th> <th rowspan="2">p*</th> <th rowspan="2">plasma sparfloxacin</th> </tr> <tr> <th>alone</th> <th>+ sparfloxacin</th> </tr> </thead> <tbody> <tr> <td>Tmax (h)</td> <td>1.5 (0.53)</td> <td>1.4 (0.52)</td> <td>0.73</td> <td>3.7 (1.73)</td> </tr> <tr> <td>Cmax (ng/ml)</td> <td>1.42 (0.32)</td> <td>1.7 (0.37)</td> <td>0.06</td> <td>1110 (499)</td> </tr> <tr> <td>t1/2 (h)</td> <td></td> <td></td> <td></td> <td>19.36 (3.8)</td> </tr> <tr> <td>AUC0-12 (ng.h/ml)</td> <td>9.12 (1.18)</td> <td>9.93 (1.26)</td> <td>0.03</td> <td></td> </tr> <tr> <td>AUC0-∞ (ng.h/ml)</td> <td></td> <td></td> <td></td> <td>26015 (8360)</td> </tr> </tbody> </table> p*: calculated with the paired student t test (statistical significance for p ≤ 0.05) SD**: standard deviation			Mean (SD**)	plasma digoxin		p*	plasma sparfloxacin	alone	+ sparfloxacin	Tmax (h)	1.5 (0.53)	1.4 (0.52)	0.73	3.7 (1.73)	Cmax (ng/ml)	1.42 (0.32)	1.7 (0.37)	0.06	1110 (499)	t1/2 (h)				19.36 (3.8)	AUC0-12 (ng.h/ml)	9.12 (1.18)	9.93 (1.26)	0.03		AUC0-∞ (ng.h/ml)				26015 (8360)
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NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 38 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Results - conclusions (continued):

Pharmacodynamics:

Standard ECG and signal averaged ECG recordings: during treatment with digoxin alone, the mean heart rate decreased (not significantly). No significant variation was observed after sparfloxacin administration (neither in heart rate, nor in PR, QRS and QTc durations).

Ambulatory ECG recording: no abnormality could be directly related to the administration of sparfloxacin. The abnormalities occurred most of the time during night sleep, while the vagal tone is of utmost importance; They all were within a normal range of defects possibly occurring in young healthy volunteers.

ECG parameters

Mean (sem*)	Day 1	Day 9	
		H0	H6
heart rate (beats/min)	66.7 (3.84)	57.9 (2.68)	60.8 (2.53)
PR (ms)	160 (6.67)	183.12 (5.32)	176.3 (6.26)
QRS (ms)	82 (5.54)	101.5 (4.85)	103.5 (3.81)
QTc(Bazett)	388 (8.24)	378.09 (8.23)	387.53 (7.49)

*: standard error of mean

Safety

23 clinical events (5 and 2⁽¹⁾ headache episodes, 2 and 1⁽¹⁾ asthenia, some digestive symptoms) and 2 clinically significant ECG modifications leading to study discontinuation during digoxin treatment occurred ; the relationship with the study drug (either digoxin, or both drugs) was most often rated as possible, was unrelated for 1 conjunctivitis and probable for the ECG modifications.

(¹): after sparfloxacin intake).

NAME OF COMPANY: Rhône-Poulenc Rorer NAME OF FINISHED PRODUCT: Sparfloxacina	INDIVIDUAL STUDY TABLE REFERRING TO PART 2.7 OF THE NDA Volume: Page:	(FOR FDA USE ONLY)
Title of study: (Phase)	The Effect of Sparfloxacina on the Steady-State Pharmacokinetics of Digoxin in Healthy Male Volunteers (Phase I).	
Investigator:		
Publication (reference):	Johnson RD, Wilson J, Talbot G, Conway S, Heald D. The Effect of Sparfloxacina on the Steady-State Pharmacokinetics of Digoxin in Healthy Male Volunteers. Pharm Res 1994; 11(10):S-429.	
Study center:		
Objectives:	To determine whether sparfloxacina has a significant effect on the pharmacokinetics of digoxin at steady-state in healthy male volunteers.	
Methodology:	The study was conducted as a double-blind, placebo-controlled, multiple-dose, two-way crossover trial. Twenty-four subjects were randomly assigned to one of two treatment groups in a 1:1 ratio. Group 1 received oral digoxin 0.3 mg on Days 1-20 along with oral sparfloxacina on Days 1-10 (400 mg on Day 1 and 200 mg on Days 2-10) and oral placebo on Days 11-20 (two tablets on Day 11 and one tablet on Days 12-20). Group 2 received identical treatment except that placebo was given on Days 1-10 and sparfloxacina was given on Days 11-2	
Number of subjects:	24	
Diagnosis and criteria for entry:	Healthy male volunteers between the ages of 18 and 50 years weight and no clinically relevant laboratory or electrocard abnormalities or other disease were eligible for study participatio	
Test product: dose, route of administration, lot number:	Sparfloxacina 200 and 400 mg oral (1 x 200 mg tablet and 2 x 2 number 9208221, manufactured by Digoxin capsu 0.1 mg capsules; lot number 9307754, manufactured by Burroughl	
Duration of treatment:	Subjects received digoxin for 20 days and sparfloxacina for 10 day	
Reference therapy: dose, route of administration, lot number:	Placebo tablets to match sparfloxacina 200 mg tablets (lot 1 manufactured by	
Safety measurements:	Adverse clinical and laboratory experiences and changes in physical examination, vital sign, and ECG findings.	
Pharmacokinetics parameters:	Maximum steady-state plasma digoxin concentration (C _{max-ss}), time to reach the maximum steady-state plasma digoxin concentration (T _{max-ss}), trough plasma digoxin concentrations (C _{min-ss}), and area under the steady-state plasma digoxin concentration-time profile over the 24-hour dosing interval (AUC(0-24)-ss).	
Statistical methods:	Analysis of variance (ANOVA) for a two-way crossover design was used to test for differences in the test means for each pharmacokinetic parameter compared to the reference (placebo) means at an α level of 0.05. In addition, 90% Confidence Intervals (two one-sided test) were constructed for natural logarithmically transformed least squares mean C _{max-ss} and AUC(0-24)-ss values.	

NAME OF COMPANY: Pulse-Pulse Paper NAME OF FINISHED PRODUCT: Spartanocin Resale:	INDIVIDUAL STUDY TABLE REFERRING TO PART 2 OF THE NDA Volume: Page:	(FOR FDA USE ONLY)
	Spartanocin did not affect the steady-state pharmacokinetics of digoxin. The mean steady state plasma digoxin concentration-time profiles during spartanocin and placebo treatment were essentially superimposable. Neither the rate nor the extent of digoxin absorption was altered by concomitant administration of spartanocin. There were no severe or serious clinical or laboratory adverse experiences. One subject receiving digoxin plus spartanocin in Period 1 experienced complete atrioventricular (AV) block on Day 10 before receiving study medication and was discontinued from the study. A second subject (Placebo to Spartanocin Group) experienced first degree AV block during both treatment periods. No clinically relevant changes in physical examination, laboratory tests, or vital signs occurred during the study.	Subjects receiving digoxin plus placebo generally experienced a small decrease in the QTc interval. At steady-state, spartanocin produced a placebo-adjusted increase in QTc of 13 to 21 msec, which was independent of digoxin therapy. Combination therapy produced no effect on the PR interval.
Conclusions:	• Spartanocin did not affect the steady-state pharmacokinetics of digoxin. • Concomitant administration of spartanocin and digoxin was well tolerated, the two instances of AV block are attributed to the effect of digoxin alone. • No apparent treatment effect of spartanocin relative to placebo on the QTc or PR intervals was observed during administration of spartanocin and digoxin.	• Based on both pharmacokinetic and pharmacodynamic data from this study, no changes in drug dosing or monitoring of serum digoxin concentrations are necessary during coadministration of spartanocin and digoxin.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 39 Page :	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, double-blind, randomized, crossover study of the effect of cimetidine versus placebo on the pharmacokinetics of sparfloxacin administered as a single 400 mg oral dose to 10 healthy volunteers.	
Investigators: Study centre:		
Publication (reference):	None	
Study period (years):	1992	
Objectives:	• Primary objective: To determine the effect of coadministration of cimetidine and sparfloxacin on the pharmacokinetics of sparfloxacin. • Secondary objective: To assess the safety of sparfloxacin when coadministered with cimetidine in healthy volunteers.	
Methodology:	Single centre, double-blind, randomized, crossover, placebo-controlled study.	
Number of subjects:	10	
Diagnosis and criteria for inclusion:	Male healthy volunteers aged 18-40 years; written informed consent; body weight within 10% of ideal weight according to Metropolitan Life Insurance Actuary Tables.	
Test product, dose, mode of administration, batch No.:	• Cimetidine 400 mg film-coated tablets, batch 41/90 0 15/01, in opaque capsules each containing 400 mg. One capsule orally 3 times a day. • Placebo capsules similar in appearance to cimetidine capsules, batch CB 5052P. One capsule orally 3 times a day. • Sparfloxacin 100 mg film-coated tablets, batch CB 4654. Single oral dose of 400 mg (4 tablets).	
Duration of treatment:	• Cimetidine or placebo: 8 days. • Sparfloxacin: Single oral dose on D3 of cimetidine or placebo treatment.	
Reference therapy:	None	
Study procedures:	The 10 subjects, randomized in 2 groups of 5, received the following treatments : -Group A: 8-day placebo treatment and single oral dose of sparfloxacin on D3, 10-day washout, followed by 8-day cimetidine treatment and single oral dose of sparfloxacin on D3. - Group B: 8-day cimetidine treatment and single oral dose of sparfloxacin on D3, 10-day washout, followed by 8-day placebo treatment and single oral dose of sparfloxacin on D3. - Blood samples on D3 before sparfloxacin intake then 1, 2, 3, 4, 6, 8, 12, 24 (D4), 48 (D5), 72 (D6), 96 (D7), 120 (D8) and 144 h (D9). - Urine collection on D3 before sparfloxacin intake then for the following intervals 0-12, 12-24 (D4), 24-48 (D5), 48-72 (D6), 72-96 (D7), 96-120 (D8) and 120-144 h (D9).	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 39 Page :	(FOR NATIONAL AUTHORITY USE ONLY)																																													
Criteria for evaluation: Pharmacokinetics: Safety:	C _{max} , t _{max} , AUC 0-∞, t _{1/2} , MRT, Cl _o , A _e (unchanged and conjugated sparfloxacin), Cl _r , urinary metabolic ratio. Adverse events; vital signs on D1, D3, D6; 12-lead ECG on D3 before sparfloxacin and 4-8 hours postdose.																																														
Statistical methods:	Pharmacokinetic parameters: Analysis of variance for C _{max} and AUC, paired t-test for the other continuous variables and Wilcoxon's test for T _{max} . Vital signs: Mean baseline ± SD and mean differences ± SD with respect to baseline at the different scheduled time points as a function of treatment sequence. ECG parameters: Mean ± SD as a function of treatment sequence.																																														
Results - Conclusions: There were no dropouts in this study. Pharmacokinetic results • Plasma pharmacokinetic parameters No statistically significant differences between plasma pharmacokinetic parameters or urinary excretion of sparfloxacin with or without concomitant treatment with cimetidine was observed. However, there was a significant group effect; P=4.35% therefore mean AUC values are given by group.																																															
<table border="1"> <thead> <tr> <th>PARAMETER</th> <th>PLACEBO + SPARFLOXACIN (Mean ± SD; N = 10)</th> <th>CIMETIDINE + SPARFLOXACIN (Mean ± SD; N = 10)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/ml)</td> <td>19.7 ± 9.08</td> <td>16.6 ± 7.08</td> </tr> <tr> <td>t_{max} (h)</td> <td>2.5 ± 1.7</td> <td>4.3 ± 3.0</td> </tr> <tr> <td>AUC 0-∞ (ng.h/ml) group A</td> <td>60845.4 ± 13310</td> <td>69378.0 ± 17990.8</td> </tr> <tr> <td>AUC 0-∞ (ng.h/ml) group B</td> <td>54577.0 ± 9385.5</td> <td>43213.6 ± 13614.8</td> </tr> <tr> <td>t_{1/2}</td> <td>26.2 ± 3.9</td> <td>25.5 ± 4.1</td> </tr> <tr> <td>MRT (h)</td> <td>36.8 ± 6.7</td> <td>36.5 ± 6.3</td> </tr> <tr> <td>Cl (ml/min)</td> <td>118.7 ± 28.2</td> <td>141.8 ± 42.1</td> </tr> <tr> <td>Cl (ml/min/kg)</td> <td>1.8 ± 0.3</td> <td>2.0 ± 0.6</td> </tr> <tr> <td>A_e 0-144 (% dose)</td> <td></td> <td></td> </tr> <tr> <td>• Sparfloxacin</td> <td>13.0 ± 2.7*</td> <td>12.3 ± 4.9</td> </tr> <tr> <td>• Conjugate</td> <td>24.8 ± 6.5*</td> <td>23.5 ± 6.2</td> </tr> <tr> <td>Cl_r (ml/min)</td> <td></td> <td></td> </tr> <tr> <td>• Sparfloxacin</td> <td>15.6 ± 3.2</td> <td>16.5 ± 3.9</td> </tr> <tr> <td>Urinary metabolic ratio</td> <td>1.8 ± 0.6</td> <td>2.0 ± 0.6</td> </tr> </tbody> </table>	PARAMETER	PLACEBO + SPARFLOXACIN (Mean ± SD; N = 10)	CIMETIDINE + SPARFLOXACIN (Mean ± SD; N = 10)	C _{max} (ng/ml)	19.7 ± 9.08	16.6 ± 7.08	t _{max} (h)	2.5 ± 1.7	4.3 ± 3.0	AUC 0-∞ (ng.h/ml) group A	60845.4 ± 13310	69378.0 ± 17990.8	AUC 0-∞ (ng.h/ml) group B	54577.0 ± 9385.5	43213.6 ± 13614.8	t _{1/2}	26.2 ± 3.9	25.5 ± 4.1	MRT (h)	36.8 ± 6.7	36.5 ± 6.3	Cl (ml/min)	118.7 ± 28.2	141.8 ± 42.1	Cl (ml/min/kg)	1.8 ± 0.3	2.0 ± 0.6	A _e 0-144 (% dose)			• Sparfloxacin	13.0 ± 2.7*	12.3 ± 4.9	• Conjugate	24.8 ± 6.5*	23.5 ± 6.2	Cl _r (ml/min)			• Sparfloxacin	15.6 ± 3.2	16.5 ± 3.9	Urinary metabolic ratio	1.8 ± 0.6	2.0 ± 0.6		
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NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64205)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 39 Page :	(FOR NATIONAL AUTHORITY USE ONLY)

Results (continued)

• Mean urinary concentrations of unchanged sparfloxacin

COLLECTION PERIODS	PLACEBO + SPARFLOXACIN (µmol mean ± SD; N = 10)	CIMETIDINE + SPARFLOXACIN (µmol mean ± SD; N = 10)
0 - 12 h	21.98 ± 8.76	24.98 ± 16.80
12 - 24 h	25.10 ± 14.13	23.25 ± 10.92
24 - 48 h	10.32 ± 5.16	8.68 ± 4.44
48 - 72 h	5.21 ± 1.77	3.96 ± 1.67
72 - 96 h	2.29 ± 1.01*	2.17 ± 1.13
96 - 120 h	1.57 ± 0.67	1.40 ± 0.86
120 - 144 h	0.97 ± 0.54*	1.03 ± 1.01

* N = 9

Adverse experiences and safety profile:

• Adverse events

SUBJECTS No.	PERIOD	GROUP	ADVERSE EVENT	SEVERITY	DAY*	DURATION	RELATION
	2	A	Pain abdominal	Mild	2	20 min	Possible
	2	B	Headache	Mild	4	45 min	Possible
	2	B	Anxiety	Mild	4	45 min	Possible
	2	B	Dizziness	Mild	1	40 min	Possible

* Day of period when adverse event was observed

A: Sparfloxacin dosing on 3rd day of 8-day placebo treatment followed by sparfloxacin dosing on 3rd day of 8-day cimetidine treatment

B: Sparfloxacin dosing on 3rd day of 8-day cimetidine treatment followed by sparfloxacin dosing on 3rd day of 8-day placebo treatment

- Vital signs: No clinically significant variations.
- ECG: No clinically significant increases in QTc values.

Conclusion:

The concomitant treatment with cimetidine did not modify the plasma pharmacokinetics and urinary excretion of sparfloxacin following a single oral dose of 400 mg. Clinical and electrocardiographic safety was good.

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 17 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, randomized, comparative study, versus placebo, in two parallel groups of the effects of sparfloxacin given for 8 days on the normal faecal flora in 12 healthy volunteers.	
Investigators		
Study centres: Clinical investigator		
Bacteriological investigator		
Publication (reference):	Ritz M. et al. Multiple dose pharmacokinetics of : influence on faecal flora. ICAAC 1992, Anaheim, 1991	
Study period (years):	1991	
Objectives:	To analyse comparatively the modifications of <i>E. coli</i> and anaerobes bacterial populations of faeces c sparfloxacin or placebo; determine the quantity recovery of the bacterial populations after stopping To correlate bacteriological results with compl data in blood, urine and faeces. To assess the safety of sparfloxacin in healthy male volunteers.	
Methodology:	Double blind, randomized, multiple dose comparative study vs placebo (1/3 of the patients) in two parallel groups	
Number of subjects:	Twelve.	
Diagnosis and criteria for inclusion:	Healthy male subjects aged 21-49 years. Body weight within 25% of ideal range. No diarrhoea or loose stools at the start of the study. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Film-coated tablets each containing 100 mg of sparfloxacin Batch: CB 4385 Oral administration Eight-day treatment: D1: 400 mg (4 tablets) D2 to D8: 200mg (2 tablets)	
Duration of treatment:	8 days.	
Reference therapy, dose, mode of administration, batch n°:	Matching placebo tablets. Same conditions of administration as test drug. Batch CB 4113 P	
Study procedures:	Eight subjects received sparfloxacin, 4 received placebo. After the administration of sparfloxacin (400 mg on day 1, 200 mg on day 2 to day 8), the following samples were collected for the pharmacokinetic and bacteriological analysis: - faecal samples: days -7, -4, 2, 4, 8, 11, 21, 28 and 56 - blood samples: day -4 and H0, H2, H6, H10, H24 on days 1 and 4. - urine samples: days 1 and 8 (0-6, 6-12, 12-24 hrs), days 11, 21, 28 (0-24hrs)	

NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: S ACTIVE INGREDIENT: (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 17 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Criteria for evaluation Pharmacokinetics: Bacteriology Safety:	Determination of the following pharmacokinetic parameters: . Plasma : Cmax, Tmax, half-life, AUC . Faeces : concentration at days 1,4 and 8 . Urine : drug elimination over time , mean urine 24h concentration after first dose and last dose. Repeated qualitative and quantitative faecal flora analysis before treatment until follow-up after treatment (day 56) Clinical examination: day -7, day 1 and day 8; adverse events recording; laboratory tests on day -4 and day 8.	
Statistical methods: *	Pharmacokinetics: Mean ± SD, min - max values Vital signs: Mean ± SD, min - max values	

Results - conclusions:

Bacteriological results

Sparfloxacin administration resulted in immediate eradication of Enterobacteriaceae (detection level : 2 log/g) and in diminution of Enterococci. Colonization after stopping treatment was slow and limited for Enterobacteriaceae, rapid for Enterococci. Total counts of anaerobes were not modified during treatment. C. difficile or its cytotoxin has not been detected in any sample. Flora from placebo control group were not modified during the study period but marked individual variations could be observed.

Pharmacokinetics results:

The pharmacokinetic results are always expressed as a " 200mg single dose " equivalent. They were calculated for 200mg after day 1 and recalculated as a single dose on day 4. Final results may be summarized as follows:

PARAMETER	DAY 1	DAY 4	DAY 8
PLASMA			
Cmax (µg/ml)	0.56 ± 0.13	0.61 ± 0.16	
Tmax (h)	3.5 ± 0.9		
AUC _{0-∞} (mg.h/l)	16.4 ± 2.3	18.3 ± 5.1	
t _{1/2 β} (h)	18.3 ± 3.9		
URINE			
Mean conc (12-24h, mg/l)	13.6 ± 7.2		17.8 ± 11.1
Cumulative recov (24h, %)	5.89 ± 1.4		6.58 ± 3.3
FAECES			
Mean conc (mg/kg)	759.6 ± 484.4	671.7 ± 474.8	476.46 ± 7.2
Elimination (%)	47.5 ± 30.3	31.4 ± 20.7	22.6 ± 11.1

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 17 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Safety results: As regards safety, clinical events possibly related to sparfloxacin were observed in five subjects: they consisted on headache (3 events, mild), flatulence (3 events, mild) associated with diarrhea in 2 cases (loose stools) and mild itching after sun exposure (1 case). In the placebo group, one myalgia and 1 headache were mentioned in 2 patients. No biological or haematological event or significant variations were mentioned. Conclusions: Sparfloxacin induced slight and transient modifications of fecal flora in relation with susceptible organisms like <i>Enterobacteriaceae</i> and <i>Enterococci</i>. No emerging <i>Cl. difficile</i> could be demonstrated. Pharmacokinetic analysis has revealed a high concentration in feces and a limited urinary excretion. Clinical tolerance was good.		

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART (V.A OF THE DOSSIER Volume: 37 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (Phase I)	A Phase I, open study of the effect of sparfloxacin (400 mg for 1 day followed by 200 mg for a further 6 days) on warfarin pharmacodynamics in ten healthy volunteers	
Investigators:		
Study centre:		
Publication (reference):	None	
Study period (years):	1992	
Objectives:	• Primary: Assessment of the effect of sparfloxacin coadministration on the pharmacodynamics of warfarin. • Secondary: Clinical and biological safety of sparfloxacin and warfarin coadministration.	
Methodology:	Open, one-way study.	
Number of subjects:	10 (11 included, 1 withdrawal).	
Diagnosis and criteria for inclusion:	Male adult healthy volunteers aged 18-45 years, body weight within 15% of ideal range; written informed consent.	
Test product, dose, mode of administration, batch No.:	• Warfarin 2 mg (Batch N° 1203) and 10 mg (Batch N° 1202) tablets (Coumadine® - Merrell): 10 mg on D1 and D2; dosage according to the measured International Normalised Ratio (INR) from D3 onward to obtain steady-state INR of 1.3-1.7. Dosage fixed at least 1 day before sparfloxacin intake (except for subject 8 whose dose was fixed on the day of the first dose of sparfloxacin) and maintained until last day of sparfloxacin. Oral administration. • Film-coated tablets each containing 100 mg of sparfloxacin, batch no CB 4654: Dose of 400 mg (4 tablets) on D11 and of 200 mg (2 tablets) on D12-D17, could be delayed until D16 (400 mg) and D17-D22 (200 mg) according to the time to reach INR steady-state. Oral administration.	
Duration of treatment:	• Warfarin: 17 to 22 days (D1 to D17, end could be delayed until D22) • Sparfloxacin: 7 days (start: D11 or D16; end: D17 or D22)	
Reference therapy:	None.	
Criteria for evaluation: Pharmacodynamics:	Measurement of INR once a day from D1 to D7, twice a day from D7 to the last day of warfarin administration alone. On the first day of administration of both drugs (D11 or D16), measurement of INR before dosing and 6 and 12 hours after dosing.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 37 Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Criteria for evaluation continued: Pharmacodynamics: Safety:	On the six following days, measurement of INR before coadministration and 12 hours later (and 24 hours later, after the last dose). During recovery period, measurement of INR once a day until recovery of pre-inclusion value. - Clinical examination including vital signs at screening, on D1, D7, day of the first dose of sparfloxacin, 24 hours after the last dose of sparfloxacin and at the end of recovery period. 12-lead ECG at screening, predrug and 4-8 h postdrug on the day of the first and last dose of sparfloxacin, 24 hours after the last dose of sparfloxacin and at the end of the recovery period. - Laboratory tests at screening, on D7, 24 hours after the last dose of sparfloxacin and at the end of recovery period. Potassium assay 4 to 8 hours postdrug on day of the first dose of sparfloxacin. - Adverse events recording throughout the study.
Statistical methods:	- Prothrombin ratio : Mean steady-state values on warfarin alone compared with measurements made on warfarin plus sparfloxacin by calculation of 95% confidence interval. - Vital signs and laboratory tests: Mean value $\pm$ SD and mean difference from baseline ($\pm$ SD) at scheduled time points. - ECG: Mean value $\pm$ SD at scheduled time points of all intervals.

Results :
 Withdrawal: One subject was withdrawn because of too high INR values.
 Mean values of difference(Δ) between the mean steady-state INR on warfarin alone and measurements made on warfarin plus sparfloxacin together with the 95% confidence interval and relative differences(% of steady state values) are shown in the following table:

SPARFLOXACIN ADMINISTRATION DAY	MEASUREMENT TIME	MEAN $\Delta \pm$ SEM	RELATIVE VARIATION (% Δ)	95% CONFIDENCE INTERVAL OF % Δ
First day (day 11 or day 16)	Predrug	-0.03 $\pm$ 0.03	-2.19	[- 6.45; 2.07]
	6 h	-0.06 $\pm$ 0.03	-5.26	[- 8.85; -1.67]
	12 h	-0.07 $\pm$ 0.03	-4.75	[- 8.94; -0.56]
Second day (day 12 or day 17)	Predrug	-0.04 $\pm$ 0.04	-2.56	[- 8.27; 3.15]
	12 h	-0.14 $\pm$ 0.05	-9.75	[- 16.3; -3.23]
Third day (day 13 or day 18)	Predrug	-0.15 $\pm$ 0.05	-9.81	[- 15.8; -3.78]
	12 h	-0.14 $\pm$ 0.06	-9.18	[- 16.7; -1.69]
Fourth day (day 14 or day 19)	Predrug	-0.12 $\pm$ 0.06	-7.92	[- 15.9; 0.03]
	12 h	-0.13 $\pm$ 0.06	-8.77	[- 16.0; -1.51]
Fifth day (day 15 or day 20)	Predrug	-0.12 $\pm$ 0.06	-7.74	[- 17.0; 1.53]
	12 h	-0.19 $\pm$ 0.06	-12.1	[- 19.1; -5.11]
Sixth day (day 16 or day 21)	Predrug	-0.19 $\pm$ 0.06	-12.2	[- 19.7; -4.67]
	12 h	-0.17 $\pm$ 0.07	-10.8	[- 20.1; -1.52]
Seventh day (day 17 or day 22)	Predrug	-0.21 $\pm$ 0.08	-13.5	[- 23.7; -3.25]
	12 h	-0.18 $\pm$ 0.07	-11.5	[- 19.8; -3.30]
end of administration (day 18 or day 23)	24 h postdrug	-0.24 $\pm$ 0.08	-15.6	[- 25.8; -5.35]

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140)(RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 37 Page :	(FOR NATIONAL AUTHORITY USE ONLY)

Results (continued)

The upper limit of the 95% confidence interval of the mean % difference: prothrombin ratio (INR) after sparfloxacin minus INR before sparfloxacin never reached clinically significant value of 15%.

Adverse experience and safety profile (11 patients included):

ADVERSE EVENTS	NUMBER OF EPISODES	NUMBER OF SUBJECTS	SEVERITY	RELATIONSHIP
Paresthesia	6	6	Mild	Probable
	1	1		Possible
Rash	3	3	Mild	Probable
	1	1	Moderate	Probable
Headache	3	2	Mild	Possible
Tremor	2	1	Mild	Possible
Pain	1	1	Mild	Possible
	1	1		Probable
Dizziness	1	1	Mild	Possible
Chelitis	1	1	Mild	Possible
Asthenia	1	1	Mild	Possible
Somnolence	1	1	Mild	Possible
Epistaxis	1	1	Mild	Possible
Testis disease	1	1	Mild	Possible
Myalgia	1	1	Mild	Possible
Nausea	1	1	Moderate	Possible
Vomiting	1	1	Moderate	Possible

- Vital signs: No clinically significant changes
- ECG recording: Measurements made by the investigator revealed QTc prolongations $\geq 15\%$ with respect to value before sparfloxacin in 6 subjects
 - Exceeded the value of 440 msec in one case (441 msec; subject
 - Probably related to sparfloxacin.

However, analysis by an external consultant indicated that there were QTc prolongations $\geq 15\%$ with respect to value before sparfloxacin in 2 subjects. It was also found that the QTc exceeded the value of 440 msec in subjects with maximum values of 449 and 473 msec, respectively.

- Laboratory tests:
 - Haematology: No clinically significant changes.
 - Biochemistry: No clinically significant changes.
 - Coagulation factors: Reversible decreases in factors VII, IX and X in most subjects, probably related to warfarin.
 - Urinalysis: No clinically significant changes.

Conclusion:

The coadministration of sparfloxacin with warfarin did not increase the anticoagulant activity of the latter drug although there was a tendency for a decrease. The concomitant administration of the two drugs was generally well tolerated by the subjects.

TABULATED SUMMARY REPORT

Title of study: (Phase I)	Randomized, Parallel Group, Multiple-Dose Study of the Effect of Sparfloxacin and Terfenadine (Seldane®) at Steady State on the Electrocardiograms of Healthy Adult Male Volunteers, Protocol RP 64206X-151 (Phase I)
Investigator:	
Publication (reference):	None.
Study Period:	First Subject Treated: 14 December, 1992 Last Subject Discharged: 12 February, 1993
Study Center:	
Objectives:	- To define whether terfenadine and sparfloxacin, when given in combination, affect the ECGs of healthy male volunteers, with particular reference to the QTc interval. - To define whether terfenadine and sparfloxacin, in combination, have an interactive effect on the QTc interval, as determined by comparison to the effect of each given alone.
Methodology:	This study was conducted as a randomized, double-blind, parallel-group, multiple-dose, single-center study. Subjects were randomly assigned to one of four treatment groups: <u>Placebo</u> (placebo sparfloxacin: four tablets p.o. Day 1; two tablets p.o. QD Days 2-4); <u>Sparfloxacin</u> (sparfloxacin: 400 mg p.o., Day 1; 200 mg QD Days 2-4); <u>Terfenadine</u> (placebo sparfloxacin: four tablets p.o. Day 1; two tablets p.o. QD Days 2-4; terfenadine: 60 mg p.o. q12h Days 1-4 x seven doses); <u>Combination</u> (sparfloxacin: 400 mg p.o. Day 1; 200 mg p.o. QD Days 2-4; terfenadine: 60 mg p.o. q12h Days 1-4 x seven doses).
Number of subjects:	88 enrolled; 87 subjects completed all study procedures.
Diagnosis and criteria for entry:	Healthy adult male volunteers with normal screening physical and laboratory examinations, ECGs, and 24-hour Holters were eligible for study participation.
Test product: dose, route of administration, lot number:	Sparfloxacin 100 mg tablets, manufactured by Daiinippon oral (lot number 9204834).
Duration of treatment:	4 days
Reference therapy: dose, route of administration, lot number:	Seldane® (terfenadine) 60 mg tablets, manufactured by (lot number 9211468); sparfloxacin placebo, manufactured by (lot number 9204833).
Safety measurements:	ECG (mean and maximum QTc at 3, 4, and 5 hours following sparfloxacin dosing on Dosing Days 1 and 4, compared to baseline QTc obtained 0.5 hour before the first dose) and Holter monitoring. The QTc was calculated by the methods of Bazett ("QTc-b"), Fridericia ("QTc-f"), and Sagie ("QTc-s"). In addition, adverse events, physical examinations, vital signs, and clinical laboratory determinations were assessed.
Pharmacokinetics parameters:	Maximum plasma concentration (C _{max}) and time at which it occurred relative to the administered dose (T _{max}), area under the plasma sparfloxacin concentration-time curve (AUC(0-24)).
Statistical methods:	Two-way analysis of variance (ANOVA) model with main effect for each of sparfloxacin, terfenadine, and the interaction term. One-sided t-tests were used. ANOVA for a parallel design was used to test for differences in the treatment means for each biopharmaceutic parameter at an alpha level of 0.05.*

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 18 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of the study: (phase I)	A phase I, double blind, placebo-controlled, crossover study of the effect of a single oral dose of sparfloxacin (400 mg or 200 mg) on the ventricular repolarisation at rest and during exercise in 15 healthy male volunteers.	
Investigator:		
Study centre:		
Publication (reference):	None	
Study period (years):	1993	
Objective:	The objective of the study was to evaluate the effect of sparfloxacin on the ventricular repolarisation (assessed from QT interval) and reverse rate dependence at rest and during exercise tolerance test (at different heart rates).	
Methodology:	Double-blind, randomised, three period crossover, placebo controlled study (latin square randomisation)	
Number of subjects:	15 subjects were planned, 15 were included.	
Diagnosis and criteria for inclusion:	Healthy male subjects aged 18-35 years. Body weight within 15% of ideal range (Metropolitan Life Insurance). Recruitment by advertising in a pool of healthy volunteers. Written informed consent.	
Test product, dose, mode of administration, batch No.:	Oral administration of 400 mg or 200 mg as 4 or 2 film-coated tablets each containing 100 mg of sparfloxacin; batch No CB 05136.	
Duration of treatment:	Single dose. Three administrations at 7-day interval.	
Reference therapy:	Matching placebo tablets, Batch No CB 04655 P	
Study procedure:	Administration of 4 tablets at each period of treatment: either 4 tablets of sparfloxacin (400 mg) or 2 tablets of sparfloxacin (200 mg) and 2 tablets of placebo or 4 tablets of placebo. Subjects were randomised into 3 groups of 5 corresponding to 3 treatment sequences (treatments separated by a 7-day washout period): -Treatment sequence A/B/C: treatment A in period 1, treatment B in period 2 and treatment C in period 3. - Treatment sequence B/C/A: treatment B in period 1, treatment C in period 2 and treatment A in period 3. - Treatment sequence C/A/B: treatment C in period 1, treatment A in period 2 and treatment B in period 3.	

NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 18 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																												
Criteria for evaluation: Electrocardiographic Safety Pharmacokinetics	- ECG obtained during exercise tolerance tests (E.T.T.): 2 E.T.T. at selection visit (1 for training, 1 for determination of Wmax), 2 E.T.T. at each period of dosing (1 at H0, 1 at H5) for the following parameters: RR, QT, estimated QT intervals (calculated by exponential fitting method). - ECG at rest: 1 at selection visit, 1 before drug intake (3 recordings at 5 minutes interval) and then 1 each hour after (1H, 2H, 3H, 4H, 5H, 6H, 7H, 8H) at each period of treatment. Friderica QTc values were directly measured. Physical examinations and vital signs measurements at selection and at the beginning of each visit. ECGs. Adverse events recording. Blood samples were collected for measurement of plasma concentration of Sparfloxacin at H0 (before intake) and immediately before exercise tolerance test (H5).																													
Statistical methods:	The statistical method used was an analysis of variance for crossover design in order to test the dose effect on exponential fitting estimates of QTc for each RR interval and to perform paired comparisons between regimens. Mean values $\pm$ SD and mean differences $\pm$ SD from baseline according to treatment sequence were calculated for vital signs.																													
Results - conclusions: The 15 subjects included were analysed Means and ranges (msec) of estimated QT values 5 hours after dosing (n=15 each) are displayed in the following Table: <table border="1" data-bbox="338 1461 1285 1713"> <thead> <tr> <th>RR</th> <th>PLACEBO</th> <th>SPARFLOXACIN 200 MG</th> <th>SPARFLOXACIN 400 MG</th> </tr> </thead> <tbody> <tr> <td>400</td> <td>262.73 (248 - 287)</td> <td>267.53 (252 - 298)</td> <td>269.33 (252 - 316)</td> </tr> <tr> <td>500</td> <td>296.67 (281 - 325)</td> <td>305.47 (283 - 344)</td> <td>306.33 (284 - 351)</td> </tr> <tr> <td>600</td> <td>320.20 (304 - 354)</td> <td>331.00 (307 - 368)</td> <td>330.60 (309 - 358)</td> </tr> <tr> <td>700</td> <td>336.47 (319 - 373)</td> <td>348.73 (326 - 390)</td> <td>347.93 (328 - 373)</td> </tr> <tr> <td>800</td> <td>347.80 (329 - 386)</td> <td>361.27 (334 - 405)</td> <td>360.27 (338 - 383)</td> </tr> <tr> <td>1000</td> <td>361.67 (339 - 400)</td> <td>377.47 (341 - 421)</td> <td>375.47 (348 - 406)</td> </tr> </tbody> </table>			RR	PLACEBO	SPARFLOXACIN 200 MG	SPARFLOXACIN 400 MG	400	262.73 (248 - 287)	267.53 (252 - 298)	269.33 (252 - 316)	500	296.67 (281 - 325)	305.47 (283 - 344)	306.33 (284 - 351)	600	320.20 (304 - 354)	331.00 (307 - 368)	330.60 (309 - 358)	700	336.47 (319 - 373)	348.73 (326 - 390)	347.93 (328 - 373)	800	347.80 (329 - 386)	361.27 (334 - 405)	360.27 (338 - 383)	1000	361.67 (339 - 400)	377.47 (341 - 421)	375.47 (348 - 406)
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NAME OF COMPANY: RHÔNE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 18 Page:	(FOR NATIONAL AUTHORITY USE ONLY)																																			
Results - conclusions (continued) Comparison of estimated QT values between placebo, sparfloxacin 200 mg and sparfloxacin 400 mg at different RR intervals provide the following p values: <table border="1" data-bbox="299 628 1286 940"> <thead> <tr> <th>RR (ms)</th> <th>400</th> <th>500</th> <th>600</th> <th>700</th> <th>800</th> <th>1000</th> </tr> </thead> <tbody> <tr> <td>Overall dose effect</td> <td>0.01 (s)</td> <td>0.002 (s)</td> <td>< 0.001 (s)</td> <td>< 0.001 (s)</td> <td>< 0.001 (s)</td> <td>0.002 (s)</td> </tr> <tr> <td>Placebo versus sparfloxacin 200 mg</td> <td>0.03 (s)</td> <td>0.003 (s)</td> <td>< 0.001 (s)</td> <td>< 0.001 (s)</td> <td>< 0.001 (s)</td> <td>0.001 (s)</td> </tr> <tr> <td>Placebo versus sparfloxacin 400 mg</td> <td>0.004 (s)</td> <td>0.001 (s)</td> <td>0.001 (s)</td> <td>< 0.001 (s)</td> <td>0.001 (s)</td> <td>0.004 (s)</td> </tr> <tr> <td>sparfloxacin 200 mg versus 400 mg</td> <td>0.42</td> <td>0.76</td> <td>0.89</td> <td>0.80</td> <td>0.77</td> <td>0.66</td> </tr> </tbody> </table>			RR (ms)	400	500	600	700	800	1000	Overall dose effect	0.01 (s)	0.002 (s)	< 0.001 (s)	< 0.001 (s)	< 0.001 (s)	0.002 (s)	Placebo versus sparfloxacin 200 mg	0.03 (s)	0.003 (s)	< 0.001 (s)	< 0.001 (s)	< 0.001 (s)	0.001 (s)	Placebo versus sparfloxacin 400 mg	0.004 (s)	0.001 (s)	0.001 (s)	< 0.001 (s)	0.001 (s)	0.004 (s)	sparfloxacin 200 mg versus 400 mg	0.42	0.76	0.89	0.80	0.77	0.66
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NAME OF COMPANY: RHONE D.P.C. EUROPE NAME OF FINISHED PRODUCT: Sparfloxacin NAME OF ACTIVE INGREDIENT: Sparfloxacin (AT4140) (RP 64206)	INDIVIDUAL STUDY TABLE REFERRING TO PART IV.A OF THE DOSSIER Volume: 18 Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Adverse events and safety profile The 15 subjects included were analysed. Two events (nausea and hay fever) were reported in two subjects. They were mild and were considered as no related to the treatment. No clinically significant variation of vital signs occurred. Conclusions: Although QT intervals at different RR intervals were prolonged by an administration of sparfloxacin at a dose of 200 mg or 400 mg, the differences from placebo were small. The reverse rate dependence of QT prolongation was only observed with the 200 mg sparfloxacin dose; non significant reverse rate dependence of QT prolongation was observed with the 400 mg dose. No clear relationship between estimated QT intervals and sparfloxacin plasma concentrations was observed. The 200 mg or 400 mg single dose of sparfloxacin was well tolerated, even under high heart-rate conditions. 2 adverse events were reported: hay fever and nausea were reported in 2 subjects (intensity: mild). These two events were judged as unrelated with sparfloxacin by the investigator		

STUDY 360: POPULATION PHARMACOKINETICS OF SPARFLOXACIN

This was a multicenter study performed to delineate the pharmacokinetics (PK) of sparfloxacin (SPAR) under treatment conditions approximating eventual clinical use and, in particular, to delineate those variables associated with significant changes in SPAR PK. It was also to provide data for correlating PK parameters (e.g. AUC, C_{max}) with clinical outcome and microbiologic outcomes, possibly safety.

The population PK study was conducted as part of the North American Phase III studies with SPAR. A sparse sampling strategy was applied in this study. Patients had plasma samples drawn according to one of two sampling schedules at the second visit (Day 4 ± 1 of treatment) to the clinical investigator's office. The sampling schedules were as follows: (a) trough and 1.5 h postdose, and (b) 4 and 6 h postdose. In addition, participating patients who were prematurely discontinued from these studies had two samples drawn 2 h apart. The aim was to determine the full PK profile for the drug over the whole population (rather than for an individual in a typical Phase I study). Fig. 1 shows the population plasma concentration time profile. Subjects were administered a loading dose of 400 mg SPAR followed by a maintenance dose of 200 mg q24h orally. Of the 279 subjects who completed all study procedures, 143 (79 males and 64 females) of the 148 subjects who were on SPAR were evaluable. Samples were assayed using a validated HPLC assay.

The distributions of continuous covariates are summarized in figure 2. There were 32 smokers and the rest were non-smokers. The subjects were of three ethnic groups as coded in the data set, but the Sponsor's report is silent on the names of the ethnic groups. One ethnic group contributed 2 subjects, another 11 subjects to the study population, while the third made up the rest of the population. The relationships between covariates on one hand and covariates and individual Bayesian PK parameter estimates (from initial NONMEM analysis without covariates) on the other hand were investigated using exploratory data analysis techniques. Fig. 3 (a - d) summarizes the relationships between PK parameters and covariates.

The population PK analysis was performed with NONMEM in three steps: determination of the structural (PK) and statistical models; building the full model which incorporated all covariates causing a significant reduction of the objective function (log-likelihood difference (LLD) = 3.84, $p < 0.05$); and comparing full and reduced models (LLD = 7.88, $p < 0.005$) in which nonsignificant covariates were removed to build the final model. The identification of significant covariates for apparent oral clearance (CL/F) preceded that for apparent volume of distribution (V/F). Only creatinine clearance (CLCR), body weight (BWT), and abnormal renal function (RF) were significant predictors of CL/F. Of these only CLCR remain in the final model as a predictor of CL/F as follows:

```
IF (CLCR.LT.80) then
CL/F = THETA(1) * CLCR
ELSE
CL/F = THETA(1) * 80.
```

The choice of the CL/F model was due to the fact that the relationship between CLCR and CL/F was increasing up to 80 ml/min and constant above 80 ml/min.

Age, BWT, albumin, height (BHT), and CLCR were selected from univariate regression as predictors of V/F, however, only BWT (i.e. $V/F = \text{THETA}(1) + \text{THETA}(2) * \text{BWT}$) remained in the final population model as a predictor of this parameter. The variability in CL/F was reduced by 5.3% (i.e. from 44.9% (17.7%, %RSE) to 39.6% (15.4%, %RSE), and the variability in V/F was reduced by 14.1% (i.e. from 97.5% (20.5%, %RSE) to 83.4% (15.5%, %RSE)). The precision of interindividual variability in Ka was 74.9%, suggesting poor estimation of this parameter which was subsequently removed from the model. Residual intrasubject variability was best described with a constant coefficient of variation error model, and was estimated to be 7.6%. A plot of how well the model was predictive of individual concentrations is provided in Fig. 4. Individuals are identified by the numbers in the plot.

Given the data set, CL/F and V/F can be estimated from the following equations:

$CL/F = 0.203 (3.4\%) * CLCR$ (if CLCR is < 80 ml/min), or

$CL/F = 0.203 (3.4\%) * 80$ (if CLCR $\geq$ 80 ml/min); and

$V/F = 120 (43.5\%) + 2.48 (28.7\%) * \text{BWT}$, where the values in parentheses are percent relative standard errors. Ka was estimated to be 0.814 (16.3%).

Dosing Recommendations: Predictions of concentrations were carried out to ascertain the appropriateness of the Sponsor's proposal of alternate day dosing for compromised renal function (i.e. CLCR $\leq$ 50 ml/min). A loading dose of 200 mg followed with a maintenance dose of 200 mg q48h (Fig. 5) is recommended for patients with CLCR of 15 ml/min (i.e. 15 - 30 ml/min), while a loading dose of 400 mg followed by a maintenance dose of 200 mg q48h would be suitable for those with CLCR of 30 - 50 ml/min (Fig. 6) to keep the C_{max} about 1.0 mg/L. The Sponsor's report did not specify any changes in the loading dose. These figures show predictions of plasma concentrations with 95% confidence intervals for patients with various CLCR and weight combinations. Fig. 7 shows predictions for subjects with normal to moderate renal function. Fig. 8 shows predictions for patients with impaired renal function when there is no dosage adjustment.

COMMENT

Although the individual concentrations were well predicted as seen from Fig. 4 generated by the reviewer, the Sponsor did not test the predictive performance of the population model developed. In future, the Sponsor should test the predictive performance of any population model developed. This is of great importance because of the exploratory nature of the technique.

SPH-C
10/7/96
Eric I. Ete, Ph.D., FCP, FCCP
Pharmacometrics Staff, HFD-855

Pharm/Tox

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA #: 20,677-000

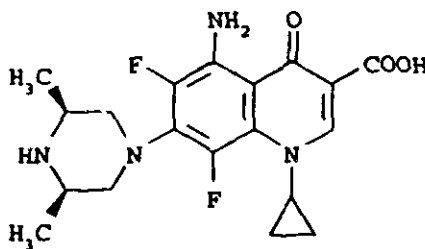
SPONSOR: Rhône-Polenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107
(610) 454-8000

AUTHORIZED REPRESENTATIVE: John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs
(or Mr. Mark Learn)
(610) 454-3053

DRUG NAMES: Zagam®; sparfloxacin; CI-978; AT 4140; PD 131501; 5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

CATEGORY: Fluoroquinolone anti-infective

STRUCTURAL FORMULA:



RELATED SUBMISSIONS: IND

NUMBER OF VOLUMES: 610 (50 for Pharm/Tox)

DATE CDER RECEIVED: 12/27/95

DATE ASSIGNED: 1/3/96

DATE REVIEW STARTED: 1/8/96

DATE 1ST DRAFT COMPLETED: 10/30/96

DATE REVIEW ACCEPTED BY TEAM LEADER:

REVIEW OBJECTIVES: To ascertain whether the nonclinical studies submitted by the sponsor adequately demonstrate the potential toxicity of this compound and to determine if this drug product meets safety standards allowing it to be approved for marketing.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION: Oral tablets
Each immediate release film-coated tablet contains:

<u>Tablet Core:</u>	mg
↓ Sparfloxacin	200
↓ Microcrystalline Cellulose	
↓ Corn Starch	
↓ L-Hydroxypropylcellulose	
↓ Magnesium Stearate	
↓ Colloidal Anhydrous Silica	

<u>Coating:</u>
↓ Methylhydroxypropylcellulose
↓ Polyethylene Glycol 6000
↓ Titanium Dioxide

The recommended dosing regimen for patients with normal renal function is a 400 mg loading dose on day 1 of therapy followed by 9 daily doses of 200 mg. In cases of renal impairment, 400 mg loading dose is given on day 1 followed by 200 mg doses every 48 hours for a total of 9 days of therapy. Proposed indications include community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis,

INDEX OF NONCLINICAL STUDIES SUBMITTED TO THIS NDA
(and location of review):

Pharmacology Studies:**Neuropharmacological Effects:**

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On General Behavior in Mice Report GP 87-0101, RR 740-02717)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Locomotor Activity in Mice Report GP 87-0102, Report RR 740-02718)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Rotarod Performance in Mice Report GP 87-103, Report RR 740-02719)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Acetic Acid-Induced Writhing Syndromes in Mice Report GP 87-0105, Report RR 740-02721
IND

Neuro-excitatory Effect of Sparfloxacin, a New Quinolone Antimicrobial Agent, in Combination with Non-steroidal Anti-inflammatory Drugs (translated from the Japanese journal Chemotherapy 39 (S-4): 167-174, 1991; Report C402)
Reviewed below

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Spontaneous EEGs in Immobilized Cats Report GP 87-107, Report RR 740-02725
IND

Cardiovascular/Respiratory Effects:

Cardiac Conduction of CI-978 (AT-4140) Administered Intravenously in Anesthetized Rabbits Report RR 740-02760)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Heart Rate and ECG in Conscious Dogs (Report GP 87-0201-2, Report RR 740-02727)
IND

Cardiovascular Effects of the Anti-infective Agent CI-978 (AT-4140) Administered Intravenously in Conscious Dogs (CACD Test) Report RR 740-02758)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Hemodynamic Parameters in Anesthetized Dogs Report GP 87-0201-1, Report RR 740-02726)
IND

Hemodynamic Evaluation of the Anti-infective Agent CI-978 (AT-4140) Administered Intravenously in Anesthetized Dogs (CAAD Test) Report RR 740-02759)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Blood Pressure and Heart Rate Responses to Noradrenaline in Anesthetized Cats . . . Report GP 87-0301, Report RR 740-02731)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Spontaneous and Electrically-Paced Contractions in Isolated Guinea Pig Atrium Report GP 87-0202, Report RR 740-02728)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Membrane Potentials of Isolated Papillary Muscles of Guinea Pigs Report GP 87-0204, Report RR 740-02730)
IND

Analysis of the Effects of Three Compounds (A: Sparfloxacin; B: Ciprofloxacin; and C: Ofloxacin) on Cell Action Potential and Contraction in the Guinea Pig Papillary Muscle
IND

Comparative Effects of Sparfloxacin and Erythromycin on Cellular Action Potential in Guinea Pig Papillary Muscle
IND

The Effects of Sparfloxacin on Repolarizing Potassium Currents in Rat Ventricular Myocytes
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Noradrenaline-Induced Contractions in Rabbit Aorta Report GP 87-0203, Report RR 740-02729)
IND

Gastrointestinal Effects:

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Intestinal Propulsion of Charcoal Meal in Mice Report GP 87-0303, Report RR 740-02734)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Gastric Emptying in Rats Report GP 87-0304, Report RR 740-02735)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Gastric Acid Secretion in Rats Report GP 87-0305, Report RR 740-02736)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Bile Excretion in Anesthetized Rats Report GP 87-0402, Report RR 740-02739)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Resting Tension of Isolated Guinea Pig Ileum Report GP 87-0302-1, Report RR 740-02732)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Spontaneous Movements of Isolated Rabbit Ileum Report GP 87-302-2, Report RR 740-02733)
IND

Genitourinary Effects:

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Urine Volume and Urinary Electrolyte Excretion in Saline-Loaded Rats Report GP 87-0401, Report RR 740-02738)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Spontaneous Movements of the Isolated Non-Gestational Rat Uterus Report GP 87-0306, Report RR 740-02737)
IND

Local Anesthetic Effects:

Local Anesthetic and Irritant Activity of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, In Rabbits Report GP 87-0403, Report RR 740-02740)
IND

Blood Functions:

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Blood Functions Report GP 87-0404, Report RR 740-02741)
IND

Interaction With Fenbufen:

Effect of Coadministration of Quinolones and Fenbufen (NSAID) Causing Seizures in Mice Report RR 740-02490)
IND

Interaction of CI-978 (AT-4140) and Fenbufen for Convulsion-Inducing Effect in Mice
Report GP 87-0106-1, Report RR 740-02722)
IND

Structure-Epileptogenicity Relationship of Quinolones with Special Reference to their Interaction with γ -Aminobutyric Acid Receptor Sites (Antimicrobial Agents and Chemotherapy 33: 1704-1708, 1989)
IND

A Study on Convulsive Effects of Sparfloxacin With or Without Non-steroidal Anti-Inflammatory Drugs Report C401, Chemotherapy 39(S-4): 161-166, 1991)
Reviewed below

Interaction of CI-978 (AT-4140) and Fenbufen. [^{3} H]GABA Binding Assay in Rat Brain Synaptic Membranes Report GP 87-0106-2, Report RR 740-02723)
IND

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Population Spikes in Rat Hippocampal Slices Report GP 87-0106-3, Report RR 740-02724)
IND

Toxicology Studies:**Single Dose Toxicity Studies:**

Acute Toxicity Study of CI-978 in Mice, Rats, and Beagle Dogs Report RR 745-01474, Report B101)
IND

Multidose Oral Toxicity Studies (Subchronic, Chronic, Carcinogenicity):

A Two-Week Dietary Study of CI-978 in Mice: Dose-Finding Study for Preliminary Carcinogenicity Study Report B801, Report RR 745-01778)
IND

A Thirteen-Week Dietary Toxicity Study of AT-4140 in Mice: Preliminary Carcinogenicity Study Report B802)
IND

A 104-Week Carcinogenicity Study of AT 4140 in Mice Report B1822)
IND

Four-Week Oral Toxicity Study of CI-978 in Rats ; Report RR 745-01475,
Report B201)
IND

**A Thirteen-Week Dietary Toxicity Study of AT-4140 in Rats: Preliminary
Carcinogenicity Study** Report B803)
IND

Twenty-six Week Oral Toxicity Study of CI-978 in Male and Female Rats
Report RR 745-01281, Report B302)
IND

A 104-Week Carcinogenicity Study of AT-4140 in Rats Report B1821)
IND

Four-Week Oral Toxicity Study of CI-978 in Beagle Dogs Report RR 745-
01476, Report B202)
IND

**Twenty-six Week Oral Toxicity Study of CI-978 (AT-4140) in Male and Female Beagle
Dogs** Report RR 745-01512, Report B301)
IND

Special Toxicity Studies:

Phototoxicity Studies:

Photosensitivity Study of Sparfloxacin: (V) Oral Phototoxicity Test in Mice
Report D24)
IND

**Phototoxic Lesions Induced by Quinolone Antibacterial Agents in Auricular Skin and
Retina of Albino Mice (Toxicologic Pathology 21(6): 554-561, 1993)**
Reviewed below

**Phototoxicity Screen of Sparfloxacin with Ultraviolet Radiation in Hairless Mice (Rhône-
Poulenc Rorer Report DS 94-076)**
IND

**Ninety-Day Range-Finding Study of Orally Administered Sparfloxacin in Hairless Mice
Exposed to UV Radiation (Rhône-Poulenc Rorer Report DS 94-077)**
IND

Photosensitivity Study of Sparfloxacin (II): Oral Phototoxicity Test in Rats
Report D-21S)
IND

**Phototoxicity Test of CI-978 in Wistar Rats (Parke-Davis Report RR 745-01513,
Report B902)**
IND

Phototoxicity Study in Guinea Pigs After Oral Exposure with PD 131501 (AT-4140)
Report RR 745-01329)
IND

Phototoxicity Test of CI-978 in Guinea Pigs Report RR MEMO 745-01777,
Report B906)
IND

Photosensitivity Test of CI-978 in Guinea Pigs Report RR 745-01523,
Report B901)
IND

Photosensitivity Study of Sparfloxacin (IV): Oral Photoallergy Test in Guinea Pigs (GLP)
Report D-23)
IND

Photosensitivity Study of Sparfloxacin: Oral Photoallergy Study in Guinea Pigs
(Confirmation Study) (GLP) Report D-23S)
IND

**Evaluation of Photosensitizing Ability of Quinolones in Guinea Pigs (5th International
Quinolone Symposium, 1994, Japan, Poster Presentation)**
Reviewed below

**Photosensitization Test of Sparfloxacin: Photoallergenicity in Guinea Pigs After
Percutaneous Treatment with Sparfloxacin (performed according to GLP)**
Report D-20S)
IND

Arthrototoxicity Studies:

Effect of CI-978 on Joints in Juvenile Beagle Dogs Report RR 745-01522,
Report B903)
IND

Cardiotoxicity Studies:

Effect of CI-978 on Cardiac Function in Dogs Report RR 745-01333,
Report B904)

IND

Exploratory Seven-Day Oral Toxicity Study of PD 131501 in Beagle Dogs

Report RR 745-01473)

Reviewed below

Ocular Toxicity Studies:

Ocular Toxicity Test of CI-978 in Cats Report RR 745-01539,
Report B905)

IND

Ocular Toxicity Study of Sparfloxacin in Cats Report D-25)

Reviewed below

***In Vitro* Interaction of CI-978 with Melanin** Report RR 745-01380)

IND

RP 64206: Experimental Cocataractogenesis Study in Brown Norway Rats (Rhône-Poulenc Rorer Report SM 94-0053)

Reviewed below

Intravenous Toxicity Studies:

RP 64206: Four-Week Toxicity Study in the Rat by Intravenous Route
(RPR/RD/CRVA/SM 616)

IND

Four-Week Intravenous Toxicity Study of RP 64206 in Male Rats (RPR/RD/CVL/DS 94-112)

IND

RP 64206: Four-Week Toxicity Study in the Beagle Dog by Intravenous Route
(RPR/RD/CRVA/SM 640)

IND

Four-Week Intravenous Toxicity Study of RP 64206 in Dogs (RPR/RD/CVL/DS 94-117)

IND

Batch Comparison Studies:

A Toxicological Study of AT 4140A and AT 4140B by a Single Oral and Intraperitoneal Administration in the Mouse Report B103)
Reviewed below

A Toxicological Study of AT 4140A and AT 4140B by a Single Oral and Intraperitoneal Administration in the Rat Report B102)
Reviewed below

A Toxicological Study of AT 4140A and AT 4140B by a Single Oral and Intraperitoneal Administration in the Male Rat Report B204)
Reviewed below

Other Studies:

Effect of Sparfloxacin on Liver Function of Rats with Liver Failure Induced by D-galactosamine Report D-26)
Reviewed below

In Vitro Analytical Interference Testing of CI-978 Report RR 745-01680)
IND

Antigenicity Study of Sparfloxacin Report D-13 (87309Z))
Reviewed below

Reproduction Studies:**Segment I - Fertility and Reproductive Performance Studies:**

Fertility Study of CI-978 in Male Rats Report RR 745-01556,
Report B402)
IND

Reproduction Studies of CI-978: Fertility Study in Female Rats Report RR
MEMO 745-01549, Report B403)
IND

AT-4140: Preliminary Segment I Study in Rat Report EUR B415)
IND

AT-4140: Reproductive Function and Fertility Study in the Rat-(Segment 1) Report
B416)
IND

Segment II - Teratology Studies:

Dose Range-Finding Study in Pregnant Rats with CI-978 Given Orally
 Report RR-MEMO 745-01652, Report B405)
 IND

Teratology Study in Rats with CI-978 Given Orally (Cesarean Section and Delivery and Wean)
 Report RR-MEMO 745-01454, Report B401-R-1)
 IND

Sparfloxacin: Preliminary Teratology Study in the Rat Report EUR386)
 IND

Sparfloxacin: Teratology Study in the Rat Report No.: 91/RHS090/616)
 IND

Effect of Maternal Treatment with AT-4140 on Fetal Development in Rats. Evaluation of the Developmental Stage Specificity of AT-4140-Induced Fetal Deaths and Ventricular Septal Defect Report B411)
 IND

Effect of Maternal Treatment with AT-4140 on Fetal Development in Rats. A Range-Finding Study for Assessment of Postnatal Recovery of AT-4140-Induced Ventricular Septal Defect Report B412)
 IND

Effect of Maternal Treatment with AT-4140 on Fetal Development in Rats. Assessment of Postnatal Recovery of AT-4140-Induced Ventricular Septal Defect Report B413)
 IND

Oral Dose Range Finding Study in Rabbits with CI-978 Report RR-MEMO 745-01756, Report B407)
 IND

Oral Teratology Study in Rabbits with CI-978 Report RR-MEMO 745-01757, Report B406)
 IND

Teratogenicity Study in Rabbits (Additional Study) Report B410)
 IND

Sparfloxacin: Preliminary Oral (Gavage) Maternal and Embryotoxicity Study in the Pregnant Cynomolgus Monkey Report EUR962-002)
 Reviewed below

Sparfloxacin: Oral (Gavage) Teratogenicity Study in the Cynomolgus Monkey
Report EUR962-002)

Reviewed below

Segment III - Perinatal and Postnatal Studies:

Perinatal and Postnatal Study in Rats with CI-978 Given Orally Report RR-
MEMO 745-01651, Report B404)
IND

Mutagenicity Studies:

In Vitro Studies:

Bacterial Mutagenicity Study of CI-978 Report RR 745-01479,
Report B701)
IND

Bacterial Mutagenicity Study of CI-978 Report RR 745-01542,
Report B701-R-1)
IND

Mutagenicity Test of AT-4140: Reverse Mutation Assay in Bacteria (Supplementary Test)
Report B701-R-2)

Reviewed below

**Bacterial Mutagenicity Assay of CI-978 in *Salmonella typhimurium* by the Induced-
Mutation-Frequency Method** Report B705, Report RR 745-01480)
IND

**Bacterial Mutagenicity Assay of CI-978 in *Salmonella typhimurium* by the Induced-
Mutation-Frequency Method** Report RR 745-01564, Report B705-
R-1)
IND

**DNA Damage Caused by Antibiotic Drugs: Quinolones (International Journal of Oncology
5: 855-859, 1994)**

Reviewed below

**Quinolones and Induction of *umuC* and Mutagenicity (Drugs 45 (Suppl. 3): 278-279,
1993)**

Reviewed below

Mutagenicity Test of AT-4140: Gene Mutation Test of AT-4140 in Cultured Mammalian Cells Report B707)

In Vitro Chromosomal Aberration Study of CI-978 Report RR 745-01481,
Report B702)

IND (Note that the initial reviewer did not mention that sparfloxacin was clastogenic at 256 $\mu\text{g/ml}$ with 6 hours of treatment in the absence of S-9)

In Vivo Studies:

Mouse Bone Marrow Cytogenetic Study of CI-978 Report RR 745-01477,
Report B704)

IND

Mouse Micronucleus Study of CI-978 Report RR 745-01478,
Report B703)

IND

Mouse Micronucleus Study of CI-978 Report RR 745-01774,
Report B706)

IND

Absorption, Distribution, Metabolism and Excretion:

In Vitro Dissolution Test and Comparison of Pharmacokinetic Parameters After Oral Administration in Dogs Between Sparfloxacin Anhydrous and Sparfloxacin Trihydrate (Rhône-DPC Europe Report EUR 5550)

Reviewed below

Plasma and Red Blood Cell Levels of Radioactivity After a Single Intravenous and Oral Administration of [^{14}C] Sparfloxacin in Rats [4.4 mg/kg i.v., 4.4 and 10 mg/kg p.o.]. Protein Binding in Rat Plasma After Oral Administration of [^{14}C] Sparfloxacin [10 mg/kg]. Report D102-1; Report RR 764-01326)

IND

Excretion of [^{14}C] Sparfloxacin After a Single Intravenous and Oral Administration at a Dose Range of 0.88 to 500 mg/kg in Male and Female Rats Report D102-4)

IND

Metabolic Profile in Plasma, Urine, Bile and Milk After Oral Administration of [^{14}C] Sparfloxacin in Rats at the Dose of 10 mg/kg Report D102-6)

Reviewed below

In Vitro Protein Binding Study of [¹⁴C] Sparfloxacin Report D102-9)
Reviewed below

Biliary Excretion and the Enterohepatic Circulation of Radioactivity After a Single Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg in Male Rats (Report D102-5)
IND

Synthesis of [Carbonyl-¹⁴C] Sparfloxacin (Arzneim.-Forsch./Drug Res. 41(II): 744-746, 1991)
Methodology appears reasonable.

Bioassay Method for Sparfloxacin in Biological Fluids Report D121)
Reviewed below

Microbiological Assay of Sparfloxacin in Human Plasma (RPR Report EUR 236)
Reviewed below

Determination of AT-4140 and its Glucuronide in Plasma, Urine and Bile
Report D103; Report RR 764-01347)
Reviewed below

Validated Liquid Chromatographic Assay for CI-978 in Rat Plasma Report
RR 764-01313)
Reviewed below

Validated Liquid Chromatographic Assay for CI-978 in Dog Plasma Report
RR 764-01307)
Reviewed below

Metabolism of Sparfloxacin: Identification of Sparfloxacin and its Metabolite and Stability of its Metabolite Report D112)
Reviewed below

Correlation Between AT-4140 Concentrations Measured by HPLC and Bioassay
Report D113)
Reviewed below

Sparfloxacin: Assessment of Absorption in the Pregnant Rat Report
91/RHS097/1022)
Reviewed below

RP 64206: Plasma Pharmacokinetics of Sparfloxacin After Single and Repeated (15 Days) 25 mg/kg/day Oral Dose in the Dog (RPR/IBP/Biodyn. 1720)
Reviewed below

Ocular Toxicokinetic Study of RP 64206 (Sparfloxacin) After Repeated Oral Administration of 25 mg/kg/day for 21 Days in the Female Dog 1637)
Reviewed below

RP 64206 - Sparfloxacin: Oral (Gavage) Pharmacokinetic Study in the Pregnant Rat (AT 7151) (RPR Report EUR 7151, 1734)
Reviewed below

RP 64206 - Sparfloxacin: Oral (Gavage) Pharmacokinetic Study in the Pregnant Cynomolgus Monkey (AT 7524) (RPR 1735)
Reviewed below

Validation of an HPLC Assay for the Determination of RP 64206 in the Skin and Plasma of Hairless Mice (RPR Report DD-95-023)
Reviewed below

Effect of Sparfloxacin on Hepatic Drug-Metabolizing Enzyme Systems in Rats Study D130)
Reviewed below

Pharmacokinetics of Sparfloxacin in Rats Using HPLC Method Report D101-1; part of Report RR 764-01309)
IND

Single-Dose Pharmacokinetics and Bioavailability of CI-978 in Rats Following 6.25 mg/kg Intravenous and Oral Doses Report RR 764-01306)
IND

Plasma Levels and Urinary Excretion of Sparfloxacin in Dogs Using HPLC Method Report D101-2; part of Report RR 764-01309)
IND

Plasma and Urine Levels and Bioavailability of AT-4140 and Ciprofloxacin in Dogs After Single Oral or Intravenous Administration Determined by Bioassay Method Report D116)
Reviewed below

Single-Dose Pharmacokinetics and Absolute Bioavailability of CI-978 in Beagle Dogs Report RR 764-01361)
Reviewed below

Plasma Levels and Urinary Excretion of Sparfloxacin in Monkeys Using HPLC Method Report D101-3, part of Report RR 764-01309)
IND

**Plasma and Urine Levels of AT-4140 in Mice After Single Oral Administration
Determined by Bioassay Method (Report D115)**
Reviewed below

**Plasma and Urine Levels of AT-4140 in Rats After Single Oral Administration
Determined by Bioassay Method (Report D114)**
Reviewed below

**Plasma and Urine Levels of AT-4140 in Monkeys After Single Oral Administration
Determined by Bioassay Method (Report D117)**
Reviewed below

**Plasma Levels of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C]
Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats (Report D110-2)**
Reviewed below

Toxicokinetic Study of AT-4140 in Rats (Report B304)
Reviewed below

**Plasma Concentrations of CI-978 in Mice Following Dietary Administration for 7 Days
(part of Report B203; Report RR 745-01982)**
IND

**Toxicokinetics of AT-4140 in the Dog Following Once Daily Oral Administration of 5, 15
and 45 mg/kg for 4 Weeks (part of Report B203)**
Reviewed below

**Toxicokinetics of AT-4140 in the Dog Following Once Daily Oral Administration of 4, 10
and 25 mg/kg for 26 Weeks (Report B303)**
Reviewed below

Pharmacokinetics of Sparfloxacin in Rats - Effects of Food (Report D128)
Reviewed below

**Gastrointestinal Tract Absorption of AT-4140 in the Rat (Report D105;
Report RR 764-01417)**
IND

**Absorption of [¹⁴C] Sparfloxacin After Administration in Gastrointestinal Loops of the
Male Rat at the Dose of 10 mg/kg (Report D102-7)**
Reviewed below

Autoradiographic Study on the Distribution of Radioactivity After a Single Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg in Male Rats (Report D102-2)
Reviewed below

Autoradiographic Study on the Distribution of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats (Report D109-1)
Reviewed below

Autoradiographic Study on the Distribution of Radioactivity After a Single Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg in the Pregnant Rat (Report D111-1)
Reviewed below

Quantitative Tissue Distribution of Radioactivity After a Single Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg in Male Rats (Report D102-3)
Reviewed below

Quantitative Tissue Distribution of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats (Report D109-2)
Reviewed below

Quantitative Tissue Distribution of Radioactivity After a Single Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg in the Pregnant Rat (Report D111-2)
Reviewed below

Uptake and Subcellular Localization of Sparfloxacin (AT-4140, RP 64206; S) in Phagocytic Cells (30th ICAAC, Abstract 1243, 1990)
Reviewed below

Tissue Distribution of AT-4140 in Rats Following a Single Oral Administration (Report D118)
Reviewed below

Tissue Distribution of AT-4140 and Ciprofloxacin in Mice Following a Single Oral Administration (Report D119)
Reviewed below

Skin Penetration of Sparfloxacin (AT-4140) (30th ICAAC, Abstract 1256, 1990)
Reviewed below

Seven-Day Oral Pharmacokinetic Study RP 64206 in Hairless Mice (RPR/RD/CVL/DS 94-135)

Reviewed below

Intraocular Dynamic Mode of Sparfloxacin in Rabbit Eyes (3rd International Symposium on New Quinolones, Abstract 378, Vancouver, 1990)

Reviewed below

Ocular Pharmacokinetic Studies of AT-4140 (30th ICAAC, Abstract 1258, 1990)

Reviewed below

Distribution of [¹⁴C] Sparfloxacin in Jaw Bone of Experimentally Infected Rabbits After Oral Administration (Chemotherapy 39 (S4): 131-137, 1991)

Reviewed below

Plasma and Milk Levels of Radioactivity After a Single Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg in Lactating Rats Report D102-8)

Reviewed below

Biopharmaceutical Profile of CI-978 (PD 131501-0000), Lot Q
764-01416)

Report RR

Reviewed below

Bioautography Study of Pooled Urine of Mice, Rats, Dogs and Monkeys Orally Receiving AT-4140 Report D122)

Reviewed below

A Study on the Urinary Metabolites After 14 Consecutive Daily Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats Report D110-1)

Reviewed below

Plasma Levels of AT-4140 in Male and Female Rats After Single and 7 Day Repeated Oral Administration Using HPLC Method Report D107)

Reviewed below

Excretion of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats Report D110-3)

Reviewed below

Biliary Excretion of AT-4140 in Rats Following a Single Oral Administration Report D120)

Reviewed below

Renal Excretion Mechanism of AT-4140 in the Rat Report D106)

Reviewed below

***In Vitro* and *Ex Vivo* Intestinal Absorption and Secretion of Sparfloxacin (33rd ICACC, Abstract 1463, Anaheim, 1992)**

Reviewed below

Effect of Aluminum Hydroxide, an Antacid, on Pharmacokinetics of AT-4140

Report D124)

Reviewed below

Effects of Antacids and Ferrous or Calcium Drugs on the Pharmacokinetics of

Sparfloxacin in Rats (Report D129)

Reviewed below

Effects of Quinolones on Theophylline Single-Dose Pharmacokinetics in β -Naphthoflavone Treated Rats: A Potential Model for Detecting a Quinolone/Theophylline Interaction

Report RR 764-01160)

Reviewed below

Effect of AT-4140 on Pharmacokinetics of Theophylline and Caffeine in Rats Compared with Enoxacin, Ciprofloxacin and Ofloxacin (Report D123)

Reviewed below

Study of the Effect of PD 124816, CI-960, and PD 131501 on Single-Dose Theophylline Pharmacokinetics in Rats (Report RR 764-001170)

Reviewed below

Effect of CI-978 (AT-4140), A New Quinolone Antibacterial Agent, On Hexobarbital

Sleeping Times in Mice

Report RR 740-02720;

Report GP-87-0104)

Reviewed below

Dose Proportionality of Single CI-978 Oral Doses in Sprague-Dawley Rats

Report RR 764-01431)

IND

Toxicokinetics of RP 64206 in the Rat Following I.V. Administration of 12.5, 25, and 50 mg/kg for 28 Days (RPR Report EUR 1903)

IND

Toxicokinetics of RP 64206 in the Dog Following I.V. Administration of 10, 20, and 30 mg/kg for 28 Days (RPR Report EUR 1902)

IND

Toxicokinetic Study of AT-4140 in Pregnant and Non-Pregnant Rats

Report

B408)

IND

Toxicokinetic Study of AT-4140 in Pregnant and Non-Pregnant Rabbits
B409)
IND

Report

Toxicokinetic Study of AT-4140 in Pregnant Rabbits (Additional Study)
Report B414; : Report RR-MEMO 745-01943)
IND

Disposition and Metabolism of [¹⁴C] Sparfloxacin in the Rat (Arzneim.-Forsch./Drug Res. 41 (II): 747-759, 1991)
Reviewed below

Pharmacokinetics of a Novel Quinolone, AT-4140, In Animals (Antimicrobial Agents and Chemotherapy 34 (1): 89-93, 1990)
Reviewed below

Disposition and Metabolism of [¹⁴C] Sparfloxacin After Repeated Administration in the Rat (Arzneim.-Forsch./Drug Res. 41 (II): 760-763, 1991)
Reviewed below

REVIEWS OF NONCLINICAL STUDIES:

PHARMACOLOGY STUDIES:

Neuropharmacology:

Neuro-Excitatory Effect of Sparfloxacin, a New Quinolone Antimicrobial Agent, in Combination with Non-Steroidal Anti-Inflammatory Drugs Report C402;
Chemotherapy [Japan] 39 (S-4): 167-174, 1991; translated from Japanese)

Vol. 13, pp. 5-2-27 to 5-2-43

Summary: Groups of 5 male ddY mice were dosed intraperitoneally with the quinolones below with or without a simultaneous dose of 100 mg/kg biphenylacetic acid (the active metabolite of fenbufen). Other mice of the same sex and strain (5-10 per group) were fasted for 12-16 hours, then dosed orally with a quinolone plus either biphenylacetic acid, ketoprofen, or naproxen. Mice dosed with quinolones alone were observed for 6 hours following administration and mice dosed with a quinolone plus one of the NSAIDs were observed for 2-3 hours. Additionally, the ability of sparfloxacin, ofloxacin, and enoxacin to bind to GABA receptors (e.g., inhibit the specific binding of ³H-muscimol) was assessed in a rat brain synaptic membrane preparation in the presence or absence of 10 μM biphenylacetic acid.

The results of the experiments in mice are presented in the following tables:

Convulsive Activity of Quinolones in the Presence or Absence of Biphénylactaic Acid (BPA) (Both Drugs Administered IP)

Quinolone	Quinolone Dose (mg/kg)	% Mice with Clonic Seizures (Quinolone Without BPA)		Quinolone Dose (mg/kg)	% Mice with Clonic Seizures (Quinolone + 100 mg/kg BPA)
Enoxacin	2500	0		2	0
	3000	20		4	80
	3500	40		5	100
	4000	70			
	5000	100			
Norfloxacin	750	0		5	0
	1000	40		10	100
	1500	80		50	100
	2000	100			
Lomefloxacin	500	0		2	0
	750	60		5	40
	1000	80		10	100
	1500	100			
Ciprofloxacin	750	0		10	0
	1000	30		30	100
	1500	80		50	100
	2000	80			
	3000	100			
Oflloxacin	500	10		200	0
	750	30		300	20
	1000	70		500	80
	1500	100		1000	100

Sparfloxacin	2000	0	500	0
	2500	0	1000	0
	3000	0	2000	0
	3500	0	3000	20
	4000	0		

BPA dramatically enhanced the convulsive activity of enoxacin, lomefloxacin and norfloxacin when the drugs were administered intraperitoneally. The convulsive activity of ciprofloxacin was enhanced to a lesser degree. BPA treatment slightly enhanced the convulsive activity of ofloxacin; however, relatively high doses of this quinolone were still necessary to induce convulsions in the mice. Although convulsions were not observed following intraperitoneal administration of sparfloxacin without biphenyl acetic acid, CNS excitatory effects such as tremor and myoclonus were observed after doses ≥ 3000 mg/kg. Convulsions were observed in 20% of the treated mice when 3000 mg/kg sparfloxacin was administered with BPA.

When quinolones were administered orally (see table below), higher doses were required to show convulsive activity in conjunction with BPA:

Convulsive Activity (% Mice with Clonic Seizures) of Quinolones In Combination with Biphenylacetic Acid (Both Drugs Administered Orally and Simultaneously)

Quinolone	Dose (mg/kg)	Dose of Biphenylacetic Acid			
		50	100	200	400
Enoxacin	10	---	0	60	80
	20	20	40	60	60
	50	---	80	80	---
	75	---	100	100	---
Lomefloxacin	20	---	0	0	40
	50	20	60	100	---
	100	40	80	100	---
	200	100	100	---	---
Norfloxacin	50	---	---	20	---
	100	---	0	40	---
	200	20	60	100	---

Ciprofloxacin	100	---	0	0	---
	200	---	0	40	60
	300	---	20	80	---
	400	---	80	100	---
Ofloxacin	500	---	0	0	0
	1000	---	0	0	60
	1500	0	60	100	---
Tosufloxacin tosylate	1000	---	---	0	0
	1500	---	---	10	10
Sparfloxacin	500	---	---	0	---
	1000	---	0	0	0
	1500	---	---	0	0
	2000	---	0	0	0

Convulsive Activity (% Mice with Clonic Seizures) of Quinolones In Combination with Ketoprofen or Naproxen (Both Drugs Administered Orally and Simultaneously)

Quinolone	Dose (mg/kg)	Ketoprofen (mg/kg)		Naproxen (mg/kg)	
		500	1000	500	1000
Enoxacin	200	80	100	100	100
	400	90	---	100	---
Lomefloxacin	100	40	100	80	100
	200	60	---	100	---
Ciprofloxacin	500	20	80	0	100
	1000	80	100	60	100
Ofloxacin	500	0	0	0	60
	1000	0	40	60	100
Sparfloxacin	500	---	0	---	0
	1000	---	0	---	0
	1500	0	0	0	0

Larger oral doses of ketoprofen and naproxen compared to BPA were required to enhance the convulsive effects of the quinolones. Neither convulsions nor CNS excitatory effects were observed when sparfloxacin (up to 1500-2000 mg/kg) and biphenylacetic acid, ketoprofen, or naproxen were administered orally.

Enoxacin, but not sparfloxacin or ofloxacin, significantly inhibited the specific binding of ^3H -muscimol to rat synaptic membranes in the presence of $10\ \mu\text{M}$ BPA.

In this study, sparfloxacin had a lower capacity to induce convulsions in male mice than the other quinolones tested in the presence or absence of NSAIDs.

A Study on Convulsive Effects of Sparfloxacin With or Without Non-Steroidal Anti-Inflammatory Drugs

Report C401; Chemotherapy [Japan] 39(S-4): 161-166,

1991, translated from Japanese)

Vol. 13, pp. 5-2-304 to 5-2-314

Summary: Sparfloxacin was not as potent as several other fluoroquinolones at inhibiting the binding of γ -aminobutyric acid (GABA) to mouse brain synaptic membranes in the presence or absence of nonsteroidal anti-inflammatory drugs *in vitro* (see table below). Intraventricular administration of 0.25-2.5 nmol of enoxacin concomitantly with 5 nmol 4-biphenylacetate (BPA, the active metabolite of fenbufen) induced convulsions in mice in a dose-dependant fashion (5/5 at 2.5 nmol enoxacin), but intraventricular administration of up to 10 nmol sparfloxacin with 5 nmol BPA did not induce convulsions in the mice.

Concentrations (M) of Fluoroquinolones at Which GABA Binding to Mouse Brain Synaptic Membranes is Inhibited by 50% in the Presence and Absence of Non-steroidal Anti-inflammatory Drugs

NSAID	Sparflox	Enox	Norflox	Oflox	Ciproflox
None	9.1×10^{-4}	1.4×10^{-4}	1.4×10^{-5}	1.0×10^{-3}	7.6×10^{-5}
Acetyl Salicylate	1.0×10^{-3}	8.3×10^{-5}	1.4×10^{-5}	7.6×10^{-4}	1.0×10^{-4}
Fenbufen	4.0×10^{-4}	1.3×10^{-6}	1.2×10^{-7}	3.6×10^{-5}	1.3×10^{-6}
Indomethacin	2.8×10^{-4}	5.3×10^{-7}	1.9×10^{-7}	1.2×10^{-4}	1.0×10^{-4}
Flurbiprofen	1.6×10^{-4}	3.3×10^{-7}	1.4×10^{-8}	3.0×10^{-6}	1.0×10^{-6}
BPA	5.2×10^{-5}	1.1×10^{-8}	$< 10^{-8}$	8.3×10^{-7}	3.0×10^{-8}

The final concentrations of the NSAIDs was 10^{-4} M and the values are averages of 2 separate experiments.

Acetyl salicylate did not appear to potentiate fluoroquinolone inhibition of GABA binding. BPA was the most potent potentiator of fluoroquinolone inhibition of GABA binding, but even this NSAID metabolite did not potentiate sparfloxacin inhibition of GABA binding to as great an extent as it did for the other quinolones.

TOXICOLOGY STUDIES:

Phototoxicity:

Phototoxic Lesions Induced by Quinolone Antibacterial Agents in Auricular Skin and Retina of Albino Mice (Document 5.46; Toxicologic Pathology 21(6): 554-561, 1993)

Vol. 33, pp. 5-22-331 to 5-22-338

Summary: Female albino Balb/c mice were dosed orally with sparfloxacin (50 and 100 mg/kg), enoxacin or levofloxacin (400 and 800 mg/kg for both). Animals were immediately exposed to UVA for 4 hours (FL20SBLB Black Light, Toshiba, 20 j/cm², through 3 mm pane of Flontglass to eliminate wavelengths below 320 nm). Auricle thickness was observed to increase over the first 8 hours after dosing (4 hours following UVA), with a slight decrease observed at 12 hours post dosing; then gradually increase until the last animals were sacrificed at 96 hours post dosing when thickness was about 3 and 5.5 times that in the untreated UV control group for 50 and 100 mg/kg sparfloxacin, respectively. Both doses of enoxacin caused auricle thickening, but only the higher dose of levofloxacin did. In sparfloxacin + UVA treated mice, degeneration of basal epidermal cells was first observed in animals sacrificed 2 hours after dosing (2 hours into the UV exposure). Severe edema and neutrophil infiltration were observed in the dermis 96 hours after dosing. Severity was greater in the 100 mg/kg sparfloxacin group than at 50 mg/kg. Enoxacin-induced skin damage was similar to that seen with sparfloxacin, as was 800 mg/kg levofloxacin-induced damage; however, 400 mg/kg levofloxacin produced only mild edema and cell infiltration in the dermis.

Vacuolation of photoreceptor segments and swollen retinal pigment epithelial cells in the retinal fundus were observed in the eyes of some mice 2 hours after administration of 50 mg/kg sparfloxacin (2 hours into the UV exposure). By 4 hours, thickening of the outer nuclear layer of the retina was also observed, along with some necrotic cells. Retinal damage continued to increase up to the 96 hour final sacrifice time point and was more severe in the 100 mg/kg sparfloxacin dose group. Enoxacin (either dose) appeared to cause more extensive retinal damage than 100 mg/kg sparfloxacin, but neither dose of levofloxacin was associated with retinal damage.

Concomitant sparfloxacin dosing (50 or 100 mg/kg) and UVA exposure caused skin and retinal damage in albino mice.

Evaluation of Photosensitizing Ability of Quinolones in Guinea Pigs (Document 5.56, Poster Presentation from 5th International Quinolone Symposium, 1994, Japan)

Vol. 36, pp. 5-25-106 to 5-25-107

Summary: Male Hartley guinea pigs were dosed orally with sparfloxacin, ciprofloxacin, lomefloxacin, or fleroxacin, then, 30 minutes later, were exposed to UVA (2.77 mw/cm^2 for 180 min, total dose of 30 J/cm^2). Other guinea pigs underwent induction of UVA + drug sensitization for the same compounds. In this study, the maximum non-phototoxic doses for the quinolones were (in descending order) ciprofloxacin, 25 mg/kg; sparfloxacin, 1 mg/kg; fleroxacin, 0.25 mg/kg; lomefloxacin, < 1.2 mg/kg (lowest dose tested). None of the drugs appeared to be a particularly potent photoallergen; all were weak photoallergens in this study.

Cardiotoxicity:

**Exploratory Seven-Day Oral Toxicity Study of PD 131501 in Beagle Dogs
Report RR 745-01473)**

Date issued: 9/8/89, U.S. GLP

Vol. 36, pp. 5-25-284 to 5-25-376

Animals: Male and female beagle dogs (Marshall Farms), one of each gender per dose group, 8.2-10.5 kg, approximately 11 months old

Diet: Dry Purina Certified Canine Diet 5007 was offered to the animals daily in 320-350 g portions. Canned dog food (not specified) was used to supplement the dry food starting on day 4 for both 300 mg/kg dogs and the 150 mg/kg male. Water was available *ad libitum*.

Drug Dose and Route of Administration: Sparfloxacin was administered orally, in gelatin capsules at doses of 50, 150, or 300 mg/kg. Control dogs received empty gelatin capsules. Beginning on day 3, the 150 and 300 mg/kg doses were divided b.i.d. After day 3, the males in the 150 and 300 mg/kg group were not dosed any longer due to repeated vomiting and aggressive behavior.

Length of Study: Except for the males in the 150 and 300 mg/kg dose groups, the rest of the dogs were treated for 7 days. Electrocardiograms were made before day 1, then on days 1 and 7 (where applicable) before dosing and 4-5 hours after dosing. Holter monitoring occurred before day 1, and on Days 1-2 and 7 for 19-24 hours after dosing.

Results: Emesis was observed in all dogs in the 150 and 300 mg/kg dose groups, as was

reduced food consumption and anorexia. The 50 mg/kg female also had reduced food consumption and lost about 7.5% of body weight during the treatment period.

Q-T prolongation was observed in both the male and female dogs at 150 mg/kg after dosing on day 1 (30% and 26% longer than day 1 predose Q-T) and in the female on day 7 (21% longer than day 1 predose Q-T). There were no arrhythmias observed from day 1-2 after dosing, but arrhythmia (sporadic singlets and runs of bigeminy) was observed in the 150 mg/kg female on day 7 beginning 1-2 hours after dosing and continuing for several hours.

The plasma levels measured in the animals on day 7 (blood samples collected about 5 hours after dosing) were 8.37 and 10.7 $\mu\text{g/ml}$ for the 50 mg/kg male and female, 16.0 $\mu\text{g/ml}$ for the 150 mg/kg female, and 13.8 $\mu\text{g/ml}$ for the 300 mg/kg female.

A small number of dogs was used in this study, so one cannot make generalizations (e.g., association with certain plasma drug level, or percentage of animals that will be effected at a given dose level or plasma concentration) about sparfloxacin-induced Q-T prolongation or arrhythmia beyond the fact that they were observed. Q-T prolongation occurred on day 1 in both animals dosed with 150 mg/kg sparfloxacin, but not those dosed with 50 or 300 mg/kg. It was also observed in the remaining dog in the 150 mg/kg group on day 7, along with arrhythmia.

Ocular Toxicity:

Ocular Toxicity Study of Sparfloxacin in Cats (D-25(9D301Z), translated from Japanese)

Dated 6/29/95, no mention of GLP

Vol. 37, pp. 5-26-76 to 5-26-94

Animals: Male and female laboratory cats (ICO:Fec Eur (Tif)), 3.05-3.75 kg at initiation of dosing, age not specified, 2/sex/dose group

Diet: Approximately 80 g of commercial solid food (NK-C, Nihon-Nosan-Kogyo K.K.) was offered daily and tap water was available *ad libitum*.

Drug Dose and Route of Administration: Sparfloxacin and nalidixic acid were suspended in aqueous 0.5% sodium carboxymethyl cellulose and administered orally at a dose volume of 2 ml/kg. Treatment groups were:

1. Vehicle control
2. Sparfloxacin, 60 mg/kg
3. Nalidixic acid, 120 mg/kg

The investigators mentioned using previous studies to choose the doses for the current study, but these data were not provided.

Length of Study: Drug or vehicle was administered daily for 14 days. Electroretinogram (ERG) recordings at 2 and 40 joules of photic stimulation were made for each animal prior to dosing, then 24 hours after the last dose on day 14. Fundoscopic examinations were also

performed at these times. Blood samples were drawn 0, 1, 2, and 4 hours after dosing on day 7 so that plasma levels could be determined using a microbial assay.

Results: Clinical signs of toxicity were observed in both sparfloxacin- and nalidixic acid-treated cats. Vomiting was observed after the first 1-3 doses of sparfloxacin given to each animal. Salivation and soft feces or diarrhea were observed several times in each member of the sparfloxacin dose group. One sparfloxacin-treated female had a tonic convulsion on day 2. Vomiting and salivation were observed more frequently in all of the nalidixic acid animals, and staggering was occasionally observed in two of them. A tonic convulsion was observed in one of the nalidixic acid-treated female cats on day 10; this animal was found dead later the same day. Neither drug treatment appeared to significantly affect body weight or food consumption in the surviving animals. The mean C_{max} for sparfloxacin was 11.81 ± 1.80 $\mu\text{g/ml}$ and occurred 2 hours after dosing for 1 animal and at 4 hours for the other three. It should be noted that the final blood sample was drawn at 4 hours, so it is possible that the plasma sparfloxacin levels could have risen further in some of the cats. The mean C_{max} for nalidixic acid was 91.18 ± 40.05 $\mu\text{g/ml}$ and occurred 1 hour after dosing for 3 animals and at 2 hours for the other one.

Neither funduscopy nor histopathological examination of the eyes revealed abnormalities in any cat. It is difficult to interpret the ERG findings because there appears to be some variability between animals and between readings in the same animal. There was no historical control data provided to give the reviewer an idea of how much variability is normally experienced. Additionally, the investigators compared means of actual ERG amplitudes and latencies between groups and it would seem more appropriate to compare pre- and post-treatment ERGs in the same animal, then determine whether specific changes are associated with a particular treatment. There did appear to be a consistent decrease in the amplitude of the a+b wave in the left eyes of 3/3 nalidixic acid treated cats (mean decrease of 121 ± 49 , range of 78-174 at 2 joules photic stimulation; 144 ± 67 , range of 81-215 at 40 joules), but only one of these animals had a significant a+b decrease in the right eye as well (152 and 137 at 2 and 40 joules, respectively). Comparable consistent decreases in both eyes at both levels of stimulation were not observed in cats from the other groups. The significance of the ERG data even in the nalidixic acid-treated cats is not clear because the decrease in a+b amplitude was seen only in one eye of 2/3 cats, and there is no reason why ocular toxicity would be monocular upon systemic administration of drug- one would assume that both eyes were exposed to the drug.

Although sparfloxacin did not appear to cause ocular damage in cats given a clinically toxic dose of this drug, it should be noted that the positive control (nalidixic acid) used in this study did not cause definitive damage.

**RP 64206: Experimental Cocataractogenesis Study in Brown Norway Rats
(RPR/RD/CRVA/SM 94-0053)**

J.P. Plard (Rhône-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, France)

Dated: 10/17/94, French GLP

Vol. 37, pp. 5-26-138 to 5-26-211

Animals: Male Brown Norway rats (BN/CrlBR), approximately 6 weeks old, 95-151 g at initiation of study.

Diet: UAR AO4 C certified pellet diet and filtered tap water were supplied *ad libitum*.

Drug Dose and Route of Administration: Sparfloxacin (5 mg/kg) was administered orally in a vehicle of aqueous 0.5% carboxymethyl cellulose daily for 43-45 days at a dose volume of 5 ml/kg/day. Streptozotocin (70 mg/kg), known to cause cataracts secondary to induction of diabetes, was administered intraperitoneally on days 1 and 3 at a dose volume of 3.5 ml/kg/day. Naphthalene (1000 mg/kg), known to have a metabolite that is directly cataractogenic, was given orally every other day at a dose volume of 10 ml/kg/day. Only half the dose of naphthalene was given on days 1, 3, 5, and 7 to prevent early mortality. The full dose was given daily on days 26-28 as an attempt to enhance cataract development. Treatment groups were as follows:

1. Vehicle only (oral 0.5% carboxymethyl cellulose), 10 rats
2. Sparfloxacin only, 10 rats
3. Streptozotocin + Vehicle, 20 rats at start, reduced to 13 on day 8
4. Streptozotocin + Sparfloxacin, 20 rats at start, reduced to 13 on day 8
5. Naphthalene + Vehicle, 13 rats
6. Naphthalene + Sparfloxacin, 13 rats

Blood glucose levels in the rats were determined on days 8, 15, 22, 29, 37, and 43. On day 8, 13 rats with blood glucose levels over 3 g/l were chosen to continue through the study from among streptozotocin-treated rats in the two appropriate groups.

Length of Study: Using a Topcon SL 45 Scheimpflug camera, photographs taken on 3-4 days prior to the onset of dosing, then on days 24 and either 44 or 45 were used to determine opacification of the lenses of each rat's eyes. The animals' eyes were examined weekly (approximately) using a slit lamp by two independent ophthalmologists. Rats were sacrificed on day 45 or 46.

Results: There was no mortality in the vehicle control or sparfloxacin only groups. Two to three rats (out of 13) in each of the other four groups were found dead or had to be sacrificed in moribund condition during days 13-40 of the study. Most of these deaths occurred on day 27 or later. The deaths of the streptozotocin-treated rats appeared to be secondary to drug-induced diabetes and the deaths of the naphthalene-treated rats appeared to be due to the toxicity of repeated high doses of that compound. The addition of sparfloxacin to either the streptozotocin or naphthalene treatment regimen did not increase mortality.

Treatment with sparfloxacin alone did not significantly alter mean body weight gain, but both streptozotocin and naphthalene significantly suppressed body weight gain. At the end of the study period, rats dosed with the former weighed 38-44% less than untreated controls and rats treated with the latter weighed 29-32% less than untreated controls. There was not, however, a significant difference between the mean body weights of animals treated with streptozotocin or naphthalene alone and in combination with sparfloxacin.

All streptozotocin-treated rats showed typical signs of diabetes including increased urine volume, swollen abdomen, and reduced activity. These animals were said to have been in poor general condition. Signs of toxicity in naphthalene-treated rats (most prominent during

daily dosing on days 26-28) included diarrhea and oily fur. No clinical signs of toxicity were observed in rats treated with sparfloxacin alone.

Cataracts were observed in all rats given streptozotocin. The initial signs were seen on about day 16 in almost all of these animals and by day 38, opaque areas were present on the lens. Sparfloxacin treatment did not change the time of onset, the incidence, or the severity of cataracts in rats given streptozotocin.

Induction of cataracts, in terms of onset and severity, was not as uniform in the naphthalene-treated rats as it had been using streptozotocin. Initial signs were seen in about half of these animals on day 16 and in almost all of the rats on day 23. By day 43, cataracts resembled a refractive ring around the cortex. Sparfloxacin treatment did not change the time of onset, the incidence, or the severity of cataracts in rats given naphthalene.

Daily doses of 5 mg/kg sparfloxacin for 45 days (no clinical signs of toxicity observed) did not induce cataract formation in the Brown Norway rat. Additionally, the same dose of sparfloxacin did not alter cataract induction by either streptozotocin or naphthalene in this rat species.

Batch Comparison Studies:

A Toxicological Study of AT 4140A and AT 4140B by a Single Oral and Intraperitoneal Administration in the Mouse Research Report B103)

Date issued: 2/5/92, Japanese GLP

Vol. 38, pp. 5-27-211 to 5-27-289

Summary: A single oral (5000 mg/kg) or intraperitoneal (2000 mg/kg) dose of one of two batches sparfloxacin dissolved in aqueous carboxymethyl cellulose was given to groups of 8 CD-1 mice per gender. The sparfloxacin batches were AT-4140A, lot number 054 and AT-4140B, lot number 961. The former batch was said to have been a product of a new production method, and the latter was said to have been produced by an old method. No information was given as to production method differences and certificates of analysis did not reveal any differences in chemical compositions between the batches.

There was no mortality in either dose group by either route of administration. No clinical signs or symptoms were observed in the orally dosed mice and only decrease in spontaneous movement, tremors and occasional oligopnea were observed about 6 hours following intraperitoneal administration of sparfloxacin. Upon sacrifice and necropsy on day 14, cecal dilatation was observed in about half of the animal dosed orally and cecal dilatation, adhesion of abdominal tissues and deposits of a yellow substance (probably sparfloxacin) were observed in several of the mice dosed intraperitoneally. There did not appear to be any biologically significant differences in acute toxicity between these batches of sparfloxacin when administered orally or intraperitoneally.

A Toxicological Study of AT 4140A and AT 4140B by a Single Oral and Intraperitoneal Administration in the Rat (Research Report B102)

Date issued: 2/5/92, Japanese GLP

Vol. 38, pp. 5-27-290 to 5-27-370

Summary: A single oral (5000 mg/kg) or intraperitoneal (2000 mg/kg) dose of one of two batches sparfloxacin dissolved in aqueous carboxymethyl cellulose was given to groups of 8 Wistar rats per gender. The sparfloxacin batches were AT-4140A, lot number 054 and AT-4140B, lot number 961. The former batch was said to have been a product of a new production method, and the latter was said to have been produced by an old method. No information was given as to production method differences and certificates of analysis did not reveal any differences in chemical compositions between the batches.

There was no mortality in either dose group by either route of administration. Greenish feces were observed in the orally dosed rats on days 1-4 following administration and only brown smudges in the perinasal area (day 2), unkempt fur (days 3-9), and decreased spontaneous movement (one female only on day 3) were observed following intraperitoneal administration of sparfloxacin. Upon sacrifice and necropsy on day 14, cecal dilatation was observed in most male and several female animals dosed orally and cecal dilatation, enlargement of mesenteric lymph nodes, adhesion of abdominal tissues and deposits of a yellow substance (probably sparfloxacin) were observed in about half of the rats dosed intraperitoneally. There did not appear to be any biologically significant differences in acute toxicity between these batches of sparfloxacin when administered orally or intraperitoneally.

A Toxicological Study of AT 4140A and AT 4140B by a 15-Day Repeated Oral Administration in the Male Rat (Research Report B204)

Date issued: 2/5/92, Japanese GLP

Vol. 39, pp. 5-28-1 to 5-28-136

Animals: Male Crj:Wistar SPF rats, approximately 6 weeks old, 169-200 g, 10 per treatment group

Diet: Pelleted CRF-1 diet (Oriental Yeast Co.) and tap water were provided ad libitum.

Drug Dose and Route of Administration: Sparfloxacin batches AT-4140A, lot number 054 and AT-4140B, lot number 961 were used in this study. The former batch was said to have been a product of a new production method, and the latter was said to have been produced by an old method. No information was given as to production method differences and certificates of analysis did not reveal any differences in chemical compositions between the batches.

Sparfloxacin was dissolved in 0.5% carboxymethyl cellulose and administered once daily orally via gavage at a dose volume of 0.5 ml/100 g of body weight. Treatment groups were as follows:

1. Vehicle
2. 50 mg/kg, AT-4140A
3. 200 mg/kg, AT-4140A
4. 800 mg/kg, AT-4140A
5. 50 mg/kg, AT-4140B
6. 200 mg/kg, AT-4140B
7. 800 mg/kg, AT-4140B

Length of Study: Sparfloxacin or vehicle was administered daily for 15 days and the rats were sacrificed and necropsied on day 16.

Results: There was no mortality during the study and no general clinical abnormalities were observed. Additionally, no statistically significant differences in mean body weights were found between the treatment groups although a dose-dependent decrease in food consumption in the 200 and 800 mg/kg groups was seen at the beginning of the treatment period (days 1 and 3 of dosing). There was a tendency toward lower body weight gain in the 800 mg/kg dose groups. There did not appear to be any biologically significant sparfloxacin-mediated changes in urinary, serum chemistry, or hematologic parameters although urinary pH tended to be lower in rats from the 200 and 800 mg/kg groups compared to control.

Gross examination revealed that mesenteric lymph nodes were yellow in 9/10 and 8/10 rats in the 800 mg/kg groups (AT-4140A and B, respectively) with yellow Peyer's patches in 2 animals from each 800 mg/kg group. The yellow color is thought to be from the test agent. Cecal dilatation was observed in 6 and 7 rats from each 200 mg/kg group and in all animals from both 800 mg/kg groups. Mean absolute and relative cecal weights were significantly greater than control in all 200 and 800 mg/kg groups. Histopathological examination showed slight regeneration of renal tubules in 3 and 4 rats from the AT-4140A and B 200 mg/kg dose groups and 4 and 5 rats from the 800 mg/kg A and B dose groups. There did not appear to be any other sparfloxacin-related gross or microscopic changes in the rats.

There appeared to be no significant difference in toxicity between sparfloxacin batches AT-4140A and B when both were orally administered to male rats for 15 days. The NOEL for both batches was 50 mg/kg in this study and cecal dilatation and regeneration of renal tubules was observed beginning at 200 mg/kg no matter which batch was administered to the groups of rats.

"Other" Toxicology Studies:

Effect of Sparfloxacin on Liver Function in Rats with Liver Failure Induced by D-Galactosamine
Report D-26)

Dated 6/28/95, no mention of GLP

Vol. 39, pp. 5-28-137 to 5-28-147

Animals: Male Wistar rats, 9 weeks old, 215-262 g at the beginning of treatment, 6 rats per treatment group

Diet: CE-2 pellet diet and tap water were provided *ad libitum*.

Drug Dose and Route of Administration: Liver failure was induced in the rats by subcutaneous administration of 250 mg/kg D-galactosamine once daily for 2 days. Sparfloxacin was suspended in aqueous 0.5% carboxymethyl cellulose and a single dose was administered orally via gavage at a volume of 0.5 ml/100 g 6 hours after the second dose of D-galactosamine. The treatment groups were as follows:

1. "Normal Control" (no D-galactosamine or sparfloxacin)
2. D-galactosamine only
3. D-galactosamine + 5 mg/kg sparfloxacin
4. D-galactosamine + 50 mg/kg sparfloxacin

Length of Study: Animals were sacrificed 4 days after the administration of sparfloxacin.

Results: D-galactosamine-induced liver failure appeared to be reversible. On the day after the first administration of this compound, the rats' plasma levels of SGOT and SGPT rose significantly above control, peaked at levels 20 to 30-fold higher than control the next day, then fell over the ensuing 3 days to approximately control levels. Alkaline phosphatase and total bilirubin levels rose and fell in the same general pattern. The pattern of the rise and fall of these indicators of liver function was not altered by administration of sparfloxacin. At necropsy, no gross abnormalities were observed in the liver of any animal; however, no microscopic examination was done.

A single oral dose of sparfloxacin up to 50 mg/kg did not appear to enhance D-galactosamine-induced liver failure or prevent recovery of liver function, but it is unclear how these data would relate to sparfloxacin administration to patients with liver failure.

Antigenicity Study of Sparfloxacin Report D-13 (87309Z))

Dated 7/10/95, no mention of GLP

Vol. 39, pp. 5-28-208 to 5-28-226

Summary: Male Japanese albino rabbits, female Hartley guinea pigs, and female BALB/c and C3H/He mice were sensitized using sparfloxacin or sparfloxacin-protein (bovine serum albumin [BSA] or ovalbumin) conjugates. Freund's complete adjuvant was used in the sensitization of rabbits and guinea pigs and aluminum hydroxide gel was used in the sensitization of mice. Enoxacin-protein conjugates were used to stimulate antigen formation in rabbits. If a drug-BSA conjugate was used for sensitization, then the drug-ovalbumin

conjugate was used for detection as BSA and ovalbumin do not show immunological cross reactivity.

Sparfloxacin plus adjuvant did not induce antibody formation in rabbits or mice as measured via passive cutaneous anaphylaxis reaction or agglutination of sheep red blood cells. Sparfloxacin-protein conjugates were able to induce antibody formation in rabbits or mice that could be detected using another sparfloxacin-protein conjugate, but not unconjugated sparfloxacin. Sparfloxacin-ovalbumin conjugate sensitized guinea pigs to sparfloxacin-BSA conjugate as demonstrated by active systemic anaphylactic response and delayed-type skin reaction. Unconjugated sparfloxacin neither sensitized guinea pigs nor elicited the responses above in guinea pigs sensitized using sparfloxacin-ovalbumin conjugate. Passive cutaneous anaphylaxis reaction in guinea pigs sensitized with rabbit anti-sparfloxacin- or anti-enoxacin-protein conjugates showed that sparfloxacin- and enoxacin-protein conjugates were somewhat, but not completely, cross reactive.

The data indicate that sparfloxacin is not strongly antigenic. It was necessary to conjugate this drug with protein (creating a much larger molecule) in order to induce antibody formation and/or sensitivity in rabbits, guinea pigs, or mice. As the drug will not be clinically administered as a protein conjugate, sensitization appears to be unlikely in the clinic.

Reproductive Toxicology Studies:

Sparfloxacin: Preliminary Oral (Gavage) Maternal and Embryotoxicity Study in the Pregnant Cynomolgus Monkey (EUR962-001)

Dated 11/3/92, U.S. GLP

Vol. 47, pp. 5-36-2 to 5-36-116

Animals: Female cynomolgus monkeys (*Macaca fascicularis*, obtained from

at least 4 years old, 2.5-6.2 kg on day 20 of pregnancy, 5 animals per dose group (one of the animals in the 40 mg/kg group was found to have had a false positive pregnancy test and was replaced).

Diet: Ssniff P 10 standard primate diet was given twice daily in 50 g portions. Tap water was available *ad libitum*.

Drug Dose and Route of Administration: Sparfloxacin was suspended in 0.5% carboxymethyl cellulose and administered daily via intragastric intubation at volume of 10 ml/kg/day from days 20-50 of pregnancy. Dose groups were 40, 60, or 80 mg/kg/day. Plasma drug levels were determined in 2 monkeys each from the low and intermediate dose groups 2 hours after sparfloxacin administration sometime between day 46-50 of gestation, but those data were not included in this report.

Length of Study: Females were mated with untreated fertile male monkeys and the day that a vaginal smear showed the presence of sperm was considered day 0 of pregnancy. On day 18, 19, or 20 post-mating, an ultrasonic exam was performed to determine pregnancy. Ultrasonography was conducted approximately weekly to monitor pregnancy. Females were dosed with drug from day 20-50 of pregnancy. Fetuses were removed by cesarean section on day 60.

Results: Clinical signs such as vomiting and diarrhea were observed in monkeys from all 3 dose groups, but the incidence and severity were dose-dependant. One monkey from the 60 mg/kg group was found dead on day 45 of pregnancy and the investigators reported that no gross abnormalities were observed during the necropsy. The investigators did not believe that this death was treatment-related, but presented no data to support this belief. There were slight reductions in body weights in animals in both the 40 and 80 mg/kg groups, but the relationship to drug treatment is unknown in the absence of a control group.

Two animals in the 80 mg/kg group aborted between days 26-30 and 33-40 of gestation (heavy bleeding observed). One monkey in the 60 mg/kg group aborted on day 53 of pregnancy. Following at least 3 positive sonograms, live embryos were no longer detected in two monkeys from the 40 mg/kg group on days 48 and 39. No implantation site was visible in the former monkey, but placental remains were observed in the latter. The remaining 3 animals in each dose group delivered a live fetus via cesarean section. The investigators stated that rate of embryonic loss and/or abortion in these animals were comparable to historical controls, but as no historical control data was submitted, this cannot be verified from the report. The reviewer agrees with the investigators statement that one cannot exclude a treatment-related effect due to the limited number of animals used in the study. No treatment-related external malformations were observed, nor did there appear to be an effect on fetal or placental weights. Internal examination of the fetuses did not seem to have been performed.

Dose-related maternal toxicity was observed in each group (40-80 mg/kg), but toxicity did not appear intolerable in any of the animals. No external malformations were observed, but the possibility of drug-related embryonic loss cannot be excluded.

Sparfloxacin: Oral Gavage Teratogenicity Study in the Cynomolgus Monkey (EUR962-002)

Dated 6/25/93, U.S. GLP

Vol. 47, pp. 5-36-117 to 5-36-359

Animals: Female cynomolgus monkeys (*Macaca fascicularis*, obtained from

, at least 4 years old, 2.0-4.2 kg on day 20 of pregnancy, 10-15 animals per dose group (one of the animals in the 20 mg/kg group was found to have had a false positive pregnancy test).

Diet: Ssniff P 10 standard primate diet was given twice daily in 50 g portions. Tap water was available *ad libitum*.

Drug Dose and Route of Administration: Sparfloxacin was suspended in 0.5% carboxy methylcellulose and administered daily via intragastric intubation at volume of 10 ml/kg/day from days 20-50 of pregnancy. Dose groups were 0 (vehicle control), 20, 35, or 50 mg/kg/day. One female in the 35 mg/kg group was inadvertently dosed with 28 ml of drug suspension as opposed to 21 ml from days 28-33, but this error did not appear to have affected the outcome of the study.

Length of Study: Females were mated with untreated fertile male monkeys and the day that a vaginal smear showed the presence of sperm was considered day 0 of pregnancy. On day 18, 19, or 20 post-mating, an ultrasonic exam was performed to determine pregnancy. Ultrasonography was conducted approximately every 14 days to monitor pregnancy, or more frequently if signs of abortion were observed. Females were dosed with drug from day 20-50 of pregnancy. Fetuses were removed by cesarean section on day 150.

Results: No clinical signs of maternal toxicity were observed in the monkeys from the 20 mg/kg dose group, but vomiting after sparfloxacin administration was observed in 3/10 animals at 35 mg/kg and 7/15 at 50 mg/kg with a dose-related frequency. Occasional reduced food consumption and diarrhea were observed in a few monkeys from each group, so they did not appear to have been drug-related.

During the first week of drug treatment, 8/14 monkeys from the 50 mg/kg dose group lost from 0.2 to 0.4 kg (about 5-10%) of body weight compared to 1/13 in the control group (only animals who had not aborted during the first week are considered). This appeared to indicate toxicity as only 1/7 and 1/10 monkeys in the 20 and 35 mg/kg groups lost at least 0.2 kg during this time period. However, total body weight gain over the entire study period was similar between all of the treatment groups and was about 1 kg.

The incidence of abortion or fetal death (dead fetus observed via ultrasound and removed in unscheduled cesarean or premature infant born dead) in the dose groups is presented in the following table:

Abortion and Fetal Death in Monkeys Treated with Sparfloxacin During Organogenesis

Sparfloxacin Dose (mg/kg)	Incidence of Abortion	Incidence of Fetal Death	Total
0 (Vehicle Control)	4/15	0/15	4/15
20	3/9	1/9	4/9
35	0/10	2/10	2/10
50	5/15	0/15	5/15

Sparfloxacin did not appear to have an effect on embryo/fetal loss in the monkey. A live premature infant was born to one monkey each in the control (day 149) and 35 mg/kg

(day 142) group. A premature cesarean section was performed on one control animal on day 136 due to incomplete parturition and a live fetus was removed. The remaining monkeys underwent cesarean section on about day 150 of gestation and a live fetus was removed from each.

Sparfloxacin did not appear to have an effect on fetal size. Of the fetuses delivered on day 150, only 1/9 controls, 1/5 20 mg/kg, and 2/7 35 mg/kg weighed less than 230 g. No drug-related external anomalies were observed and there appeared to be no treatment-related effect on placenta size or weights of the fetal internal organs. The internal organs appeared to have been only grossly examined (no histopathology), but no treatment-related visceral findings were reported. In particular, no ventricular septal defects were observed in the monkey fetuses as had been present in fetuses from sparfloxacin treated rats. Punctiform hemorrhages were observed on the inner gastric wall and/or heart in several fetuses from each treatment group. Skeletal defects (the majority occurred in the tails) are summarized in the table below:

**Skeletal Defects in Fetuses from Monkeys Treated
with Sparfloxacin During Organogenesis**

Sparfloxacin Dose (mg/kg)	Incomplete Ossification	Misshapen Vertebrae or Sternabrae	Misaligned Vertebrae	Fused Vertebrae	Overall Incidence of Misshapen, Misaligned, or Fused Vertebrae
0	9/11	2/11	3/11	0/11	5/11
20	5/5	0/5	1/5	0/5	1/5
35	7/9	2/9	0/9	3/9	5/9
50	9/10	2/10	2/10	2/10	4/10

Incomplete ossification was observed in most of the fetuses from each dose group. Of the other skeletal defects observed, fused vertebrae was the only one observed in the 35 or 50 mg/kg dose groups that was not observed in the controls. One fetus in the 50 mg/kg group had a combination of fused and misaligned vertebrae that caused a kink in the tail. The investigators point out that the overall incidence of fused vertebrae for the entire study (5/35 fetuses) is close to the overall historical control of 4/40 fetuses delivered via cesarean section on day 150 of gestation (the two most recent historical control groups had 2/12 and 1/6 fetuses with fused coccygeal vertebrae). Additionally, the fused vertebrae observed in the current study were terminal coccygeal and these vertebrae are not observed in cynomolgus monkey fetuses until approximately day 100 of gestation and beyond, although it is possible that the primordia of these vertebrae are present during organogenesis.

When administered to the cynomolgus monkey during the period of organogenesis at doses up to 50 mg/kg, sparfloxacin did not appear to be embryolethal, teratogenic, or

fetotoxic. Maternal toxicity (occasional vomiting after drug administration) was observed at 35 and 50 mg/kg.

Genetic Toxicology:

Mutagenicity Test of AT-4140: Reverse Mutation Assay in Bacteria (Supplementary Test) (AT-4140-B701-R2)

Dated 7/20/92, Japanese GLP

Vol. 50, pp. 5-39-140 to 5-39-178

Assay and Results: This set of 2 experiments was a repeat of a previous study that had a negative result from the positive control group in the presence of S-9. *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and the *E. coli* strain WP2 *uvrA* were treated with sparfloxacin, vehicle, or 2-aminoanthracene (2-AAN, positive control) in the presence of S-9 from the livers of rats induced with phenobarbital and 5,6-benzoflavone.

Bacteria were plated in the presence of S-9 and test substances (as indicated in the table below) in triplicate on Vogel-Bonner's minimal E agar medium and incubated at 37°C for 48 hours. Sparfloxacin was dissolved with equimolar NaOH in distilled water and 2-AAN was dissolved in DMSO. Distilled water was used as the vehicle control.

**Average Number of Revertant Bacterial Colonies on
Triplicate Plates in Independent Experiments
(Experiment 1/Experiment 2)**

Amount of Test Substance (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>
Vehicle Control	39/43	208/217	11/12	13/15	33/28
Sparfloxacin					
0.00063	37/43	199/213	15/13	13/14	---
0.00125	39/41	203/225	15/11	13/13	---
0.0025	34/48	207/201	11/12	13/13	---
0.005	33/38	206/199	11/12	11/12	36/35
0.01	17/23	169/197	8/7	10/12	39/36
0.02	10/12	87/80	4/4	6/5	39/38

0.039	5*/0*	10*/5*	2*/0*	2*/1*	44/41
0.078	---	---	---	---	42/39
0.156	---	---	---	---	14/14
0.313	---	---	---	---	0*/0*
2-AAN** Positive Control	359/151	1013/652	150/162	127/106	501/494
					649/579

*Growth inhibition observed (grossly) at this dose

**Different concentrations of 2-AAN were used in the different strains of bacteria as a positive control. They were as follows ($\mu\text{g}/\text{plate}$): TA98, 0.5; TA100, 1.0; TA1535 and TA1537, 2.0; WP2 *uvrA*, 10.0 and 20.0.

Although sparfloxacin in the presence of S-9 did not appear to induce mutation in any of the strains of bacteria used in this assay and the positive control did appear to induce mutation, the toxicity of sparfloxacin to *S. typhimurium* and *E. coli* severely limited the concentration of drug that could be used to treat the bacteria. The reviewer does not believe that a bacterial reversion assay was ideal for determining the potential mutagenicity of sparfloxacin because only very low concentrations of this drug could be tested.

DNA Damage Caused by Antibiotic Drugs: Quinolones (Internat J Oncol 5: 857-859, 1994)

Vol. 50, pp. 5-39-254 to 5-39-258

Summary: Several quinolones (sparfloxacin, ciprofloxacin, norfloxacin, rosoxacin, nalidixic acid, ofloxacin, fleroxacin, enoxacin, pipemidic acid, and cinoxacin) were tested for their potential to induce the "SOS response" in *E. coli* PQ37 (SOS chromotest). The *sfIA* gene (part of the SOS system induced by DNA-damage) was coupled with a *lacZ* reporter gene. Additionally, an Ames test using *S. typhimurium* strains TA97, TA98, TA100, and TA102 was performed.

Sparfloxacin was the most potent quinolone inducer of the SOS response. The order of potency was: sparfloxacin < < < ciprofloxacin < norfloxacin < rosoxacin < ofloxacin < < fleroxacin < enoxacin < pipemidic acid < < < cinoxacin = nalidixic acid. A drug's potency in the SOS chromotest correlated with its bactericidal MIC. The greatest number of revertants in the Ames assay with TA102 was observed after sparfloxacin treatment. None of the quinolones tested induced reversions in TA97, TA98, or TA100.

Unfortunately, the assays used were not adequately described so it is difficult to determine the significance of the results (particularly of the SOS chromotest) or to know whether proper procedures were followed and appropriate positive and negative controls used. Additionally, as no validation data were submitted for the *E. coli* PQ37 assay, the significance

of the DNA-damaging potencies of the chemicals tested is not known. The fact that sparfloxacin (or any other quinolone) can induce damage in bacterial DNA is not surprising as they are known inhibitors of bacterial gyrase. It is interesting that these investigators had positive results with sparfloxacin using *S. typhimurium* strain TA102, a bacterial tester strain that had not been utilized in the Ames assays performed by the sponsor. TA102 has intact excision repair, but the other bacterial test strains used do not.

Quinolones and Induction of *umuC* and Mutagenicity (Drugs 45(3): 278-279, 1993)

Vol. 50, pp. 5-39-259 to 5-39-261

Summary: Several quinolones were tested for their capacity to induce the gene *umuC* in *E. coli* GW1104, involved in the SOS response to DNA damage. The order of potency was: ciprofloxacin < < sparfloxacin < tosufoxacin < ofloxacin < difloxacin < temafloxacin < norfloxacin < < enoxacin < < < nalidixic acid. These drugs were positive in an Ames test in *S. typhimurium* strain TA102 (10-100 ng/plate), but not TA98 or TA100. The potencies of these quinolones to induce *umuC* and reversion of TA102 correlated significantly ($r=0.89$).

This article was an extended abstract and contained no methodology for the assays. As above, the positive response of sparfloxacin in an Ames assay using TA102 is of interest-particularly since it has been observed in 2 independent laboratories.

PHARMACOKINETIC STUDIES:

***In Vitro* Dissolution Test and Comparison of Pharmacokinetic Parameters After Oral Administration in Dogs Between Sparfloxacin Anhydrous and Sparfloxacin Trihydrate (Rhône-DPC Europe Report EUR 5550)**

F. Bigeard and M. Trelu (Rhône-DPC Europe)

Dated 6/29/93, no mention of GLP

Vol. 1.52, pp. 5-41-1 to 5-41-19

Summary: The only difference in the synthesis of sparfloxacin trihydrate and anhydrous sparfloxacin is in the drying process. Solubility of anhydrous sparfloxacin and sparfloxacin trihydrate in water appeared to be similar after 10 minutes of stirring, up to 120 minutes.

These authors also report on 2 dog studies conducted in Japan by In study D116, 5 mg/kg of anhydrous sparfloxacin was orally administered in capsules to 3 male beagle dogs and in study D101-2, 5 mg/kg sparfloxacin trihydrate was suspended in 0.5% tragacanth gum and administered via gavage to 3 male beagles. Pharmacokinetic parameters determined in both studies were similar:

D101-2 (trihydrate) D116 (anhydrous)

C_{max}	1.32 µg/ml	1.16 µg/ml
T_{max}	4.0 h	4.0 h
T_{1/2}	8.2 h	8.4 h
AUC_{0-∞}	21.5 µg.h/ml	18.6 µg.h/ml

There did not appear to be any significant pharmacokinetic differences between anhydrous sparfloxacin and sparfloxacin trihydrate when each was administered to beagle dogs orally.

Metabolic Profile in Plasma, Urine, Bile, and Milk After Oral Administration of [¹⁴C]Sparfloxacin in Rats at the Dose of 10 mg/kg Report D102-6)

Dated 4/5/93, not GLP

Vol. 1.52, pp. 5-41-165 to 5-41-205

Summary: [Carbonyl-¹⁴C]-sparfloxacin was suspended in 0.5% tragacanth gum and administered orally via gavage to male and female (lactating and not) Wistar rats at a dose of 10 mg/kg. Plasma was collected from some of the animals 30 minutes after administration of drug and urine was collected from others for a total of 24 hours after administration. Some rats underwent bile duct cannulation, and bile samples were collected for 24 hours after sparfloxacin was given. Lactating females were sacrificed (via bleeding) 1 hour following sparfloxacin dosing and mammary glands were removed, then the milk drained.

Using thin-layer chromatography, two peaks in urine, plasma, bile, and milk were observed. One was unchanged sparfloxacin (confirmed using HPLC with mass spectrometry); the other was a polar metabolite tentatively identified as sparfloxacin-glucuronide on the basis of sample treatment with NaOH or β-glucuronidase. The average percentages (for 3-4 animals) of the two peaks in each body fluid were as follows:

Sample Type	Male	Female	Female (Lactating)
Urine (% unchanged/% glucuronide)	49/51	33/67	---
Plasma	44/56	---	40/60
Bile	43/57	---	
Milk	---	---	72/28

The investigators stated that the percentages of sparfloxacin and metabolite in the urine of male and female rats were not statistically different; thus, there did not appear to be a major sex-related difference in the metabolism of sparfloxacin in the rat. Milk contained less sparfloxacin-glucuronide metabolite than plasma of lactating rats.

In Vitro Protein Binding Study of [¹⁴C]Sparfloxacin Report D102-9)

Dated 3/31/93, not GLP

Vol. 52, pp. 5-41-206 to 5-41-230

Summary: Plasma was obtained from the blood of male Wistar rats and male humans. A reconstituted human "serum" was made by dissolving Moni-Trol I in distilled water to give a final protein concentration of 70 mg/ml. ¹⁴C-Sparfloxacin was added to the plasma to give a concentration of 0.38 µg/ml and added to the "serum" to give concentrations of 0.086, 0.38, and 1.9 µg/ml. After 30 minutes of incubation, the samples went ultrafiltration to remove protein. Protein binding of sparfloxacin in each of these fluids was around 43-46%. Gel filtration was used to identify albumin as the protein mainly associated with the radioactive sparfloxacin. Protein binding was believed to be reversible as the percentage of drug bound to protein fell when "serum" was diluted with PBS prior to undergoing ultrafiltration and quantitation of sparfloxacin associated with protein.

This *in vitro* assay suggests that sparfloxacin is moderately, but not extensively, protein bound in the plasma.

Bioassay Method for Sparfloxacin in Biological Fluids Report D 121)

Dated 4/5/93

Vol. 52, pp. 5-41-275 to 5-41-326

Summary: Known concentrations of sparfloxacin were dissolved in plasma and urine from dogs, rats, mice, monkeys, and humans as well as in bile and tissue extracts from rats. Various dilutions of these fluids were placed in wells on agar plates of *E. coli* Kp and the bacterial growth inhibitory zone was measured and compared with sparfloxacin standards diluted with 1/15 M phosphate buffer. Sparfloxacin concentrations and mean inhibitory zone diameters were linear and the limit of detection was 0.01 µg/ml. Plasma did not interfere with detection if it was diluted at least 3-fold, nor urine if it was diluted 20-fold, bile if it was diluted 50-fold, or tissue extracts prepared by the method used in this experiment. Serum and urine could be stored at 4° or below for 2 weeks without losing sparfloxacin antibacterial activity measured by this assay.

Microbiological Assay of Sparfloxacin in Human Plasma (RPR Report EUR 236)

B.J. Conard, V. Cuypers, F. Jacotot, M.C. Ternary (Rhône-Poulenc Rorer, Antony Cedex, France)

Dated 2/17/92

Vol. 52, pp. 5-41-328 to 5-41-346

Summary: Human plasma samples with known concentrations of sparfloxacin were placed in wells of agar plates of *E. coli* Kp 1976-712 and the bacterial growth inhibitory zone was measured and compared with sparfloxacin standards that were dissolved in human plasma. The relationship between the zones of inhibition and the log of the concentrations was linear between 0.020 and 0.320 $\mu\text{g}/\text{ml}$. Sparfloxacin was stable in human plasma for 11 days at -20°C . The assay was reproducible (coefficient of variance $< 17\%$) on 6 different days using fresh preparations of solutions, culture media, and inoculum of bacteria.

Determination of AT-4140 and its Glucuronide in Plasma, Urine, and Bile
Report D 103 and Parke-Davis Report RR-764-01347)

report dated 10/25/91 (study performed in 1987 at

Vol. 52, pp. 5-41-348 to 5-41-422

Summary: HPLC methods were developed to measure the concentration of sparfloxacin in plasma, urine, and bile. Rat plasma samples (with AT-4117 added as internal standard) were extracted with an equal amount of dichloromethane-ether (8:2) and the solvent evaporated under vacuum. Residue was dissolved in mobile phase (70:15:15, 5% acetic acid:acetonitrile:methanol) and injected onto a YMC A-312 column with spectrophotometric detection at 364 nm. Undiluted human urine (internal standard could not be used due to interference) and bile diluted by $\frac{1}{2}$ with internal standard in 5% acetic acid were injected onto a YMC A-312 column and a linear gradient program of combinations of 5% acetic acid and 1:1 acetonitrile:methanol was used to elute the drug which was quantitated by spectrophotometric detection at 364 nm. The amount of sparfloxacin glucuronide was determined by measuring sparfloxacin concentration in a urine or bile sample before and after alkaline hydrolysis (0.1 ml NaOH added to 1 ml sample and incubated for 5 minutes at room temperature). Sparfloxacin concentrations and chromatogram peak areas had a linear relationship between 0.01-1.7 $\mu\text{g}/\text{ml}$ in plasma and 3-55 $\mu\text{g}/\text{ml}$ in urine. The minimum detectable concentrations in plasma and urine were said to be 0.005 and 0.1 $\mu\text{g}/\text{ml}$, respectively (signals above 3X background). The coefficients of variance for the plasma HPLC method were from 1.0-4.3% for three different 0.43 $\mu\text{g}/\text{ml}$ samples run on three different days and from 3.8-8.1% for 0.043 $\mu\text{g}/\text{ml}$ samples. Sparfloxacin was stable for 24 hours in rat plasma at 37°C and for 28 days at -20°C .

Validated Liquid Chromatographic Assay of CI-978 in Rat Plasma
RR 764-01313)

Report

Dated 11/8/89

Vol. 53, pp. 5-42-2 to 5-42-23

Summary: An isocratic HPLC method was developed for the routine detection of sparfloxacin in rat plasma using a Whatman C 18 column with mobile phase of 21% acetonitrile and 79% aqueous (0.05M citric acid, 0.1% ammonium perchlorate, and 1.15 mM tetrabutylammonium hydroxide) and spectrophotometric detection at 380 nm. Plasma proteins were precipitated using 4:1 acetonitrile:perchloric acid (25 μ l added per 100 μ l of plasma with 100 μ l of internal standard solution). PD 115100 (dissolved in water) was used as the internal standard. The assay was validated over a range of 0.1 to 20.0 μ g/ml. The relationship between concentration of sparfloxacin and chromatogram peak height for sparfloxacin was linear. The percent relative standard deviation for fresh calibration standards checked on three separate days ranged from 0.6-9.0%.

Validated Liquid Chromatographic Assay of CI-978 in Dog Plasma
RR 764-01307)

Report

Dated 11/8/89

Vol. 53, pp. 5-42-24 to 5-42-46

Summary: The HPLC assay described above (Report RR 764-01313) was validated for dog plasma over a range of μ g/ml. The percent relative standard deviation for fresh calibration standards checked on three separate days ranged from %.

Metabolism of Sparfloxacin: Identification of Sparfloxacin and its Metabolite and Stability of its Metabolite (Report D 112)

Dated 11/26/91

Vol. 53, pp. 5-42-47 to 5-42-82

Summary: Rats, dogs, and monkeys were given a 5 mg/kg oral dose of sparfloxacin. Over the next 24 hours, urine was collected from all species, with plasma, bile, and feces collected from rats only. Human plasma, urine, and feces were collected for 24 hours following a 200 mg oral dose of sparfloxacin and human bile was collected after a 300 mg oral dose. Urine was also obtained from humans receiving 300 mg of sparfloxacin once daily for 7 days. HPLC with spectrophotometric detection was used to separate and identify sparfloxacin and its metabolite and mass spectrometry and nuclear magnetic resonance was used to confirm the identities of purified chromatographic peaks.

The only sparfloxacin-related peaks identified in the urine of all species were identified as unchanged sparfloxacin and an ester-type glucuronide conjugate. Both sparfloxacin and its conjugate were observed in rat and human plasma and bile. Only unchanged sparfloxacin was observed in rat or human feces. There did not appear to be any major species differences in the metabolism of sparfloxacin following oral administration. The glucuronide conjugate of

sparfloxacin was demonstrated to be relatively stable. Its half life in an aqueous buffer at pH 5.0 was 740 hours at 37°C and at pH 7.4 was 82 hours. At 4°C, no breakdown of the glucuronide conjugate occurred in a pH 7.4 aqueous buffer after 96 hours.

**Correlation Between AT-4140 Concentrations Measured by HPLC and Bioassay
Report D 113)**

Dated 1/28/92

Vol. 53, pp. 5-42-83 to 5-42-103

Summary: Sparfloxacin concentrations in plasma (collected over a 48 hour period) and urine (collected over a 72 hour period) from humans given a single oral dose of 100, 200, or 400 mg were determined using the bioassay described in report D 121 and the HPLC method described in report D 103. The data obtained from both methods had correlation coefficients of 0.999 for plasma samples and 0.985 for urine specimens when concentrations obtained using both methods were plotted versus one another.

Sparfloxacin: Assessment of Absorption in the Pregnant Rat Report No. 91/RHS097/1022)

Dated 3/3/92

Summary: Sparfloxacin suspended in carboxymethyl cellulose was administered daily via oral gavage to pregnant rats on gestation days 6-15. Dose levels were 100, 200, or 300 mg/kg/day. Plasma was collected from all dams 2 and 24 hours after sparfloxacin dosing on days 6 and 15 of gestation (n=8 at each dose level). Samples of amniotic fluid, placental tissue and fetal tissue were taken from dams in the 300 mg/kg group 2 or 24 hours after the final dose of sparfloxacin was administered on day 15 (n=4 at each timepoint). Sparfloxacin levels were quantified using a validated HPLC assay.

Average Plasma Sparfloxacin Concentrations ($\mu\text{g/ml} \pm \text{SD}$) in Pregnant Rats

Dose	Day 6		Day 15	
	2 hours	24 hours	2 hours	24 hours
100 mg/kg	4.75 $\pm$ 1.17	0.26 $\pm$ 0.12	4.88 $\pm$ 0.83	0.15 $\pm$ 0.03
200 mg/kg	8.24 $\pm$ 1.67	0.79 $\pm$ 0.17	7.46 $\pm$ 1.15	0.57 $\pm$ 0.21
300 mg/kg	9.01 $\pm$ 1.93	1.77 $\pm$ 1.12	8.46 $\pm$ 1.79	0.88 $\pm$ 0.49

Average Sparfloxacin Concentrations (+SD) on Day 15 of Gestation in Placentae, Fetuses, and Amniotic Fluid from Pregnant Rats Treated with 300 mg/kg

	2 hours	24 hours
Amniotic Fluid	8.27 ± 1.08 µg/ml	0.95 ± 0.43 µg/ml
Placentae	25.44 ± 4.24 µg/g	3.03 ± 1.20 µg/g
Fetuses	18.39 ± 2.34 µg/g	2.14 ± 1.05 µg/g

There did not appear to be evidence of sparfloxacin accumulation in plasma over the course of treatment. The concentration of sparfloxacin in plasma and amniotic fluid were similar in the 300 mg/kg dose group, but its concentration in placentae and fetuses was higher. The rat dams and fetuses in this study appear to have been adequately exposed to sparfloxacin after oral administration during the period of organogenesis.

RP 64206: Plasma Pharmacokinetics of Sparfloxacin After Single and Repeated (15 Days) 25 mg/kg/day Oral Dose in the Dog (RPR . No. 1720)

A. Paccaly, G. Montay, A. Frydman (Rhône-Poulenc Rorer, Antony Cedex, France)

Dated: 5/7/93

Vol. 53, pp. 5-42-162 to 5-42-335

Summary: Four beagle dogs (2 per sex) were given a single oral 25 mg/kg dose of sparfloxacin in capsule form. Blood samples were drawn prior to dosing, then 1, 2, 3, 4, 5, 6, 8, 12, 24, 28, 32, 36, 48, 56, 72, 96, 168, 216, 264, and 336 hours after administration. Sparfloxacin plasma concentrations remained quantifiable until 168-216 hours after the single dose. About 4 days after the last blood sample was drawn, the same animals were then given daily oral sparfloxacin doses of 25 mg/kg for a period of 15 days. Blood samples were drawn after the last dose of drug at the time points listed above and also several times during the 15 day administration period immediately prior to the next daily dose so that steady state could be determined. Sparfloxacin plasma concentrations remained quantifiable until 216-336 hours after the final dose of the 15 day regimen. Plasma levels of sparfloxacin were quantitated using a validated HPLC method that had a lower limit of detection of 0.010 µg/ml and utilized an internal standard.

T_{max} in all dogs was reached in 3-4 hours regardless of treatment day. Besides the pharmacokinetic parameters listed below, it was observed that in 3/4 dogs, the first elimination half life was 7-13 hours (accounting for 87-96% of excreted drug), with a prolonged second elimination half life from 80-104 hours (accounting for 4-13% of excreted drug). The fourth dog, male R1X5, eliminated the drug more quickly than the other animals with a first elimination half life of 2.4 hours (82% of excreted drug) and a second elimination half life of 26 hours (18% of excreted drug). Additionally, steady state was reported to have been reached on about day 7 of daily dosing.

**Pharmacokinetics of Sparfloxacin in Beagle Dogs After a Single 25 mg/kg Dose
or 15 days of Daily Dosing**

Dog I.D.	C _{max}		C ₂₄		AUC 0-24		AUC 0-t*	
	day 1	day 15	day 1	day 15	day 1	day 15	day 1	day 15
	4.5	8.23	0.73	1.71	48.2	90.1	74.5	148.7
	4.97	6.99	1.14	2.41	55.0	103.6	90.4	187.6
	8.20	9.06	1.37	2.03	90.8	116.7	110.7	168.5
	6.28	7.72	1.15	1.53	68.6	92.3	85.4	163.4

*where t equals the time until sparfloxacin could no longer be detected in the dog's plasma

The investigators believed that the prolonged second elimination phase observed in most of the dogs may represent elimination from deep compartments into plasma. The reviewer notes that sparfloxacin, like several other quinolones, binds to melanin and suggests that this might be one of the compartments that slowly releases the drug.

Ocular Toxicokinetic Study of RP 64206 (Sparfloxacin) after Repeated Oral Administration of 25 mg/kg/day for 21 Days in the Female Dog 1637)

R. Bruno, A. Paccaly, G. Montay, A. Frydman (Rhône-Poulenc Rorer, Antony Cedex, France)

Dated 5/7/93

Vol. 53, pp. 5-42-336 to 5-42-412

Summary: Female beagle dogs were dosed orally with 25 mg/kg/day of sparfloxacin daily for 21 days. Groups of 3 were sacrificed after 1, 10, and 21 days of dosing and also 7 and 14 days after the dosing regimen was completed. Blood samples were drawn in all remaining dogs on days 1, 10, and 21 immediately prior to drug administration, then 1, 2, and 4 hours after dosing. Final blood samples were drawn from each animal just before sacrifice, approximately 6 hours after dosing, where applicable. At sacrifice, ocular tissue samples (aqueous and vitreous humors, and lens) were harvested. Sparfloxacin was quantitated in plasma and tissue homogenates using a validated HPLC assay with a lower limit of 50 ng/ml.

On day 1 of dosing, plasma sparfloxacin levels were 2-3 times higher than those observed in ocular tissue. On day 10, plasma and ocular tissue sparfloxacin levels were approximately equal, as were plasma, aqueous and vitreous humor levels on day 21. Lens levels on day 21, however, were approximately 50% higher than plasma levels, suggesting accumulation of sparfloxacin in this tissue. Additionally, while elimination of sparfloxacin from the humors paralleled that from plasma, elimination of sparfloxacin from the lens was prolonged, with this tissue containing drug levels approximately 14 times higher than plasma one week after dosing stopped and 9 times higher than plasma levels two weeks after dosing stopped. It should be noted that there was greater variation between dogs in the concentration

of sparfloxacin in lens tissue compared to plasma or the other ocular tissues. Nonetheless, the data indicate that it took longer to reach sparfloxacin steady state concentration in the lens than in plasma or the ocular humors (indeed, it is not certain that steady state was actually reached in the lens tissue during the 21 days of dosing in this study) and that sparfloxacin was eliminated more slowly from the lens than from the other sites.

Average ($\pm$ SD) Plasma and Ocular Tissue Levels of Sparfloxacin Six Hours After 1, 10, or 21 Days of Repeated Dosing or 1 or 2 Weeks After 21 Days of Repeated Dosing

	Plasma	Aqueous Humor	Vitreous Humor	Lens
Day 1	3.67 + 0.31	1.18 + 0.14	2.11 + 0.36	2.21 + 1.74
Day 10	4.75 + 1.85	4.35 + 0.47	5.36 + 1.42	9.13 + 8.43
Day 21	4.79 + 1.69	4.30 + 1.22	4.15 + 0.67	11.87 + 10.12
1 week post dose	0.42 + 0.13	0.48 + 0.14	0.24 + 0.10	4.62 + 1.96
2 weeks post dose	0.32 + 0.15	0.22 + 0.1	0.07 + 0.03	2.21 + 0.77

RP 64206- Sparfloxacin: Oral (Gavage) Pharmacokinetic Study in the Pregnant Rat (AT 7151) (RPR Report EUR 7151, No. 1734)

A. Paccaly, Y. Le Roux, G. Montay, A. Frydman (Rhône-Poulenc Rorer, Antony Cedex, France)

Dated 5/12/93, French GLP

Vol. 54, pp. 5-43-1 to 5-43-124

Summary: Pregnant Sprague-Dawley rats were given 100, 300, or 600 mg/kg of sparfloxacin suspended in carboxymethyl cellulose daily via oral gavage from days 6-15 of pregnancy. On day 15 of pregnancy, 6 dams from each dose group were sacrificed prior to administration of sparfloxacin, then 1, 2, 4, 8, and 24 hours after the final dose. Blood samples were obtained from all animals immediately before sacrifice. Sparfloxacin concentrations were quantified in maternal plasma and spleens as well as placentas and fetuses by a validated HPLC method with a lower limit of about 50 ng/ml.

Average ($\pm$ SD) Plasma and Tissue Concentrations ($\mu\text{g/ml}$ or $\mu\text{g/g}$) of Sparfloxacin Following 10 Days of Repeated Dosing of Pregnant Rats During Organogenesis

	Pre Final Dose	1 hour Post Dose	2 hours Post Dose	4 hours Post Dose	8 hours Post Dose	24 hours Post Dose
Plasma						
100 mg/kg	0.07 $\pm$ 0.02	3.98 $\pm$ 0.75	5.64 $\pm$ 1.66	5.37 $\pm$ 0.97	2.13 $\pm$ 0.32	0.14 $\pm$ 0.08
300	1.45 $\pm$ 1.19	5.21 $\pm$ 2.97	9.59 $\pm$ 1.33	10.30 $\pm$ 1.40	8.98 $\pm$ 2.34	0.73 $\pm$ 0.11
600	1.95 $\pm$ 0.61	8.16 $\pm$ 2.47	13.65 $\pm$ 2.05	15.03 $\pm$ 1.95	16.49 $\pm$ 2.35	2.74 $\pm$ 0.75
Fetus						
100 mg/kg	0.18 $\pm$ 0.07	4.48 $\pm$ 1.20	6.22 $\pm$ 2.57	5.99 $\pm$ 0.40	2.51 $\pm$ 0.62	0.22 $\pm$ 0.08
300	0.53 $\pm$ 0.17	6.59 $\pm$ 0.83	10.84 $\pm$ 1.80	13.29 $\pm$ 1.30	10.97 $\pm$ 2.53	0.95 $\pm$ 0.23
600	2.58 $\pm$ 0.74	8.69 $\pm$ 2.25	17.87 $\pm$ 2.47	19.33 $\pm$ 2.38	24.76 $\pm$ 2.89	4.58 $\pm$ 2.21
Placenta						
100 mg/kg	0.16 $\pm$ 0.05	7.22 $\pm$ 2.51	9.92 $\pm$ 3.55	9.26 $\pm$ 1.75	4.83 $\pm$ 0.56	0.42 $\pm$ 0.18
300	1.01 $\pm$ 0.46	14.06 $\pm$ 1.53	19.96 $\pm$ 3.42	21.35 $\pm$ 3.37	19.51 $\pm$ 3.02	1.41 $\pm$ 0.46
600	4.40 $\pm$ 0.68	17.73 $\pm$ 5.42	28.20 $\pm$ 4.29	35.07 $\pm$ 5.12	43.74 $\pm$ 8.04	8.56 $\pm$ 3.67
Spleen						
100 mg/kg	1.10 $\pm$ 0.56	17.48 $\pm$ 3.45	24.58 $\pm$ 6.00	28.30 $\pm$ 5.67	11.06 $\pm$ 1.69	1.80 $\pm$ 1.18
300	4.77 $\pm$ 1.33	33.75 $\pm$ 3.32	49.03 $\pm$ 7.59	58.88 $\pm$ 7.51	47.47 $\pm$ 9.21	7.05 $\pm$ 3.69
600	43.54 $\pm$ 25.89	41.81 $\pm$ 18.56	149.03 $\pm$ 53.47	296.91 $\pm$ 325.74	110.50 $\pm$ 25.11	34.78 $\pm$ 48.23

**Average ($\pm$ SD) Pharmacokinetic Parameters of Sparfloxacin Following
10 Days of Repeated Dosing of Pregnant Rats During Organogenesis**

	C_{max} (μ g/ml or μ g/g)	T_{max} (h)	C_{min} (μ g/ml or μ g/g)	AUC_{0-24h} (μ g.h/ml or μ g h/g)
Plasma				
100 mg/kg	5.64 $\pm$ 1.66	2	0.14 $\pm$ 0.08	51
300	10.30 $\pm$ 1.40	4	0.73 $\pm$ 0.11	147
600	16.49 $\pm$ 2.35	8	2.74 $\pm$ 0.75	262
Fetus				
100 mg/kg	6.22 $\pm$ 2.57	2	0.22 $\pm$ 0.08	59
300	13.29 $\pm$ 1.30	4	0.95 $\pm$ 0.23	180
600	24.76 $\pm$ 2.89	8	4.58 $\pm$ 2.21	379
Placenta				
100 mg/kg	9.92 $\pm$ 3.55	2	0.42 $\pm$ 0.18	102
300	21.35 $\pm$ 3.37	4	1.41 $\pm$ 0.47	315
600	43.74 $\pm$ 8.04	8	8.56 $\pm$ 3.67	673
Spleen				
100 mg/kg	28.30 $\pm$ 5.67	4	1.80 $\pm$ 1.18	265
300	58.88 $\pm$ 7.51	4	7.05 $\pm$ 3.69	817
600	296.91 $\pm$ 325.74	4	34.78 $\pm$ 48.23	2561

Steady state plasma, spleen, placental, and fetal sparfloxacin concentrations appeared to have been reached during the dosing period as drug levels were not significantly different before the final dose was administered and 24 hours after that dose was given. Plasma, tissue, and fetal concentrations were dose-dependant and the times to C_{max} were longer as the dose increased. Fetal and placental exposure (AUC) were slightly to moderately higher than observed in maternal plasma, but the maternal spleen contained much higher (and more variable) concentrations of sparfloxacin than plasma. The investigators did not explain why spleen was chosen as an indicator of maternal tissue concentration, and it is not known whether it would indeed be indicative of other maternal tissues. The data indicate that sparfloxacin crosses the rat placenta and the fetuses were exposed to sparfloxacin administered maternally.

RP 64206- Sparfloxacin: Oral (Gavage) Pharmacokinetic Study in the Pregnant Cynomolgus Monkey (AT 7524) (RPR/ . 1735)

A. Paccaly, G. Montay, A. Frydman (Rhône-Poulenc Rorer, Antony Cedex, France)

Dated 4/28/93, French GLP

Vol. 54, pp. 5-43-125 to 5-43-265

Summary: Pregnant cynomolgus monkeys (3 per dose group) were given 20 or 50 mg/kg of sparfloxacin suspended in carboxymethyl cellulose daily via oral gavage from days 20-50 of pregnancy. Blood samples were obtained on days twenty and thirty-five 2, 4, 8, and 24 hours after dosing, on day forty-nine 0, 1, 2, 4, 8, and 24 hours after dosing, and on day fifty 2 hours after dosing (at the time of sacrifice). Sparfloxacin concentrations were quantified in maternal plasma and fetuses by a validated HPLC method with a lower limit of about 0.05 µg/ml for plasma and 0.25 µg/g for fetuses. It should be noted that the monkeys vomited on several occasions after the administration of the 50 mg/kg dose of sparfloxacin; therefore it is probable that the entire dose was not absorbed.

As C_{min} and C_{max} did not differ significantly on days 35 and 49 of gestation, steady state appeared to have been reached within the first 15 days of sparfloxacin administration. Fetal sparfloxacin levels were 50-100% higher than maternal plasma levels at sacrifice indicating that this drug crosses the cynomolgus monkey placenta and the fetuses were exposed to sparfloxacin administered maternally.

Average (±SD) Pharmacokinetic Parameters of Sparfloxacin in Pregnant Monkeys

	C _{max} (µg/ml)	T _{max} (h) Range	C _{min} (µg/ml)	AUC _{0-24h} (µg.h/ml)	AUC _{2-24h} (µg.h/ml)
20 mg/kg					
Day 20 (First Dose)	3.24 ± 2.41	4-8	0.82 ± 0.18	38.36 ± 11.74	36.71 ± 11.36
Day 35	5.10 ± 1.07	4	1.95 ± 0.90	---	76.33 ± 24.13
Day 49	5.15 ± 1.61	1-2	1.30 ± 0.25	60.41 ± 11.65	54.41 ± 9.49
50 mg/kg					
Day 20 (First Dose)	4.32 ± 0.50	2-4	1.07 ± 0.23	58.84 ± 14.36	54.83 ± 13.91
Day 35	5.66 ± 0.53	2	1.95 ± 0.88	---	73.76 ± 12.20
Day 49	5.40 ± 1.39	2-4	2.10 ± 0.82	89.10 ± 37.36	81.11 ± 33.68

**Average ($\pm$ SD) Maternal Plasma and Fetal Concentrations ($\mu\text{g}/\text{ml}$ or $\mu\text{g}/\text{g}$)
of Sparfloxacin at Time of Sacrifice Following 31 Days of Repeated Dosing**

Sparfloxacin Dose	Maternal Plasma	Fetus
20 mg/kg/day	4.35 $\pm$ 1.26	9.59 $\pm$ 0.59
50 mg/kg/day	5.55 $\pm$ 0.80	8.72 $\pm$ 2.62

Validation of an HPLC Assay for the Determination of RP 64206 in the Skin and Plasma of Hairless Mice (RFR Report DD-95-023)

Dated 3/27/95

Vol. 54, pp. 5-43-266 to 5-43-292

Summary: An isocratic HPLC method was developed for the routine detection of sparfloxacin in skin and plasma of hairless mice using a YMC Basic C8 column with mobile phase of 36% methanol and 64% potassium phosphate buffer (23 mM, pH 3.0) and spectrophotometric detection at 300 nm. Ciprofloxacin was used as the internal standard. Drugs were extracted from plasma or skin with methylene chloride and ethyl acetate (9:1). Skin samples were digested with potassium hydroxide prior to extraction. This caused degradation of the quinolones by about 30%, but, according to the investigator, the relative extraction efficiencies between sparfloxacin and ciprofloxacin were not altered. The assay was validated over a range of $\mu\text{g}/\text{ml}$ for plasma and $\mu\text{g}/\text{g}$ for skin. The relationship between concentration of sparfloxacin and chromatogram peak height for sparfloxacin was linear. The percent difference between measured concentrations and theoretical concentrations for mouse skin and plasma standards ranged from % for plasma and % for skin.

Effect of Sparfloxacin on Hepatic Drug-Metabolizing Enzyme Systems in Rats (Study D130)

Dated 6/30/95

Vol. 54, pp. 5-43-293 to 5-43-299

Summary: Sparfloxacin suspended in 0.5% tragacanth gum was administered to male Wistar rats via gavage daily for 7 days. Dose groups included a vehicle control, 10, or 100 mg/kg sparfloxacin, and a positive control (40 mg/kg phenobarbital given intraperitoneally for 7

days). Livers were harvested 24 hours after the final drug dose, homogenized, and microsomal fractions prepared via centrifugation and ultracentrifugation. The amounts of protein, cytochrome P-450, and cytochrome b₅, and the activities of NADPH-cytochrome P-450 reductase, aminopyrine N-demethylase, and aniline hydroxylase were quantified in the microsomal fractions. Phenobarbital caused a significant increase in liver weight and microsomal protein and cytochrome content, and enzyme activities compared to control. Microsomal fractions from livers of sparfloxacin-treated rats did not have significantly different protein or cytochrome contents or enzyme activities than control. Over a 7 day period, at doses up to 100 mg/kg, sparfloxacin did not induce the rat hepatic microsomal enzymes quantitated in this experiment.

Plasma and Urine Levels and Bioavailability of AT-4140 and Ciprofloxacin in Dogs After Single Oral or Intravenous Administration Determined by Bioassay Method
Report D116)

Dated 12/7/91

Vol. 54, pp. 5-43-439 to 5-43-470

Summary: Fasted male beagle dogs received either an oral (in gelatin capsules) or intravenous dose of 5 mg/kg sparfloxacin or ciprofloxacin (3 dogs per dose group). Blood samples were drawn 0.5, 1, 2, 4, 6, 8, and 24 hours after oral dosing and 0.1, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after intravenous dosing. Urine samples were collected from 0-24 hours and 24-48 hours. Plasma and urine sparfloxacin and ciprofloxacin levels were determined using a validated bioassay.

Pharmacokinetic Parameters (Mean $\pm$ SD) of Sparfloxacin and Ciprofloxacin in Male Beagles Following an Intravenous or Oral Dose of 5 mg/kg

	C _{max} (μ g/ml)	T _{max} (h)	T _{1/2} (h)	AUC ₀₋₂₄ (μ g.h/ml)
Sparfloxacin				
I.V.	---	---	9.2 $\pm$ 0.6	22.68 $\pm$ 3.43
Oral	1.16 $\pm$ 0.16	4.0 $\pm$ 2.0	8.4 $\pm$ 0.3	18.62 $\pm$ 1.95
Ciprofloxacin				
I.V.	---	---	2.9 $\pm$ 0.3	10.98 $\pm$ 0.81
Oral	0.78 $\pm$ 0.49	1.3 $\pm$ 0.6	3.9 $\pm$ 0.7	4.95 $\pm$ 2.81

Sparfloxacin had greater bioavailability than ciprofloxacin in the dogs (82 vs. 45%) after oral administration. Half life and AUC for sparfloxacin were also greater than for

ciprofloxacin after either oral or intravenous dosing. The volume of distribution after intravenous administration was also greater for sparfloxacin than ciprofloxacin (2.94 ± 0.29 vs. 1.91 ± 0.19 l/kg). As might be expected from the half life data, the clearance rate for ciprofloxacin was greater than for sparfloxacin following intravenous administration (7.62 ± 0.57 vs. 3.73 ± 0.54 ml/min/kg). The urinary recovery of sparfloxacin after oral dosing was $8.6 \pm 0.1\%$ over 48 hours, with the greatest amount of the drug excreted in the first 24 hours. Treatment of urine with β -glucuronidase did not significantly change measurement of urinary sparfloxacin, but as a bioassay method was used, it would not be expected to change if a sparfloxacin-glucuronide had similar antibacterial activity as the parent compound. Ciprofloxacin urinary data was not provided.

Single-Dose Pharmacokinetics and Absolute Bioavailability of CI-978 in Beagle Dogs
Report RR 764-01361

Dated 12/11/89

Vol. 55, pp. 5-44-1 to 5-44-30

Summary: Male and female beagle dogs (2/sex, fasted) received single sparfloxacin doses of 6.25 mg/kg via the oral (gelatin capsule) and intravenous routes with 14 days between the doses. Blood samples were collected prior to dosing, then 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after administration of drug. Sparfloxacin plasma levels were measured using a validated HPLC assay.

**Mean Pharmacokinetic Parameters (+ SD) of Sparfloxacin in Beagle Dogs
After Oral and Intravenous Administration**

	Oral Dosing	Intravenous Dosing
C _{max} (μg/ml)	1.47 ± 0.14	---
T _{max} (h)	3.8 ± 1.7	---
T _{1/2} (h)	9.7 ± 0.7	8.7 ± 1.4
AUC ₀₋₂₄ (μg.h/ml)	16.7 ± 1.2	21.2 ± 2.0
AUC _∞ (μg.h/ml)	21.6 ± 1.4	25.9 ± 1.3
Clearance (ml/min)	---	36.7 ± 3.6
Volume of Distribution (l/kg)	---	3.1 ± 0.49
Bioavailability (%)	84 ± 8	---

Data from male and female dogs were combined as there did not appear to be gender differences in sparfloxacin pharmacokinetics. Sparfloxacin was quantifiable in plasma through the end of the 24 hour blood sampling period. Half life of sparfloxacin in plasma was similar after either oral or intravenous dosing.

**Plasma and Urine Levels of AT-4140 in Mice After Single Oral Administration
Determined by Bioassay Method (Report D115)**

Dated 12/7/91

Vol. 55, pp. 5-44-53 to 5-44-74

Summary: Fasted male Std-ddY mice were dosed orally via gavage with 5 mg/kg of sparfloxacin suspended in 0.2% sodium carboxymethyl cellulose solution. Blood samples were drawn from 5 mice at each of the following times after administration: 0.25, 0.5, 1, 2, 4, 6, and 8 hours. Urine was collected 0-6, 6-24, and 24-48 hours after sparfloxacin was given (pooled from 5 mice per collection time). Plasma and urine sparfloxacin and ciprofloxacin levels were determined using a validated bioassay.

Pharmacokinetic parameters calculated in mice were as follows:

C_{max}: 0.25 ± 0.13 µg/ml
T_{max}: 0.25 - 0.5 h
T_{1/2}: 4.1 h
AUC_{0-∞}: 0.71 µg.h/ml

Individual calculations of T_{1/2} and AUC_{0-∞} for each mouse were not provided, nor were standard deviations of the mean. Urinary excretion of sparfloxacin over 48 hours was 6.7% with the majority excreted during the first 24 hours. Treatment of urine with β-glucuronidase did not change measurement of urinary sparfloxacin, but as a bioassay method was used, it would not be expected to change if a sparfloxacin-glucuronide had antibacterial activity similar to the parent compound.

**Plasma and Urine Levels of AT-4140 in Rats After Single Oral Administration
Determined by Bioassay Method (Report D114)**

Dated 12/7/91

Vol. 55, pp. 5-44-75 to 5-44-99

Summary: Fasted male Wistar rats were dosed orally via gavage with 5 mg/kg of sparfloxacin suspended in 0.2% sodium carboxymethyl cellulose solution. Blood samples were drawn from 5 rats at each of the following times after administration: 0.25, 0.5, 1, 2, 4,

6, and 8 hours. Urine was collected 0-6, 6-24, and 24-48 hours after sparfloxacin was given. Plasma and urine sparfloxacin and ciprofloxacin levels were determined using a validated bioassay.

Pharmacokinetic parameters calculated in rats were as follows:

C_{max}: 0.5 ± 0.07 µg/ml
 T_{max}: 0.4 ± 0.1 h
 T_{1/2}: 3.3 ± 0.3 h
 AUC_{0-∞}: 2.05 ± 0.14 µg.h/ml

Urinary excretion of sparfloxacin over 48 hours was 12.9 ± 4.0% with the majority excreted during the first 24 hours. Treatment of urine with β-glucuronidase may have slightly increased measured sparfloxacin concentration in urine (recovery increased to 16.3 ± 1.4%), but it is not possible to ascribe great meaning to this change because a bioassay method was used to measure sparfloxacin- any metabolite that has some antibacterial activity will be measured in this assay and considered to be sparfloxacin.

Plasma and Urine Levels of AT-4140 in Monkeys After Single Oral Administration Determined by Bioassay Method Report D117)

Dated 12/7/91

Vol. 55, pp. 5-44-100 to 5-44-123

Summary: Four fasted male cynomolgus monkeys were dosed orally via gavage with 5 mg/kg of sparfloxacin suspended in 0.5% tragacanth gum solution. Blood samples were drawn 0.5, 1, 2, 4, 6, 8 and 24 hours after administration. Urine was collected 0-24 and 24-48 hours after sparfloxacin was given. Plasma and urine sparfloxacin and ciprofloxacin levels were determined using a validated bioassay.

Pharmacokinetic parameters calculated in monkeys were as follows:

C_{max}: 0.49 ± 0.27 µg/ml
 T_{max}: 2.0 ± 0 h
 T_{1/2}: 9.3 ± 1.6 h
 AUC_{0-∞}: 4.66 ± 1.64 µg.h/ml

Urinary excretion of sparfloxacin over 48 hours was 12.7 ± 1.2% with the majority excreted during the first 24 hours. Treatment of urine with β-glucuronidase appears to have slightly increased measured sparfloxacin concentration in urine (recovery increased to 18.9 ± 5.0%), but it is not possible to ascribe great meaning to this change because a bioassay method was used to measure sparfloxacin- any metabolite that has some antibacterial activity will be measured in this assay and considered to be sparfloxacin.

Plasma Levels of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats (Report D110-2)

Dated 3/29/93

Vol. 55, pp. 5-44-124 to 5-44-150

and

Quantitative Tissue Distribution of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C] Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats (Report D109-2)

Dated 3/26/93

Vol. 56, pp. 5-45-231 to 5-45-279

Summary: These studies were reviewed together as some of the same dosed animals were used for both. Male Wistar rats (3 sacrificed per distribution time point) were given 10 mg/kg sparfloxacin (combination of ¹⁴C-radiolabeled and unlabeled drug; about 50 μ Ci/dose) suspended in 0.5% tragacanth gum once daily for 14 days via oral gavage. For tissue distribution studies, groups of rats were sacrificed 0.5, 6, 24, and 168 hours after the final dose of sparfloxacin was given. The rats sacrificed 168 hours after the last sparfloxacin dose were used for the plasma level study. For determination of plasma radioactivity, blood samples were collected 0.5, 1, 2, 6, 8, 10 and 24 hours after both first and last doses of sparfloxacin; additional samples were collected 48, 72, 96, and 168 hours after the last dose of sparfloxacin was given. Radioactivity was quantitated using liquid scintillation counting following digestion of samples as appropriate.

Estimated pharmacokinetic parameters were as follows:

	First Dose	Last Dose
T _{max}	1 hr	1 hr
C _{max}	1.38 μ g eq/ml	1.38 μ g eq/ml
T _{1/2}	3.2 hr	3.6 hr
AUC ₀₋	7.4 μ g eq.hr/ml	7.3 μ g eq.hr/ml

Pharmacokinetic parameters of sparfloxacin in the male rat did not appear to be changed by 14 days of repeated daily dosing at a level of 10 mg/kg.

Sparfloxacin was well-distributed after oral administration; levels were higher in many tissues than in plasma (see table below). The highest tissue levels were found in the GI tract, kidney, liver, pancreas, and adrenals. The lowest levels were found in brain.

NDA 28-677

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**Plasma and Tissue Levels ($\mu\text{g eq/ml}$ or g) of ^{14}C -Sparfloxacin in the Rat
Following 14 Days of Oral Administration (Average $\pm$ SE)**

Tissue	Time After Final Sparfloxacin Dose			
	0.5 hr	6 hr	24 hr	168 hr
Plasma	0.83 $\pm$ 0.29	0.39 $\pm$ 0.07	0.05 $\pm$ 0.01	*
Red Blood Cells	0.14 $\pm$ 0.05	0.15 $\pm$ 0.02	*	*
Brain	0.09 $\pm$ 0.04	0.09 $\pm$ 0.01	*	*
Eye Ball	0.23 $\pm$ 0.08	0.31 $\pm$ 0.04	0.07 $\pm$ 0.01	*
Harderian Gland	1.04 $\pm$ 0.45	1.07 $\pm$ 0.14	0.09 $\pm$ 0.01	*
Hypophysis	1.21 $\pm$ 0.53	1.23 $\pm$ 0.27	*	*
Thyroid	1.65 $\pm$ 0.28	2.06 $\pm$ 0.04	0.93 $\pm$ 0.06	0.63 $\pm$ 0.18
Adrenal	2.64 $\pm$ 0.49	2.20 $\pm$ 0.95	1.76 $\pm$ 0.12	0.43 $\pm$ 0.08
Pancreas	2.68 $\pm$ 1.24	3.00 $\pm$ 0.50	0.16 $\pm$ 0.01	*
Submaxillary Gland	1.84 $\pm$ 0.83	2.11 $\pm$ 0.21	0.09 $\pm$ 0.04	*
Heart	1.09 $\pm$ 0.48	0.91 $\pm$ 0.13	0.09 $\pm$ 0.00	*
Lung	1.23 $\pm$ 0.43	1.00 $\pm$ 0.11	0.11 $\pm$ 0.01	*
Aorta	0.46 $\pm$ 0.16	0.37 $\pm$ 0.05	0.08 $\pm$ 0.02	*
Thymus	0.83 $\pm$ 0.43	1.11 $\pm$ 0.14	0.08 $\pm$ 0.00	*
Spleen	1.39 $\pm$ 0.60	1.26 $\pm$ 0.17	0.16 $\pm$ 0.02	*
Liver	2.68 $\pm$ 1.33	1.58 $\pm$ 0.27	0.17 $\pm$ 0.01	*
Kidney	4.00 $\pm$ 1.30	3.23 $\pm$ 0.51	0.46 $\pm$ 0.02	0.08 $\pm$ 0.00
Stomach	14.3 $\pm$ 1.7	1.59 $\pm$ 0.38	0.25 $\pm$ 0.07	*
Small Intestine	6.79 $\pm$ 2.83	3.21 $\pm$ 0.79	0.21 $\pm$ 0.02	*
Large Intestine	0.99 $\pm$ 0.31	2.82 $\pm$ 0.59	0.31 $\pm$ 0.02	*
Bone	1.05 $\pm$ 0.33	1.17 $\pm$ 0.10	0.44 $\pm$ 0.01	0.25 $\pm$ 0.01
Trachea	1.18 $\pm$ 0.42	1.01 $\pm$ 0.05	0.24 $\pm$ 0.08	0.14 $\pm$ 0.02
Skin	0.84 $\pm$ 0.25	0.72 $\pm$ 0.10	0.18 $\pm$ 0.02	0.12 $\pm$ 0.03

Muscle	0.74 ± 0.41	0.99 ± 0.14	0.07 ± 0.00	*
Fat	0.17 ± 0.12	0.07 ± 0.01	*	*
Brown Fat	0.61 ± 0.18	0.80 ± 0.12	0.10 ± 0.01	*
Tongue	1.08 ± 0.49	1.04 ± 0.15	0.11 ± 0.01	*
Testicle	0.34 ± 0.10	0.49 ± 0.06	0.16 ± 0.01	*
Epididymis	0.54 ± 0.26	0.73 ± 0.08	0.11 ± 0.02	*
Seminal Vesicle	0.74 ± 0.30	0.91 ± 0.31	0.11 ± 0.04	*
Prostate	0.87 ± 0.45	1.19 ± 0.21	0.07 ± 0.00	*
Mesenteric Lymph Nodes	1.15 ± 0.52	1.12 ± 0.16	0.11 ± 0.01	*

*Sample radioactivity was below reliable counting level (<0.05 µg eq/ml or g)

Toxicokinetic Study of AT-4140 in Rats

Report B304)

Dated 6/18/93

Vol. 55, pp. 5-44-151 to 5-44-223

Summary: Male and female Jcl:SD rats (5 per treatment group) were given either a single oral dose or 4 weeks of daily oral doses of sparfloxacin suspended in aqueous 0.5% carboxymethyl cellulose. Dose groups were 25, 100, or 400 mg/kg. Blood samples were drawn 0.25, 0.5, 1, 2, 4, 6, 8, 12 (100 mg only), and 24 hours after the single 25 or 100 mg/kg sparfloxacin doses. The 0.25 and 0.5 hour time points were eliminated for the animals given a single 400 mg/kg dose and a 30 hour time point was added. For the repeat dose study, blood samples were drawn on days 1, 7, 14, and 28 of dosing either 0.5 and 24 hours (25 mg/kg rats), 4 and 24 hours (100 mg/kg males), or 6 and 24 hours (100 mg/kg females and 400 mg/kg rats) after administration of sparfloxacin. The times chosen for sampling in the multiple dose study were the approximate time corresponding to C_{max} in the single dose study and 24 hours after drug was administered. Drug levels in plasma were quantified using a validated HPLC assay.

There did not appear to be significant differences in C_{max} or AUC between male and female rats from the same dose groups following a single administration of sparfloxacin. C_{max} was not dose proportional between groups after either a single dose or multiple doses of sparfloxacin. Plasma levels of sparfloxacin 24 hours after dosing did appear to be dose proportional in the rats given multiple doses of drug. There was modest accumulation of sparfloxacin after 4 weeks of administration.

**Pharmacokinetic Parameters of Sparfloxacin in Rats
Following a Single Oral Dose (Average $\pm$ SE)**

Dose	C _{max} (μ g/ml)	T _{max} (hours)	AUC _{0-t} (μ g.h/ml)
25 mg/kg	1.65 $\pm$ 0.11 (male)	1.1 $\pm$ 0.4	9.07 $\pm$ 0.85
	1.94 $\pm$ 0.10 (female)	0.25 $\pm$ 0.00	9.32 $\pm$ 0.39
100 mg/kg	4.34 $\pm$ 0.31	3.6 $\pm$ 0.4	38.04 $\pm$ 1.59
	4.65 $\pm$ 0.13	5.2 $\pm$ 0.5	40.94 $\pm$ 2.25
400 mg/kg	10.20 $\pm$ 0.63	5.2 $\pm$ 0.5	124.22 $\pm$ 5.57
	9.62 $\pm$ 0.69	6.8 $\pm$ 0.5	124.81 $\pm$ 5.66

t=24 hours for 25 and 100 mg/kg groups and 30 hours for 400 mg/kg group

Average ($\pm$ SE) Plasma Levels of Sparfloxacin After Repeated Daily Administration

	Sample Time	25 mg/kg	100 mg/kg	400 mg/kg
Day 1	C _{max}	0.96 $\pm$ 0.14 (male) 1.34 $\pm$ 0.39 (female)	2.45 $\pm$ 0.15 1.77 $\pm$ 0.22	6.81 $\pm$ 0.76 7.38 $\pm$ 0.66
	24 hr	not detected	0.07 $\pm$ 0.01 0.07 $\pm$ 0.01	0.45 $\pm$ 0.09 0.78 $\pm$ 0.18
Day 7	C _{max}	1.07 $\pm$ 0.11 1.09 $\pm$ 0.17	3.26 $\pm$ 0.40 1.52 $\pm$ 0.11	8.35 $\pm$ 1.33 6.06 $\pm$ 0.47
	24 hr	0.04 $\pm$ 0.01 0.04 $\pm$ 0.02	0.08 $\pm$ 0.00 0.12 $\pm$ 0.02	0.22 $\pm$ 0.02 0.32 $\pm$ 0.03
Day 14	C _{max}	0.99 $\pm$ 0.21 1.52 $\pm$ 0.15	3.08 $\pm$ 0.31 2.13 $\pm$ 0.18	9.04 $\pm$ 0.61 6.96 $\pm$ 1.15
	24 hr	0.07 $\pm$ 0.02 0.04 $\pm$ 0.02	0.16 $\pm$ 0.02 0.17 $\pm$ 0.02	0.44 $\pm$ 0.06 0.52 $\pm$ 0.11
Day 28	C _{max}	1.40 $\pm$ 0.34 1.76 $\pm$ 0.44	4.22 $\pm$ 0.22 2.61 $\pm$ 0.10	8.27 $\pm$ 1.34 9.92 $\pm$ 0.98
	24 hr	0.07 $\pm$ 0.01 0.05 $\pm$ 0.02	0.20 $\pm$ 0.01 0.26 $\pm$ 0.02	0.93 $\pm$ 0.15 1.18 $\pm$ 0.12

Toxicokinetics of AT-4140 in the Dog Following Once Daily Oral Administration of 5, 15, and 45 mg/kg for 4 Weeks
Report B203)

Dated 5/25/93

Vol. 55, pp. 5-44-260 to 5-44-322

Summary: Male and female beagle dogs (3-5 per dose group) were given daily oral doses of sparfloxacin (5, 15, or 45 mg/kg) suspended in 0.5% aqueous carboxymethyl cellulose. On days 1 and 26 of administration, blood samples were drawn 1, 2, 4, and 24 hours after sparfloxacin was given. A blood sample was also drawn prior to administration of drug on day 26. Plasma concentrations of sparfloxacin were quantitated by bioassay.

**Pharmacokinetic Parameters (mean $\pm$ SE) of Sparfloxacin in Dogs
Following Single and Repeated Administration**

	5 mg/kg	15 mg/kg	45 mg/kg
Day 1			
C_{max} (μ g/ml)	1.11 $\pm$ 0.08 (male) 1.32 $\pm$ 0.13 (female)	3.55 $\pm$ 0.54 3.90 $\pm$ 0.12	7.12 $\pm$ 0.64 7.18 $\pm$ 0.57
T_{max} (hours)	1.33 $\pm$ 0.33 1.33 $\pm$ 0.33	2.67 $\pm$ 0.66 2.00 $\pm$ 0.00	2.00 $\pm$ 0.71 2.40 $\pm$ 0.40
AUC_{0-24 h} (μ g.hr/ml)	14.47 $\pm$ 0.35 16.20 $\pm$ 0.66	47.87 $\pm$ 7.97 44.40 $\pm$ 0.62	93.12 $\pm$ 5.20 91.64 $\pm$ 5.71
Day 26			
C_{max} (μ g/ml)	1.81 $\pm$ 0.21 1.95 $\pm$ 0.11	3.59 $\pm$ 0.19 4.79 $\pm$ 0.29	9.38 $\pm$ 1.35 11.82 $\pm$ 2.04
T_{max} (hours)	2.67 $\pm$ 0.66 2.67 $\pm$ 0.66	2.00 $\pm$ 1.00 2.00 $\pm$ 0.00	2.80 $\pm$ 0.49 3.60 $\pm$ 0.40
AUC_{0-24 h} (μ g.hr/ml)	25.37 $\pm$ 1.78 28.27 $\pm$ 1.59	53.43 $\pm$ 3.54 56.00 $\pm$ 7.67	137.04 $\pm$ 18.90 192.94 $\pm$ 34.12

After the first dose of sparfloxacin, C_{max} and AUC increased dose-proportionally between 5 and 15 mg/kg, but not between 15 and 45 mg/kg, although there was a dose-related increase in these parameters. The increased C_{max} and AUC observed at each dose level on day 26 compared to day 1 indicated a potential for accumulation of sparfloxacin in the dog following multiple doses of the drug. There appeared to be no sex-related differences in C_{max}, T_{max}, or AUC in the dogs after the first dose of sparfloxacin, but the C_{max} and AUC were slightly higher in female dogs than male on day 26. Due to the study- due to variability it is

difficult to be certain as to whether this difference is biologically significant.

Toxicokinetics of AT-4140 in the Dog Following Once Daily Oral Administration of 4, 10, and 25 mg/kg for 26 Weeks Report B303)

Dated 5/25/93

Vol. 55, pp. 5-44-323 to 5-44-415

Summary: Male and female beagle dogs (4-6 per dose group) were given daily oral doses of sparfloxacin (4, 10, or 25 mg/kg) suspended in 0.5% aqueous carboxymethyl cellulose. On days 1, 33, 98, and 173 of administration, blood samples were drawn 1, 2, 4, and 24 hours after sparfloxacin was given. A blood sample was also drawn prior to administration of drug on days 33, 98, and 173. Plasma concentrations of sparfloxacin were quantitated by bioassay.

There did not appear to be biologically significant pharmacokinetic differences between male and female dogs. C_{max} and AUC rose with increasing dose and were considered dose proportional from 4-10 mg/kg, but not for 10 and 25 mg/kg. There appeared to have been an initial accumulation of sparfloxacin (compare C_{max} and AUC between days 1 and 33), but steady state was reached at the two lower dose groups by day 33 (compare C_{max} and AUC between days 33, 98, and 173). Accumulation continued between days 98 and 173 in the high dose group.

Pharmacokinetic Parameters (mean ± SE) of Sparfloxacin in Dogs Following Single and Repeated Administration

	4 mg/kg	10 mg/kg	25 mg/kg
Day 1			
C _{max} (µg/ml)	0.90 + 0.08 0.81 + 0.04	1.99 + 0.06 1.99 + 0.16	2.82 + 0.33 3.13 + 0.35
T _{max} (hours)	2.25 + 0.63 1.75 + 0.25	2.50 + 0.50 3.00 + 5.58	3.67 + 0.33 3.00 + 0.44
AUC _{0-24 h} (µg.hr/ml)	12.40 + 1.10 11.38 + 0.55	28.13 + 0.26 29.88 + 2.64	39.52 + 4.92 44.63 + 4.17
Day 33			
C _{max} (µg/ml)	1.30 + 0.06 1.06 + 0.07	2.77 + 0.13 1.89 + 0.20	4.57 + 0.44 4.35 + 0.51
T _{max} (hours)	1.75 + 0.25 3.50 + 0.50	2.75 + 0.75 3.50 + 0.50	2.50 + 0.49 2.50 + 0.49
AUC _{0-24 h} (µg.hr/ml)	18.40 + 1.38 16.10 + 1.09	42.85 + 1.39 31.45 + 3.41	68.28 + 4.80 68.72 + 7.54

Day 98			
Cmax ($\mu\text{g/ml}$)	1.24 + 0.10 1.29 + 0.10	2.62 + 0.19 2.79 + 0.28	4.22 + 0.34 4.51 + 0.65
Tmax (hours)	1.50 + 0.29 2.25 + 0.63	2.25 + 0.63 2.00 + 0.71	2.17 + 0.40 3.33 + 0.42
AUC_{0-24h} ($\mu\text{g}\cdot\text{hr/ml}$)	18.50 + 1.42 18.18 + 0.57	38.98 + 3.12 41.50 + 1.74	60.18 + 5.93 66.57 + 6.60
Day 173			
Cmax ($\mu\text{g/ml}$)	1.34 + 0.05 1.06 + 0.11	2.59 + 0.14 2.61 + 0.09	6.58 + 0.41 5.21 + 0.65
Tmax (hours)	3.25 + 0.75 2.00 + 0.00	2.00 + 0.00 2.75 + 0.75	2.83 + 0.54 2.67 + 0.42
AUC_{0-24h} ($\mu\text{g}\cdot\text{hr/ml}$)	20.68 + 1.09 14.65 + 1.54	39.13 + 1.85 39.45 + 1.58	94.43 + 5.59 78.95 + 8.47

Pharmacokinetics of Sparfloxacin in Rats- Effect of Food

Report D128)

Dated 6/95

Vol. 56, pp. 5-45-1 to 5-45-8

Summary: Sparfloxacin suspended in 0.5% tragacanth gum was administered orally to fasted or fed Wistar rats at a dose of 5 mg/kg. Blood samples were collected at various times (not stated) after dosing and sparfloxacin plasma levels determined via HPLC. Food appeared to slow and impair the absorption of sparfloxacin and prolong its half life in the rat.

	Cmax ($\mu\text{g/ml}$)	T _{1/2} (hr)	AUC _{0-24h} ($\mu\text{g}\cdot\text{hr/ml}$)
Fasted	0.67	3.5	3.16
Fed	0.25	4.6	2.35

Absorption of [¹⁴C]Sparfloxacin After Administration in Gastrointestinal Loops of the Male Rat at the Dose of 10 mg/kg

Report D102-7)

Dated 3/26/93

Vol. 56, pp. 5-45-80 to 5-45-108

Summary: Wistar rats underwent ligation of the common bile duct and either the pylorus, duodenum, or jejunum-ileum to determine where absorption of a 10 mg/kg dose of radiolabeled sparfloxacin occurred. The drug was administered directly into the stomach, duodenum, or jejunum, as appropriate. Blood samples were collected from 15 minutes to 6 hours after administration of sparfloxacin and radioactivity measured. Animals were sacrificed 6 hours after drug was given and the G.I. tract dissected for measurement of radioactivity and determination of sparfloxacin absorption. Sparfloxacin was absorbed poorly in the stomach (only 4% of dose during the 6 hour study period), but was absorbed almost completely in either the duodenum or jejunum (96% and 90% of administered dose, respectively, over 6 hours).

**Autoradiographic Study of the Distribution of Radioactivity After a Single Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg in the Male Rats
Report D102-2)**

Dated 3/17/93

Vol. 56, pp. 5-45-109 to 5-45-133

Summary: Radiolabeled sparfloxacin was administered intravenously or orally via gavage to male Wistar rats at a dose of 10 mg/kg. Animals were sacrificed from 5 minutes to 48 hours after drug was administered, then rapidly frozen and stored at -80°C until longitudinal whole body sections were cut, freeze dried, and applied to x-ray film. After intravenous administration, radiolabel could be observed in the G.I. tract (indicative of excretion in the bile) and bladder as early as 5 minutes after drug was given. The pancreas, kidney, spleen, heart, skeletal muscle, and parotid gland also had relatively high levels of radioactivity. Levels in liver, bone marrow, skin, cartilage, and prostate were higher than in blood, and radioactivity in lung and thymus appeared similar to blood. Little radioactivity was observed in fat or brain during the study. By 4-8 hours after administration, radioactivity in the whole body tissues was beginning to decrease relative to the earlier time points and by 24 hours, was only observed in the intestinal and bladder contents. By 48 hours, radioactivity was seen only at a low level in the intestinal contents. Patterns of distribution were similar following oral administration of sparfloxacin.

**Autoradiographic Study of the Distribution of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg in the Male Rats
Report D109-1)**

Dated 3/25/93

Vol. 56, pp. 5-45-134 to 5-45-157

Summary: Radiolabeled sparfloxacin was administered orally via gavage to male Wistar rats at a dose of 10 mg/kg daily for 14 days. Animals were sacrificed 30 minutes, 24 or 168 hours after the final dose of drug was administered, then rapidly frozen and stored at -80°C until longitudinal whole body sections were cut, freeze dried, and applied to x-ray film. At 30 minutes, radioactivity was highest in the G.I. tract and kidney. The liver, submaxillary and parotid glands, cartilage, spleen, heart, tongue, bone marrow, muscle, thymus, prostate, and skin had higher levels of radioactivity than blood. Levels of radioactivity in lungs and testes were similar to blood. Radioactivity was not seen in the brain or fat. Twenty four hours after the last dose of sparfloxacin, relatively high levels were observed in the renal pelvis and intestinal contents, with lower levels in the renal cortex and cartilage. No appreciable radioactivity was observed in the animals sacrificed 168 hours after the final dose of radiolabeled sparfloxacin.

Autoradiographic Study on the Distribution of Radioactivity After a Single Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg in the Pregnant Rat (Report D111-1)

Dated 3/24/93

Vol. 56, pp. 5-45-158 to 5-45-178

Summary: Radiolabeled sparfloxacin was administered orally via gavage to pregnant Wistar rats (gestation day 19) as a single dose of 10 mg/kg. Animals were sacrificed 30 minutes, 24 or 48 hours after the final dose of drug was administered, then rapidly frozen and stored at -80°C until longitudinal whole body sections were cut, freeze dried, and applied to x-ray film. Thirty minutes after dosing, the level of radioactivity in the fetuses was less than that observed in maternal organs such as the kidney, liver, spleen, submaxillary and parotid glands, lungs, heart, muscle, thymus, mammary glands, bone marrow and placenta. The level in amniotic fluid was slightly higher than that observed in maternal blood. Radioactivity was observed in the fetal G.I. tract 24 hours after administration of radiolabeled sparfloxacin. The level had decreased 48 hours after administration, but it was still observable. Maternal tissue levels were lower at both 24 and 48 hours than they had been at 30 minutes after dosing with most of the radioactivity confined to the digestive tract and lower levels in the kidney, adrenal glands, and amnion. The data suggest that a relatively small fraction of the total sparfloxacin dose reached the fetuses. The sparfloxacin that did distribute to the fetuses appeared confined to the intestines; thus the radioactivity observed in the fetuses was likely to have been excreted in fetal bile.

Quantitative Tissue Distribution of Radioactivity After a Single Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg in Male Rats (Report D102-3)

Dated 3/18/93

Vol. 56, pp. 5-45-179 to 5-45-230

Summary: Radiolabeled sparfloxacin was administered orally via gavage to male Wistar rats at a dose of 10 mg/kg. Animals were sacrificed from 30 minutes to 48 hours after drug was administered, then blood and organs were harvested for determination of radioactivity in plasma and tissues via liquid scintillation counting. Most tissue levels contained their maximum amounts of radioactivity 30 minutes after drug was administered. The level of sparfloxacin in plasma 30 minutes after administration was approximately 1.32 $\mu\text{g eq/ml}$. The kidney had the highest level of radioactivity (about 4.3 times the plasma level), the pancreas and liver were next at about 3 times plasma level. Other tissues that were at least equal to plasma or up to twice the plasma radioactivity level were skin, bone, thymus, muscle, seminal vesicle, prostate, heart, trachea, lung, tongue, mesenteric lymph nodes, spleen and thyroid, Harderian, adrenal, pituitary, and submaxillary glands. Tissues such as the red blood cells, aorta, epididymis and eyeball had levels of radioactivity that were lower than observed in plasma. The brain had the lowest level of radioactivity out of all of the tissues examined. Levels of radioactivity in the majority of the tissues decreased over time, with appreciable levels only in kidney, adrenal, bone and skin observed 48 hours after administration of drug.

Quantitative Tissue-Distribution of Radioactivity After a Single Oral Administration of [^{14}C]Sparfloxacin at the Dose of 10 mg/kg in the Pregnant Rat Report D111-2)

Dated 3/24/93

Vol. 56, pp. 5-45-280 to 5-45-310

Summary: Radiolabeled sparfloxacin was administered orally via gavage to pregnant Wistar rats (gestation day 19) at a dose of 10 mg/kg. Animals were sacrificed from 30 minutes or 48 hours after drug was administered, then blood, maternal organs (heart, lung, liver, kidney, ovary, oviduct uterus, placenta, and amnion), amniotic fluid, and fetuses were harvested for determination of radioactivity via liquid scintillation counting. The level of sparfloxacin in maternal plasma 30 minutes after administration was approximately 1.18 $\mu\text{g eq/ml}$. The fetal level of radioactivity was approximately 60% of the maternal plasma level 30 minutes after sparfloxacin administration. The maternal reproductive organs had levels of radioactivity slightly higher than the plasma level, the placenta was similar, and the amniotic fluid slightly lower. High levels were seen in liver and kidney, as had been observed in the male rats. By 48 hours after sparfloxacin administration, the fetal levels were approximately half of what they had been at 30 minutes- but now several times higher than the current plasma level. The level of radioactivity in the amniotic fluid 48 hours after dosing was twice what it had been at 30 minutes. In conjunction with the autoradiography study in pregnant rats and fetuses reviewed above, this suggests that radiolabeled compound may be excreted into the amniotic fluid by the fetuses.

Uptake and Subcellular Localization of Sparfloxacin (AT-4140, RP64206; S) in Phagocytic Cells (30th ICAAC, Abstract 1243, 1990)

Vol. 56, pp. 5-45-311 to 5-45-312

Summary: Sparfloxacin was taken up by J774 macrophages and human PMN cells when they were incubated in medium containing 10 mg/l of drug. Concentrations in the cells were 11.9 times higher and 4.4 times higher than the extracellular concentration, respectively. The drug was found in the soluble fraction of the J774 macrophages, but in the PMNs, 30% was associated with azurophilic granules.

**Tissue Distribution of AT-4140 in Rats Following a Single Oral Administration
Report D118)**

Dated 11/1/91

Vol. 57, pp. 5-46-1 to 5-46-23

Summary: Sparfloxacin suspended in 0.2% carboxymethyl cellulose was administered orally via gavage to non-fasted male Wistar rats at a dose of 5 mg/kg. Spinal fluid, blood, and organs (brain, heart, lung, liver, spleen, kidney, muscle, and prostate) were harvested from rats sacrificed 15 minutes to 24 hours after drug was administered. Concentrations of sparfloxacin were determined via bioassay. Sparfloxacin could not be detected in the tissues 24 hours following administration (assay detection limit $\mu\text{g/g}$). Sparfloxacin distributed rapidly throughout the rats' bodies. The concentration of sparfloxacin tended to be higher in most tissues than in plasma, with the exception of brain and spinal fluid. The kidney and liver were the tissues exposed to the greatest amounts of the drug.

The exposure of various tissues to sparfloxacin may be summarized as follows (mean $\pm$ SD):

Tissue	C _{max} ($\mu\text{g/ml}$ or g)	T _{max} (hours)	AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{h/ml}$ or g)
plasma	0.24 $\pm$ 0.09	0.5	0.85
muscle	0.28 $\pm$ 0.07	0.5	1.5
heart	0.78 $\pm$ 0.12	0.5	2.99
lung	0.79 $\pm$ 0.28	0.5	2.89
spleen	0.73 $\pm$ 0.12	0.5	3.24
prostate	0.68 (pooled sample)	1.0	3.37
liver	1.86 $\pm$ 0.39	0.25	4.51
kidney	2.53 $\pm$ 0.37	0.5	8.11
brain	not detected		
spinal fluid	0.043 $\pm$.002	1.0	0.23

Tissue Distribution of AT-4140 and Ciprofloxacin in Mice Following a Single Oral Administration
 Report D119)

Dated 11/1/91

Vol. 57, pp. 5-46-24 to 5-46-47

Summary: Sparfloxacin suspended in 0.2% carboxymethyl cellulose or ciprofloxacin dissolved in deionized water was administered orally via gavage to fasted male STD-ddY mice at a dose of 5 mg/kg. Blood and organs (heart, lung, kidney, and muscle) were harvested from rats sacrificed 30 minutes to 8 hours after drug was administered. Concentrations of drugs were determined via bioassay. Tmax in all samples was 0.5 hours for both drugs. Sparfloxacin levels and half lives were higher than those measured for ciprofloxacin in plasma and all tissues examined. Sparfloxacin also appeared to have greater tissue penetration.

Comparison of Pharmacokinetic Parameters for Sparfloxacin and Ciprofloxacin in the Mouse Following Oral Administration (Mean $\pm$ SD; n=3)

	Cmax ($\mu\text{g/ml}$ or g)	T1/2 (hours)	AUC _{0-∞} ($\mu\text{g}\cdot\text{h/ml}$ or g)
Plasma			
Sparfloxacin	0.19 $\pm$ 0.03	3.1	0.83
Ciprofloxacin	0.07 $\pm$ 0.02	1.4	0.16
Heart			
Sparfloxacin	0.37 $\pm$ 0.09	2.7	1.49
Ciprofloxacin	0.10 $\pm$ 0.02	0.9	0.16
Lung			
Sparfloxacin	0.72 $\pm$ 0.10	3.1	3.09
Ciprofloxacin	0.08 $\pm$ 0.02	1.7	0.22
Kidney			
Sparfloxacin	1.31 $\pm$ 0.26	3.3	5.41
Ciprofloxacin	0.23 $\pm$ 0.06	1.8	0.65
Muscle			
Sparfloxacin	0.42 $\pm$ 0.12	3.0	2.00
Ciprofloxacin	0.07 $\pm$ 0.01	1.0	0.16

Skin Penetration of Sparfloxacin (AT-4140) (30th ICAAC, Abstract 1256, 1990)

Vol. 57, pp. 5-46-48 to 5-46-49

Summary: Skin and plasma samples were harvested from rats given a 20 mg/kg oral dose of sparfloxacin and from humans given a 200 mg oral dose. Concentrations were determined via bioassay. Six hours after dosing, the plasma level of sparfloxacin in rats was 1.3 $\mu\text{g/ml}$ and skin level was 2.85 $\mu\text{g/g}$. In humans the concentrations were 0.82 $\mu\text{g/ml}$ and 0.97 $\mu\text{g/g}$, respectively. At approximately 24 hours after dosing, the human skin levels were about 1 $\mu\text{g/g}$ and plasma levels about 0.3 $\mu\text{g/ml}$.

Seven-Day Oral Pharmacokinetic Study RP 64206 in Hairless Mice (RPR/RD/CVL/DS 94-135)

M.S. Bonnefoi (Rhône-Poulenc Rorer, Collegeville, PA)

Dated 4/21/95

Vol. 57, pp. 5-46-50 to 5-46-90

Summary: Sparfloxacin suspended in 0.5% aqueous carboxymethylcellulose was administered daily for 7 days to Crl:SKH1 hrBR hairless mice via oral gavage at dose levels of 12.5, 25, or 50 mg/kg. Blood and skin samples were harvested from 3 mice per time point 24 hours after the day 6 dose and 0.5, 1, 2, 4, and 8 hours after the day 7 dose. A validated HPLC method was used to determine the concentration of sparfloxacin in the plasma and skin. Sparfloxacin was not detected in any of the plasma samples obtained 24 hours after the day 6 dose (limit of quantitation 0.025 $\mu\text{g/ml}$), but was present in skin. As the maximum drug concentration was usually found at the first time point, it is possible that C_{max} may have been underestimated and T_{max} overestimated in those animals. The data do indicate that sparfloxacin quickly distributes to the skin and this tissue had a higher concentration (2 to 8-fold) of the drug than plasma during the course of the study. Although plasma C_{max} and AUC tended to be the similar in male and female mice (except for 25 mg/kg animals), the females tended to have higher maximum skin concentrations of sparfloxacin than the males. Except for the males in the 25 mg/kg group, sparfloxacin levels in plasma and skin increased in proportion with dose.

Concentrations of Sparfloxacin in Plasma and Skin and Estimated Systemic Exposure in Mice Following Multiple Daily Doses of the Drug (Mean $\pm$ SD)

	C_{24} ($\mu\text{g/ml}$ or g)	C_{max} ($\mu\text{g/ml}$ or g)	AUC_{0-24} ($\mu\text{g}\cdot\text{h/ml}$ or g)
Plasma			
12.5 mg/kg	not detected	0.49 $\pm$ 0.04 (male) 0.49 $\pm$ 0.05 (female)	1.25 1.20
25 mg/kg	not detected	0.31 $\pm$ 0.09 0.85 $\pm$ 0.30	0.86 1.77
50 mg/kg	not detected	2.16 $\pm$ 0.57 2.29 $\pm$ 0.48	5.78 5.37
Skin			
12.5 mg/kg	0.035 $\pm$ 0.002 0.049 $\pm$ 0.007	1.59 $\pm$ 0.11 2.02 $\pm$ 0.13	not calculated
25 mg/kg	0.052 $\pm$ 0.019 0.060 $\pm$ 0.035	0.54 $\pm$ 0.10 3.23 $\pm$ 1.41	not calculated
50 mg/kg	0.078 $\pm$ 0.002 0.080 $\pm$ 0.021	5.55 $\pm$ 2.52 7.59 $\pm$ 0.48	not calculated

*Concentration of sparfloxacin 24 hours after the day 6 dose

Intraocular Dynamic Mode of Sparfloxacin in Rabbit Eyes (3rd International Symposium on New Quinolones, Abstract 378, Vancouver, 1990)

Vol. 57, pp. 5-46-91 to 5-46-92)

Summary: A 0.5% solution of sparfloxacin was applied to rabbit eyes at a dose of 20 mg/kg. Concentrations in aqueous and vitreous humors were determined via HPLC. Sparfloxacin concentrations in the aqueous humor were 0.28 $\pm$ 0.17, 0.38 $\pm$ 0.4, and 0.16 $\pm$ 0.05 $\mu\text{g/ml}$, at 30, 60, and 120 minutes, respectively, after dosing. Concentrations in the vitreous humor were 0.74 $\pm$ 0.11, 0.55 $\pm$ 0.21, and 1.03 $\pm$ 0.14 $\mu\text{g/ml}$ at the same time points. Sparfloxacin was not detected in either humor 24 hours after application to the eye.

Ocular Pharmacokinetic Studies of AT-4140 (30th ICAAC, Abstract 1258, 1990)

Vol. 57, 5-46-93 to 5-46-94

Summary: Sparfloxacin or ciprofloxacin was administered orally to albino rabbits at a dose of 50 mg/kg. The maximum level of sparfloxacin was about 3 times higher than ciprofloxacin (0.74 vs. 0.26 $\mu\text{g}/\text{ml}$) in the aqueous humor and the authors reported that sparfloxacin could be found in other ocular tissues at concentrations from 0.2 to 5.1 $\mu\text{g}/\text{ml}$ or g. Penetration of sparfloxacin to the ocular tissues appeared to be greater than ciprofloxacin when the drugs were given orally.

Distribution of [^{14}C]Sparfloxacin in Jaw Bone of Experimentally Infected Rabbits After Oral Administration (Chemotherapy 39 [S-4]: 131-137, 1991)

Vol. 57, 5-46-95 to 5-46-107)

Summary: A single 20 mg/kg dose of radiolabeled sparfloxacin suspended in 0.1% carboxymethylcellulose was orally administered to fasted New Zealand white rabbits with or without an experimentally induced mandibular infection (*S. milleri* and *B. fragilis*). A bioassay was used to determine sparfloxacin concentration in plasma and bone tissue collected 0.5-36 hours after administration of drug and autoradiography of the mandible was performed to visualize distribution of the radiolabeled sparfloxacin 3 or 24 hours after dosing. The data indicate that the concentration of sparfloxacin in the mandible bone was about half of the serum concentration. Autoradiography showed that radioactive drug was found around the site of the infection at a greater concentration than in the rest of the bone. Radioactivity could be seen at the infection site even 24 hours after the dose was given.

Pharmacokinetics of Sparfloxacin in Rabbits With or Without Mandibular Infection

	Non-Infected	Infected
Serum		
Cmax ($\mu\text{g}/\text{ml}$)	0.77	0.82
Tmax (h)	5.3	3.1
AUC ($\mu\text{g}\cdot\text{h}/\text{ml}$)	12.96	8.79
Mandible		
Cmax ($\mu\text{g}/\text{g}$)	0.34	0.48
Tmax (h)	5.6	3.4
AUC ($\mu\text{g}\cdot\text{h}/\text{g}$)	6.74	5.00

Plasma and Milk Levels of Radioactivity After a Single Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg in Lactating Rats Report D102-8)

Dated 3/24/93

Vol. 57, pp. 5-46-108 to 5-46-136

Summary: Three nonfasted lactating Wistar rats were given a single 10 mg/kg oral dose of radiolabeled sparfloxacin suspended in 0.5% tragacanth gum. Milk and blood were collected 1, 2, 24, and 48 hours after administration of drug and radioactivity determined in plasma and milk via scintillation counting. Radioactivity of milk was 3-5 times higher than plasma during most of the study period and could be detected as early as 1 hour following administration of drug, indicating the presence of sparfloxacin in milk.

Estimated Pharmacokinetic Parameters of Sparfloxacin in Milk and Plasma (Mean $\pm$ SD)

	Plasma	Milk
Plasma Levels ($\mu\text{g eq/ml}$)		
1 hour after dosing	1.08 + 0.27	3.06 + 0.92
2 hours after dosing	0.62 + 0.12	2.96 + 0.73
24 hours after dosing	0.09 + 0.04	0.74 + 0.08
48 hours after dosing	0.03 + 0.01	0.16 + 0.03
$T_{1/2}$, 2-48 h (hours)	10.6	10.9
$AUC_{0-\infty}$ ($\mu\text{g eq.h/ml}$)	11.1	58.6

Biopharmaceutical Profile of CI-978 (PD 131501-0000), Lot Q
Report RR 764-01416)

Research

Dated 1/5/90

Vol. 57, pp. 5-46-137 to 5-46-148

Summary: This was a brief report on several characteristics of sparfloxacin including:
1. Maximum absorbance 290 nm (5 $\mu\text{g/ml}$ solution in distilled water)

2. Solubility of 0.11 mg/ml in distilled water
3. Stable in 0.1 N HCl or NaOH for 1 hour at 97°C, 0.05 KH₂PO₄ for 24 hours at room temperature, stable in 0.5% methyl cellulose for 29 days at room temperature, and stable in rat plasma for 24 hours at 37°C or 28 days at -20°C (all confirmed via HPLC assay)
4. 44.6% bound to rat plasma proteins and 46.0% bound to human plasma proteins at approximately 370 ng/ml at 37°C *in vitro* (ultracentrifugation method)
5. Approximately 55% bound to dog plasma proteins at 37°C *in vitro* at concentrations from 0.5 to 20.0 µg/ml (equilibrium dialysis method)
6. Oral bioavailability in fasted Wistar rats and beagle dogs was 72% and 84%, respectively, following a dose of 6.25 mg/kg (plasma determinations via HPLC)

Bioautography Study of Pooled Urine of Mice, Rats, Dogs, and Monkeys Orally Receiving AT-4140 Report D122)

Dated 12/4/91

Vol. 57, pp. 5-46-149 to 5-46-164

Summary: Urine samples from mice and rats (0-6 hour collection) and dogs and monkeys (0-24 hour collection) given a single sparfloxacin dose of 5 mg/kg were subjected to thin layer chromatography. The urine of these animals contained a substance that showed a migration pattern consistent with unchanged sparfloxacin. These specimens also appeared to contain a minor metabolite believed to be sparfloxacin glucuronide, but this was not definitively identified.

A Study on the Urinary Metabolites After 14 Consecutive Daily Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats Report D110-1)

Dated 3/30/93

Vol. 57, pp. 5-46-165 to 5-46-187

Summary: Radiolabeled sparfloxacin suspended in 0.5% tragacanth gum was administered to male Wistar rats daily for 14 days via oral gavage at a dose of 10 mg/kg. Urine was collected for 24 hours following the last dose of drug and specimens (some treated with NaOH) were subjected to thin layer chromatography. Two radioactive substances were identified in the untreated urine- the predominant one (71.6%) corresponding with unchanged sparfloxacin and the other believed to be sparfloxacin glucuronide (28.4%). The amount of this secondary metabolite decreased following treatment of the urine specimens with NaOH, with a concomitant increase in the amount of unchanged sparfloxacin- suggesting that the secondary metabolite was indeed sparfloxacin glucuronide.

Plasma Levels of AT-4140 in Male and Female Rats After Single and 7 Day Repeated Oral Administration Using HPLC Method Report D107)

Dated 9/18/92

Vol. 57, pp. 5-46-188 to 5-46-209

Summary: Male and female Wistar rats were given either a single 5 mg/kg dose of sparfloxacin suspended in 0.5% tragacanth gum via oral gavage or 7 daily oral doses of the same. Blood was collected 0.25 to 24 hours after the final dose was administered. Sparfloxacin concentrations in plasma were determined via HPLC. Pharmacokinetic parameters were calculated from the mean plasma concentration-time curves of 4-5 rats. T_{max} was observed at approximately 0.5 hours. There did not appear to be gender differences between the male and female rats, repeated administration of sparfloxacin at 5 mg/kg for 7 days did not alter pharmacokinetic parameters compared to a single dose, and there was no evidence of accumulation at this dose level for this duration of treatment.

Pharmacokinetic Parameters of Sparfloxacin in Male and Female Rats After Single or Multiple Doses of Drug

	C _{max} (μg/ml)	T _{1/2} (hours)	AUC (μg.h/ml)
Single Dose			
Males	0.67	3.5	2.77
Females	0.66	3.8	2.62
Repeated Doses			
Males	0.69	3.9	2.45
Females	0.65	3.7	2.65

Excretion of Radioactivity After 14 Consecutive Daily Oral Administration of [¹⁴C]Sparfloxacin at the Dose of 10 mg/kg/day in Male Rats Report D110-3)

Dated 3/29/93

Vol. 57, pp. 5-46-210 to 5-46-246

Summary: Radiolabeled sparfloxacin suspended in 0.5% tragacanth gum was administered to 5 male Wistar rats daily for 14 days via oral gavage at a dose of 10 mg/kg. Urine and feces

were collected for 24 hours following the first 13 doses and up 96 hours after the last dose. Radioactivity was measured in the carcasses of rats sacrificed either 5 or 96 hours after the last dose of sparfloxacin, as well as in the urine and feces samples, by liquid scintillation counting. During the treatment period, urine and feces collected for each 24 hour period consistently contained approximately 20% and 73% of the previous dose. The urine and feces collected 72-96 hours after the last dose contained almost no radioactivity. This was consistent with the carcass containing about 1% of the sparfloxacin dose 96 hours after the dose was given. Sparfloxacin appeared to have been rapidly and almost completely excreted 24 hours after administration of 10 mg/kg to male Wistar rats. There was no evidence of significant accumulation at this dose level for a 14 day treatment period.

**Biliary Excretion of AT-4140 in Rats Following a Single Oral Administration
Report D120)**

Dated 11/1/91

Vol. 57, pp. 5-46-247 to 5-46-267

Summary: A single 5 mg/kg dose of sparfloxacin suspended in 0.2% carboxymethyl cellulose was administered orally via gavage to 5 male Wistar rats with bile duct cannulas. Bile samples were collected 0-3 hours, 3-6 hours, and 6-24 hours after administration and the concentrations of sparfloxacin were measured using a bioassay. Treating bile samples with β -glucuronidase or NaOH plus heat increased the amount of active drug measured in the bile, suggesting the presence of a glucuronide conjugate.

**Biliary Excretion of Sparfloxacin in Male Rats (Concentration $\mu\text{g/ml}$, Mean $\pm$ SD)
With % Recovery of Dose in Parentheses**

Sample Time	Untreated	β -glucuronidase	NaOH plus heat
0-3 hours	13.75 $\pm$ 3.70 (2.53 $\pm$ 0.75%)	60.72 $\pm$ 21.74 (11.35 $\pm$ 4.83%)	84.74 $\pm$ 13.79 (15.58 $\pm$ 3.08%)
3-6 hours	8.48 $\pm$ 4.40 (0.92 $\pm$ 0.33%)	29.82 $\pm$ 9.15 (3.40 $\pm$ 0.72%)	48.36 $\pm$ 16.57 (5.45 $\pm$ 1.28%)
6-24 hours	3.71 $\pm$ 1.25 (2.11 $\pm$ 0.36%)	11.20 $\pm$ 2.27 (6.60 $\pm$ 1.23%)	15.96 $\pm$ 2.88 (9.47 $\pm$ 1.99%)
0-24 hours	(5.56 $\pm$ 1.13%)	(21.34 $\pm$ 4.65%)	(30.50 $\pm$ 3.34%)

Dated 10/15/92

Vol. 57, pp. 5-46-268 to 5-46-299

Summary: Renal excretion of sparfloxacin administered continuously via intravenous infusion (plasma maintenance level of 1 $\mu\text{g/ml}$) was studied in fasted, anesthetized male Wistar rats with cannulated ureters. Mannitol, inulin, and PAH were also infused intravenously so that their clearances could be determined and compared with that of sparfloxacin. The "stop flow" method was used in one rat. When urine flow from catheterized kidney reached a constant rate ≥ 0.15 ml/min, the catheter was occluded for 6 minutes, then 35 urine samples (12 μl each) were consecutively collected and the concentrations of sparfloxacin, sodium, inulin and PAH were quantified. In 3 other rats, the renal clearance method was used. Urine was collected from these rats for 10 minutes after the flow reached a constant rate ≥ 0.15 ml/min (no occlusion involved) and a blood sample was drawn midway through the collection period. The concentrations of sparfloxacin, inulin and PAH in the urine and blood of the rats was quantified. The results of the "stop flow" experiment indicated that unlike PAH, sparfloxacin is not secreted by the proximal tubules. Like sodium, sparfloxacin appeared to have been reabsorbed in the distal tubules. The renal clearance method showed the glomerular filtration rate of sparfloxacin to be 0.37 $\mu\text{g/min}$, resorption rate to be 0.187 $\mu\text{g/min}$, and urinary excretion rate to be 0.183 $\mu\text{g/min}$. The average general glomerular filtration rate in the rats was 0.772. The fraction of sparfloxacin not bound to plasma protein (40-55%) was filtered through the glomerulus, with about half absorbed in the distal tubules and the other half excreted in the urine.

***In Vitro* and *Ex Vivo* Intestinal Absorption and Secretion of Sparfloxacin (33rd ICACC Abstract 1463, Anaheim, 1992)**

Vol. 57, pp. 5-46-300 to 5-46-301

Summary: The transepithelial flux of radiolabeled sparfloxacin was studied in isolated rabbit duodenum, jejunum, and ileum. Secretion and absorption rates were not significantly different from one another in duodenum and jejunum, but there was significant net secretion in the ileum. In the human intestinal cell line CaCO-2, the secretion rate of sparfloxacin was also shown to be greater than the absorption rate, but it is unknown what clinical consequence this might have.

**Effect of Aluminum Hydroxide, an Antacid, on Pharmacokinetics of AT-4140
Report D124)**

Dated 1/24/92

Vol. 57, pp. 5-46-302 to 5-46-331

Summary: Male Sprague-Dawley rats were dosed orally via gavage with 20 mg/kg of sparfloxacin, enoxacin, or norfloxacin suspended in 0.5% tragacanth gum (n=12). Immediately following quinolone administration, either 100 mg/kg of aluminum hydroxide suspended in 0.5% tragacanth gum, or the vehicle alone, was administered orally via gavage to the rats. Blood samples were collected 0.25 to 8 hours after dosing and urine (sparfloxacin rats only) was collected for 24 hours after dosing. Concentrations of quinolones in plasma and urine were quantified using HPLC. In an *in situ* absorption study, sparfloxacin suspended in tragacanth gum was injected into ligated jejunum and a second injection of aluminum hydroxide (in the presence or absence of EDTA) or vehicle (with or without EDTA) followed immediately (n=5). The jejunum was removed 15 minutes after dosing, then washed with 0.05 M NaOH. The concentration of sparfloxacin in the jejunum wash was determined via HPLC.

The presence of aluminum hydroxide appeared to inhibit the absorption of the quinolones. C_{max} and AUC were lower for all of the quinolones when aluminum hydroxide was also administered to the rats. The biggest drops in these parameters were observed for norfloxacin (decreases of about 69%- AUC and 79%- C_{max}), followed by enoxacin (decreases of about 58%- AUC and 64%- C_{max}), with sparfloxacin absorption appearing to be somewhat less inhibited (about a 30% decrease of both AUC and C_{max}). Urinary excretion of sparfloxacin (unchanged plus glucuronide) went from $17.6 \pm 1.1\%$ of the total dose to $12.6 \pm 1.0\%$ of the total dose when aluminum hydroxide was administered, about a 29% decrease. The *in situ* study in the jejunum demonstrated that about $68.2 \pm 2.7\%$ of the sparfloxacin dose was absorbed in the absence of aluminum hydroxide, but only $43.8 \pm 3.9\%$ of the dose was absorbed when the antacid was added. If EDTA was added to the antacid before injection, sparfloxacin absorption returned to control levels. These data suggest that aluminum ion inhibits the absorption of sparfloxacin in the rat intestine.

**Effect of Antacids and Ferrous or Calcium Drugs on the Pharmacokinetics of
Sparfloxacin in Rats Report D129)**

Dated 6/30/95

Vol. 57, pp. 5-46-332 to 5-46-346

Summary: Male Sprague-Dawley rats (fasted) were dosed orally via gavage with 20 mg/kg of sparfloxacin suspended in 0.5% tragacanth gum. Immediately following quinolone

administration, 100 mg/kg of aluminum hydroxide, magnesium hydroxide, or iron sulfate, or 200 mg/kg of calcium gluconate suspended in 0.5% tragacanth gum, or the vehicle alone, was administered orally via gavage to the rats (6 animals per group). Blood samples were collected 0.25 to 8 hours after dosing and urine was collected for 24 hours after dosing. Concentrations of sparfloxacin in plasma and urine were quantified using HPLC. In an *in situ* absorption study, sparfloxacin suspended in tragacanth gum was injected into ligated jejunum and a second injection of one of the metal compounds above (in the presence or absence of EDTA) or vehicle (with or without EDTA) followed immediately (n=5). The jejunum was removed 15 minutes after dosing, then washed with 0.05 M NaOH. The concentration of sparfloxacin in the jejunum wash was determined via HPLC.

None of the metal compounds caused a significant change in the T_{max} or $T_{1/2}$ of sparfloxacin, but all except calcium gluconate were associated with reductions of C_{max} . Neither ferrous sulfate nor calcium gluconate was associated with a significant reduction of AUC. When C_{max} and AUC were reduced, urinary excretion of sparfloxacin was also, although the ratios of free drug to glucuronide conjugate in the urine were unchanged. The metal compounds, except calcium gluconate also reduced absorption of sparfloxacin in the jejunum *in situ*. In the absence of the metal compounds, absorption of sparfloxacin injected into the jejunum was 68.2% and in the presence of calcium gluconate was 70.9%, essentially unchanged. On the other hand, jejunal absorption of sparfloxacin in the presence of aluminum hydroxide was 43.8%, in the presence of magnesium hydroxide was 43.0%, and in the presence of ferrous sulfate was 56.0%. The inhibition of absorption was abrogated when EDTA was added to the metal compounds before they were injected into the jejunum.

Pharmacokinetic Parameters of Sparfloxacin Following a Single Oral Administration in the Presence or Absence of Various Metal Compounds (Mean $\pm$ SE)

	C_{max} ($\mu\text{g}/\text{ml}$)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{ml}$)	% Total Dose Excreted in Urine
Sparfloxacin Alone	1.73 $\pm$ 0.23	5.91 $\pm$ 0.83	17.7 %
Aluminum Hydroxide	1.21 $\pm$ 0.21	4.15 $\pm$ 0.60	12.6%
Magnesium Hydroxide	1.08 $\pm$ 0.13	3.89 $\pm$ 0.93	10.2%
Ferrous Sulfate	1.26 $\pm$ 0.16	5.01 $\pm$ 0.52	13.6%
Calcium Gluconate	1.80 $\pm$ 0.27	5.95 $\pm$ 0.72	18.3%

Effects of Quinolones on Theophylline Single-Dose Pharmacokinetics in β -Naphthoflavone Treated Rats: A Potential Model for Detecting a Quinolone/Theophylline Interaction
Report RR 764-01160)

Dated 4/12/89

Vol. 57, pp. 5-46-347 to 5-46-435

and

Study of the Effect of PD 124816, CI-960, and PD 131501 on Single-Dose Theophylline Pharmacokinetics in Rats
Report RR 764-001170)

Dated 4/20/89

Vol. 58, pp. 5-47-32 to 5-47-97

Summary: Both of these reports describe studies in young adult male Wistar rats that were pretreated with β -naphthoflavone (two daily 40 mg/kg intraperitoneal doses in corn oil) in order to maximize metabolism and clearance of theophylline. The investigators believed that this would increase the sensitivity of the animals to quinolone-induced inhibition of theophylline clearance. Two days following the last injection of β -naphthoflavone, rats (6 per treatment group) received an oral loading dose of the test fluoroquinolone (or vehicle, for control animals) followed by five maintenance doses at 2-hour intervals. Doses were selected to attempt to maintain a plasma quinolone level of about 10 μ g/ml. Three hours after the quinolone loading dose was administered, the rats were given 15 mg/kg of theophylline orally via gavage. Blood samples were drawn 0.5 hours before theophylline administration, then from 1 to 8 hours afterward. Plasma levels of theophylline and quinolones were quantified using HPLC. In the first study, the quinolones tested were enoxacin, ofloxacin, and ciprofloxacin, and in the second study, PD 124816, CI-960, and PD 131501 (sparfloxacin) were tested.

Quinolone Doses and Range of Blood Levels During Study

Drug	Loading Dose (mg/kg)	Maintenance Dose (mg/kg)	Mean Range of Blood Levels During Study (μ g/ml)
Enoxacin	400	100	9.0-12.0
Ofloxacin	100	25	5.8-10.8
Ciprofloxacin	200	50	2.5-5.0
PD 124816	400	100	2.7-3.4
CI-960	200	50	6.8-8.7
Sparfloxacin	200	50	5.8-9.3

Enoxacin and PD 124816 caused significant decreases in theophylline plasma clearance, concomitant with increased half life and AUC. CI-960 appeared to be a less potent inhibitor

of theophylline clearance than these two quinolones. Administration of ofloxacin was associated with non-statistically significant decrease (about 30%) in theophylline plasma clearance and AUC. Sparfloxacin and ciprofloxacin were not associated with alteration in theophylline pharmacokinetics, but it should be noted that the plasma concentration of ciprofloxacin was lower than the 10 $\mu\text{g/ml}$ target concentration.

Effect of AT-4140 on Pharmacokinetics of Theophylline and Caffeine in Rats Compared with Enoxacin, Ciprofloxacin, and Ofloxacin Report D123)

Dated 1/24/92

Vol. 58, pp. 5-47-1 to 5-47-31

Summary: Male Wistar rats (4-6 per treatment group) received a dose of quinolone drug 2 hours before, then 2 and 6 hours after a single oral administration of theophylline (15 mg/kg) or caffeine (25 mg/kg). The doses and routes of administration of the quinolones were as follows: sparfloxacin, 100 mg/kg, oral; enoxacin, 300 mg/kg, oral; ciprofloxacin, 50 mg/kg, intraperitoneal; and ofloxacin, 50 mg/kg, oral. The quinolone doses were selected to give target plasma concentrations of $\mu\text{g/ml}$. Blood samples were drawn 1-24 hours after xanthine dosing and urine was collected from the theophylline-dosed rats for 24 hours after administration. Xanthine levels in plasma and urine were determined via HPLC. Sparfloxacin treatment did not alter plasma kinetics or urinary excretion of theophylline in these rats, nor did it alter caffeine plasma kinetics. Enoxacin and ciprofloxacin almost doubled theophylline half life, but ofloxacin treatment was associated with only a slight increase in this parameter. Enoxacin also increased the half life of caffeine by a factor of 2.5 (neither ciprofloxacin nor ofloxacin were tested with caffeine).

Effect of CI-978 (AT-4140), a New Quinolone Antibacterial Agent, On Hexobarbital Sleeping Time in Mice Report GP 87-0104 and Report RR 740-02720)

Dated 10/24/89

Dated 6/1/87

Vol. 58, pp. 5-47-98 to 5-47-103

Summary: Sparfloxacin suspended in 0.5% tragacanth solution was administered to male Std:ddY mice at doses of 300 and 1000 mg/kg via oral gavage. One hour later, 80 mg/kg of hexobarbital was injected intraperitoneally. Sleeping time (loss of righting reflex, about 45-50 minutes) was not affected by sparfloxacin pretreatment.

Disposition and Metabolism of [¹⁴C]Sparfloxacin in the Rat (Arzneim.-Forsch./Drug Res. 41(II): 747-759, 1991

Vol. 58, pp. 5-47-363 to 5-47-376

and

Pharmacokinetics of a Novel Quinolone, AT-4140, in Animals (Antimicrobial Agents and Chemotherapy, January 1990, 34 No.1: 89-93.

Vol. 58, pp. 5-47-377 to 5-47-382

and

Disposition and Metabolism of [¹⁴C]Sparfloxacin After Repeated Administration in the Rat (Arzneim.-Forsch./Drug Res. 41(II): 760-763, 1991

Vol. 58, 5-47-383 to 5-47-387

Summary: These three appear to be publications of several pharmacokinetic studies performed by the sponsor that have been submitted to the division as individual reports (above).

SUMMARY AND EVALUATION:

Sparfloxacin is well absorbed from the GI tract in animals and man. Bioavailability in humans, dogs, and rats is about 90%, 80%, and 70%, respectively. The drug does not appear to be biotransformed very differently between species as only unchanged sparfloxacin and its glucuronide conjugate were detected in urine from humans, rats, dogs, and monkeys. Both unchanged sparfloxacin and its glucuronide conjugate were found in the plasma and bile of the rat and human, but only unchanged drug was detected in the feces of these species, presumably due to the presence of bacteria capable of cleaving the bond between sparfloxacin and glucuronide. The plasma half life of sparfloxacin in humans, however, appears to be longer than in animal species used for nonclinical drug testing. For a single sparfloxacin dose of about 5 mg/kg, the approximate plasma half lives in various species were as follows: human, 20 hours, dog, 8-10 hours, monkey, 5-6 hours, rat, 3-5 hours, and mouse, 4 hours.

Single doses of sparfloxacin were relatively non-toxic via the oral route of

administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 600 mg/kg in the dog. Clinical signs observed included inactivity in mice and dogs, diarrhea in both rodent species, and vomiting, salivation, and tremors in dogs. These effects disappeared by 24 hours after dosing, or 5 days after dosing in the case of diarrhea. Although food consumption and body weight in sparfloxacin-treated rodents showed an initial decrease, animals recovered within a week. Additionally, single doses of sparfloxacin up to 2000 mg/kg were administered subcutaneously or intraperitoneally to mice and rats with no mortality.

Mice were fed sparfloxacin in the diet for 2 weeks at doses of 250-2000 mg/kg/day without mortality. No obvious target organ for toxicity was identified, but increased cecal weights were observed in both sexes for all dose groups, increased heart weights at doses $\geq$ 100 mg/kg, and increased liver weights at the highest dose level. Microscopically, vacuolated macrophages were associated with yellow discoloration of several tissues including lymph nodes, liver, spleen, and small intestine at 2000 mg/kg. Mice were fed a sparfloxacin-containing diet for 13 weeks without significant toxicity at doses of 62.5-250 mg/kg/day where the only anomalies at necropsy reported were increased cecal weights (all dose groups), slightly increased liver weights (males only) at doses $\geq$ 125 mg/kg/day, and yellow discoloration of lymph nodes in occasional high dose mice.

No mortality was observed in rats dosed with sparfloxacin orally via gavage daily for 4 weeks at doses from 12.5-800 mg/kg. Doses $\geq$ 200 mg/kg were associated with soft stools, bloody discharge and increased cecal weights. Microscopically, rats dosed for 4 weeks with $>$ 200 mg/kg of sparfloxacin exhibited blisters on the femoral cartilage, yellow discoloration and macrophage/neutrophil infiltration of mesenteric lymph nodes and erosion and cellular infiltration of the rectal mucosa. These effects were observed even after a two week recovery period. The NOEL in the 4 week rat study was 50 mg/kg/day. Rats were also dosed daily with 6-400 mg/kg sparfloxacin via oral gavage for 26 weeks. Mortality was observed at the high dose and the NOEL in this study was 25 mg/kg/day. At the highest dose, increases in serum enzyme levels such as the transaminases and lactate dehydrogenase, as well as increased bilirubin were indicative of liver toxicity. Increased lactate dehydrogenase was also observed at 100 mg/kg. Other toxicity-associated observations in the high dose rats included soft stools at the beginning of the study, swollen joints (histopathology showed arthritis and inflammation of capsule and bursa), increased liver, spleen, heart, and kidney weights, yellow discoloration of these and other tissues associated with mononuclear cell infiltration. It is difficult to determine whether the joint lesions observed in this study are due to the specific arthrotoxic potential of sparfloxacin or deposits of insoluble drug that induced a secondary inflammation. The yellow discoloration seen in tissues from this and other experiments is theorized to be accumulation of sparfloxacin to levels greater than what is soluble in the tissue, sometimes leading to macrophage accumulation and inflammation of the tissue at especially high doses.

Signs of toxicity observed in dogs given daily oral 5-45 mg/kg doses of sparfloxacin via gavage for 4 weeks were vomiting and significant prolongation of the Q-T interval at the highest dose. One high dose dog also had erosion of the articular cartilage. Blood urea nitrogen was increased at doses $\geq$ 15 mg/kg and increased creatinine levels were observed in the high dose animals; however, histopathologic evaluation did not reveal kidney lesions. When daily oral sparfloxacin doses of 4-25 mg/kg were given to dogs for 26 weeks, vomiting was observed at doses $\geq$ 10 mg/kg and Q-T interval prolongation was seen in the high dose group. There was, however, no mortality. At scheduled necropsy, yellow discoloration of

several tissues (gastric mucosa, duodenum, lymph nodes) was observed. The NOELs in the 4- and 26-week studies were doses of 5 and 4 mg/kg/day, respectively.

The potential cardiotoxicity of sparfloxacin was explored further in the dog. In one study, dogs were dosed orally via gavage with 300 mg/kg of sparfloxacin daily for 7 days. Electrocardiograms recorded during the treatment period demonstrated prolonged Q-T in all dogs (observed following the first dose of drug in most cases) and ventricular arrhythmia in 1/4 dogs on 2 days. In another 7-day study, Q-T prolongation was observed in dogs dosed orally with 150 mg/kg, but not 50 mg/kg. Arrhythmia was also observed in 1/2 of these dogs at the higher dose. When sparfloxacin was administered intravenously to dogs, there was a dose-related increase in Q-T prolongation between 3 and 30 mg/kg. Q-T prolongation was seen in rabbits given an intravenous bolus 30 mg/kg dose of sparfloxacin.

Like other members of the fluoroquinolone class, sparfloxacin has been shown to induce cartilage lesions in juvenile animals. Three-month old beagle dogs given 25 mg/kg of sparfloxacin daily for 7 days had lesions on the shoulder, elbow, and hip joints.

Sparfloxacin did not appear to have a great potential for ocular toxicity. In cats dosed orally with 60 mg/kg/day for 14 days, histopathological examination did not reveal ocular lesions, although electroretinography was difficult to interpret due to large variability. Ophthalmologic examination did not reveal evidence of sparfloxacin-associated ocular toxicity in Brown Norway rats dosed orally with 5 mg/kg/day for 45 days, albino rats dosed intravenously with 50 mg/kg daily for 4 weeks, dogs dosed intravenously with 30 mg/kg daily for 4 weeks, or albino mice that received up to 250 mg/kg/day via the diet for 104 weeks. However, albino mice receiving single 50 or 100 mg/kg doses of sparfloxacin via oral gavage exhibited retinal damage if exposed to UVA for 2 to 4 hours immediately after dosing.

Although several fluoroquinolones have been reported to cause convulsions in laboratory animals (and occasionally humans), sparfloxacin did not appear to be especially potent in this regard. Convulsions were not observed in dogs (a particularly sensitive animal model) at oral doses up to 45 mg/kg for 4 weeks or 25 mg/kg for 26 weeks, but were observed in dogs that received oral doses of 300 mg/kg for 7 days. As noted above, convulsions were not observed in dogs that received a single 600 mg/kg oral dose of sparfloxacin, but the animals did exhibit tremors. No convulsions were observed in dogs receiving intravenous doses (5 minute infusion) up to 30 mg/kg daily for 4 weeks. Mice that received single intraperitoneal doses of sparfloxacin up to 2000 mg/kg with or without a concomitant 100 mg/kg dose of biphenylacetic acid (the active metabolite of fenbufen) did not exhibit convulsions. However, intraperitoneal administration of 5 mg/kg enoxacin, 10 mg/kg norfloxacin or lomefloxacin, or 30 mg/kg of ciprofloxacin did induce convulsions when given with 100 mg/kg of biphenylacetic acid.

The results of *in vitro* genotoxicity tests with sparfloxacin were equivocal. The compound did not induce reverse mutation at the *his* locus of *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 in the absence or presence of metabolic activation. Similar tests in the *E. coli* strain WP2uvrA were also negative. However, mutation was induced in the *S. typhimurium* strain TA102 in the absence of metabolic activation. In mammalian cells, sparfloxacin treatment of V-79 Chinese hamster lung cells did not induce mutations at the HGPRT locus in the absence or presence of metabolic activation; however, chromosome abnormalities were observed in Chinese hamster lung cells (CHL/IU) incubated with sparfloxacin. *In vivo*, micronuclei or chromosome aberrations were not observed in bone marrow cells harvested from mice dosed with up to 5000 mg/kg of sparfloxacin via oral

gavage. Two year bioassays performed with rats and mice given up to 200 and 250 mg/kg/day, respectively, of sparfloxacin via the diet did not reveal a carcinogenic potential for this drug.

Sparfloxacin was teratogenic in the rat at maternally toxic oral doses ≥ 300 mg/kg/day given during the period of organogenesis. Ventricular septal defects were observed in some pups. Teratogenicity was not observed in the rabbit or monkey at maternally toxic oral doses of 90 or 50 mg/kg, respectively, when administered daily during organogenesis. Sparfloxacin was detected in rat and monkey fetuses at exposure levels greater than observed for maternal plasma. Additionally, sparfloxacin did not adversely affect fertility or reproductive performance of male and female rats given oral doses up to 500 mg/kg/day for at least 15 days prior to mating and continued throughout mating and gestation.

Sparfloxacin was phototoxic in some animal models, but did not appear to as potent as lomefloxacin, an FDA-approved fluoroquinolone drug product, in this regard. In a 90-day dose range finding study for the photocarcinogenicity study (to be submitted by the sponsor as a phase IV obligation), hairless mice dosed orally with 25-100 mg/kg of sparfloxacin 5 days a week and exposed to 0.27 of the MED for UVA light exhibited dose-related erythema and thickening, wrinkling, and dryness of skin. Hairless mice dosed with 12.5 mg/kg for 90 days with the same level of UVA exposure had epidermal hyperplasia that was identified histologically, but did not exhibit erythema during the study. Albino rats dosed orally with 50 mg/kg/day of sparfloxacin, then exposed to UVA for 3 hours each day for one week did not demonstrate erythema or edema of auricular skin, but those given 100 or 200 mg/kg had very slight to moderate dose-related phototoxic responses. Depilated albino guinea pigs given single oral doses of sparfloxacin, then exposed to UVA for 2 hours demonstrated slight to moderate erythema by 24 hours after exposure at the 16 mg/kg dose level and severe erythema at the 80 mg/kg dose level. Topical application of sparfloxacin in a Vaseline vehicle to depilated albino guinea pigs did not appear to be phototoxic or photoallergenic in conjunction with exposure to UVA. Orally administered sparfloxacin also did not appear to be photoallergenic in albino guinea pigs. In albino mice given single doses of fluoroquinolones, then exposed to UVA, the doses of drug causing a phototoxic response in the auricular skin of 50% of the animals was 70.7 mg/kg for sparfloxacin, 61.6 mg/kg for lomefloxacin, and 689.7 for ofloxacin. It should be noted that phototoxicity of sparfloxacin has been a serious clinical problem in Europe.

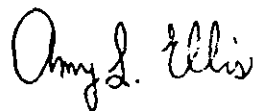
Except for the prolongation of the Q-T interval, sparfloxacin did not induce any toxicities in the nonclinical studies that would not be expected from a member of the fluoroquinolone drug class. These include phototoxicity, juvenile arthrotoxicity, and convulsions at high doses. None of the latter toxicities appeared to be worse in animals treated with sparfloxacin compared to some other approved fluoroquinolone antibiotics.

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RE JATION:

In animal models, the phototoxicity of sparfloxacin appears to be no worse than that of lomefloxacin, another fluoroquinolone approved for human use. The photocarcinogenic potential of sparfloxacin is being explored by the sponsor using a hairless mouse model and these data will be submitted to the division as a Phase IV commitment. The label contains an adequate warning about this potentially serious toxicity, along with a warning that this drug has been demonstrated to prolong the Q-T interval and should be used with caution, or avoided, in individuals who are prone to arrhythmia or are taking other drugs that prolong the Q-T. Appropriate warnings regarding sparfloxacin's arthrotoxic potential in juveniles and tendon rupture in adults are also included in the label. With these caveats, the pharmacologist does not object to the approval of the sparfloxacin NDA.



Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Orig. IND
cc:
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HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Ellis
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HFD-520/MO Team Ldr/Albuerne
HFD-520/Chem/Shetty
HFD-520/CSO/LeSane
HFD-520/Micro/Aitaie
HFD-530/Pharm/Hastings

Concurrence Only:
HFD-520/REOsterberg
HFD-520/LGavrilovich

Stat

STATISTICAL REVIEW AND EVALUATION

NDA: 20-677
Generic Drug Name: Sparfloxacin
Drug Trade Name: Zagam®
Formulation: Oral tablets
Drug Class: 1-S
Applicant: Rhône-Poulenc Rorer Pharmaceuticals, Inc.

OCT 30 1996

Indications: I. Community Acquired Pneumonia — See Dr. Sue Bell's review report
II. Acute Bacterial Exacerbations of Chronic Bronchitis

Documents Reviewed: NDA volumes 1.329-1.349 dated December 27, 1995
NDA volumes 1.350-1.366 dated December 27, 1995
NDA volume 1.386-1.404 dated December 27, 1995
NDA volume 1.496, 1.497, 1.511, 1.512 dated December 27, 1995

Type of Review Clinical

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II. ACUTE BACTERIAL EXACERBATIONS OF CHRONIC BRONCHITIS

II.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 356, as evidence to support sparfloxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 356 was a double-blind, randomized, comparative, multicenter (USA and Canada) clinical trial which compared the efficacy and safety of sparfloxacin at a 400 mg loading dose followed by 200 mg once a day versus ofloxacin at a 400 mg dose twice a day (b.i.d.), each for 10 days, in the treatment of acute bacterial exacerbations of chronic bronchitis. It was initiated on November 12, 1992 and completed on October 18, 1994.

II.B. STUDY 356

II.B.1 METHODS

In Study 356, a total of approximately 850 patients was enrolled to achieve 380 clinically and bacteriologically evaluable patients. Patients meeting the inclusion/exclusion criteria were randomized to one of the two treatment groups in a 1:1 ratio. A double-dummy system was used such that matching comparator placebos were given concurrently with the active drug during the treatment period. Eligible study population consisted of male and female patients, and were 18 years of age or older with an acute bacterial exacerbation of chronic bronchitis. Patients who met the post-admission exclusion criteria at any time during the study were removed from the study. Patients who met the inclusion/exclusion criteria were to be asked to give written informed consent for the study and were required to give informed consent before any procedure was performed solely for study purposes. Study visits were scheduled for Visit 1 (baseline), Visit 2 (Day 4±1 of treatment), Visit 3 (Day 20±3: 10 days post-treatment), and Visit 4 (Day 38±7: 28 days post-treatment). The investigators assessed the patient's sign and symptoms of the acute bacterial exacerbation of chronic bronchitis at Visits 1, 2, 3, and 4. An assessment of the patient's response to study drug treatment was to be made at Visit 3 (or premature discontinuation before Visit 3). Recurrence of infection was to be determined at Visit 4 (or premature discontinuation after Visit 3). Safety parameters included adverse clinical and laboratory events, changes in electrocardiogram (ECG), vital sign, and physical examination findings. Investigators were expected to review each patient's concomitant medications to identify potential drug interactions. All medication taken was to be recorded on the Case Report Form. The two treatment regimens were administered as below:

		Day 1	Days 2-10
<u>Sparfloxacin Group</u>	AM	2×200 mg sparfloxacin tablets	1×200 mg sparfloxacin tablet
	Dose:	1×ofloxacin placebo tablet	1×ofloxacin placebo tablet
	PM	1×ofloxacin placebo tablet	1×ofloxacin placebo tablet
	Dose:		
<u>Ofloxacin Group</u>	AM	1×400 mg ofloxacin tablet	1×400 mg ofloxacin tablet
	Dose:	2×sparfloxacin placebo tablets	1×sparfloxacin placebo tablet
	PM	1×400 mg ofloxacin tablet	1×400 mg ofloxacin tablet
	Dose:		

Table II-1 demonstrates during-treatment, and post-treatment procedures which were specified by the protocol.

TABLE II-1: STUDY 356: SCHEDULE OF PROCEDURES AND OBSERVATIONS				
Procedure	During Treatment Visits		Post Treatment Visits	
	(Baseline) Visit 1	(Day 4±1) Visit 2	(Day 20±3) Visit 3	(Day 38±7) Visit 4
Verification of Inclusion/Exclusion	X			
Informed Consent	X			
Medical History	X			
Physical Examination	X	X	X	X
Height	X			
Weight	X		X	
Clinical Evaluation of Symptoms	X	X	X	X
Pregnancy Test at Site	X			
Sputum Gram Stain at Site	X			
SciCor				
Hematology, Chemistry, & Urinalysis	X	X	X	X
Serum Pregnancy Test	X			
Sputum Gram Stain & Culture	X	X	X	X
Throat Swab	X		X	X
Theophylline Concentration	X	X	X	
Serology	X	X	X	X
Digoxin Concentration	X	X	X	
ECG	X	X	X	X
Chest X-ray	X			
FVC and FEV	X	X	X	X
Assessment of Clinical Response			X	
Assessment of Recurrence				X
Monitor Adverse Events		X	X	X
Assessment of Patient Compliance		X	X	

EFFICACY EVALUATION

There were two major time points to evaluate the efficacy:

1. Test-of-cure: either Visit 3 or when patients prematurely discontinued from the study before Visit 3;
2. Late follow-up: either Visit 4 or when the patient prematurely discontinued after Visit 3.

Patients were clinically and bacteriologically assessed at each of the two time points. Clinical response and clinical recurrence, both based on the investigator's clinical evaluation of signs and symptoms of the acute bacterial exacerbation of chronic bronchitis, were assessed by the investigator. By-pathogen and by-patient bacteriologic relapse/reinfection was derived from the by-patient bacteriologic response, and overall response was derived from the clinical response and the by-patient bacteriologic response.

APPLICANT: The primary efficacy parameter was the overall response rate, which was based on the clinical response rate and the bacteriologic response rate for each patient at test-of-cure. Each patient's overall response was classified as success, failure, and indeterminate. Since the overall response rate was based

on bacteriologic response as well as clinical response, the bacteriologically evaluate patient population was used for this primary parameter.

Secondary efficacy parameters included clinical response at test-of-cure (all-treated, clinically evaluable, and the bacteriologically evaluable populations); clinical recurrence at late follow-up (all-treated and clinically evaluable populations); by-patient bacteriologic response at late follow-up (all-treated and the bacteriologically evaluable populations); by-pathogen bacteriologic response at test-of-cure (all-treated and the bacteriologically evaluable populations); bacteriologic relapse/reinfection at late follow-up (all-treated and the bacteriologically evaluable populations).

MEDICAL OFFICER: At the test-of-cure visit: clinical responses were classified as cure, failure, improvement, and indeterminate; bacteriologic responses were classified as eradicated, indeterminate, multiple pathogens with partial eradication, persist, presumed eradicated, presumed persist, and superinfection. At the late follow-up visit: clinical sustained/delayed responses were classified as delayed cure, early failure, indeterminate, recurrence, sustained cure, and sustained improvement; bacteriologic sustained/delayed responses were classified as early persistence, indeterminate, relapse, and sustained eradicated.

It is noteworthy that the Medical Officer clinically evaluable patients were all with baseline pathogens. The four primary efficacy parameters were defined as follows:

1. The cure+improvement rate of clinical response at test-of-cure;
2. The all eradicated (eradicated+presumed eradicated) rate of bacteriologic response at test-of-cure;
3. The sustained cure+delayed cure+sustained improvement rate of clinical sustained/delayed response at late follow-up;
4. The sustained eradicated rate of bacteriologic sustained/delayed response at late follow-up.

For every organism identified as a baseline pathogen from sputum cultures for each patient, a determination was made as to the by-pathogen bacteriological response. The by-pathogen bacteriologic response was assessed at test-of-cure. Each pathogen presented at baseline was classified as eradicated, presumed eradicated, persistent, presumed persistent, superinfection, colonization, and indeterminate. The clinically and bacteriologically evaluable populations were summarized, respectively, with respect to the eradicated+presumed eradicated rate of by-pathogen bacteriologic response.

Even though the definitions of efficacy parameters were not always identical between the Applicant and the Medical Officer, this reviewer basically adopts the Medical Officer's in efficacy evaluation. Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All patients who received at least one dose of study medication were evaluable for safety (For this study, this was all of the enrolled patients). The data collected for evaluation of safety included results of medical history review, physical examinations, vital sign measurements, QT_c interval measurements, chest X-ray examination, reports of adverse clinical events, and clinical laboratory measurements.

Adverse clinical events were defined as any undesirable event associated with the use of a drug, whether or not considered drug related, and included any side effect, injury, toxicity, or sensitivity reaction. It also included any undesirable clinical or laboratory event which was not normally observed in the patient. A serious adverse event included any event, including lack of efficacy, that was fatal or life-threatening, was permanently or severely disabling, required or prolonged inpatient hospitalization, or was a congenital anomaly, cancer, and overdose. For each adverse event, the investigator was to determine the relationship to study drug and the severity based on designated definitions. All adverse events, regardless of severity, would be followed up by the investigator until satisfactory resolution.

STATISTICAL METHODS

The comparisons of particular interest in the study were conducted between sparfloxacin and ofloxacin. The clinical and bacteriologic patient populations were defined for the purpose of data analysis. There were four primary efficacy endpoints defined by the Medical Officer: for the clinically evaluable population with bacteriologic pathogen, (1) clinically response at test-of-cure; (2) clinically sustained/delayed response at late follow-up; for the bacteriologic evaluable population, (3) bacteriologic response at test-of-cure; (4) bacteriologic sustained/delayed response at late follow-up.

Prior to performing efficacy analyses, the reviewer assessed the comparability of the treatment groups with respect to demographic characteristics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using the Chi-square test.

Equivalence of the two treatment groups with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference (sparfloxacin minus ofloxacin) in proportions. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged by the draft DAIDP "Points to Consider" pertaining to results of confidence intervals.

Subset analyses by gender, age, and race were performed for the Medical Officer's efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all patients who received at least one dose of study drug. This reviewer conducted safety analyses with the incidence rates of the following variables: patients with adverse events, adverse events related to study medication, discontinuation due to adverse events, serious adverse events, and adverse laboratory events. The comparisons of the differences in the incidence rates between the two treatment groups were performed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the tests of homogeneity.

II.B.2. RESULTS

An actual total of 798 patients was enrolled across centers in USA (66 investigators) and Canada (2 investigators) between November 12, 1992 and October 18, 1994.

APPLICANT

Table II-2 is the Applicant's summary of the primary and secondary efficacy results for the clinically and bacteriologically evaluable patients. The Applicant did not incorporate a continuity correction into the calculation of confidence intervals. Note that after being made the continuity correction, the 95% confidence interval for the patient bacteriologic response at test-of-cure was $_{253, 251} (-10.4\%, 1.0\%)$ ~~87.4%, 92.0%~~. Since the lower bound was less than -10%, the confidence interval did not meet the requirement for establishing equivalence remarked by the draft DAIDP "Points to Consider" pertaining to results of confidence intervals.

TABLE II-2: STUDY 356: SUMMARY OF EFFICACY RESULTS OF THE APPLICANT			
Efficacy Parameter (Population and Time Point)	Sparfloxacin	Ofloxacin	95% C.I.
Clinical Response Rate-Cured+Improved	290/335 (86.6%)	296/337 (87.8%)	-6.3%, 3.8%
Clinical Cure Rate (clinically evaluable, at test-of-cure)	194/335 (57.9%)	207/337 (61.4%)	-10.9%, 3.9%
Clinical Recurrence Rate (clinically evaluable, at late follow-up)	25/286 (8.7%)	30/288 (10.4%)	ND
By-Pathogen Bacteriologic Response Rate Eradicated+Presumed Eradicated (bacteriologically evaluable, at test-of-cure)	339/377 (89.9%)	331/358 (92.5%)	ND
By-Patient Bacteriologic Response Rate Eradicated+Presumed Eradicated (bacteriologically evaluable, at test-of-cure)	221/253 (87.4%)	231/251 (92.0%)	-10.0%, 0.6%
Bacteriologic Relapse Rate	11/206 (5.3%)	16/206 (7.8%)	ND
Reinfection Rate	2/206 (1.0%)	2/206 (1.0%)	ND
Relapse+Reinfection Rate (bacteriologically evaluable, at late follow-up)	4/206 (1.9%)	4/206 (1.9%)	ND
Overall Response Rate Cured or Improved and Eradicated or Presumed Eradicated (bacteriologically evaluable, at test-of-cure)	216/253 (85.4%)	223/251 (88.8%)	-9.3%, 2.4%
ND: not done			

MEDICAL OFFICER

The number and percentage of the clinically and bacteriologically evaluable patients at two post treatment visits included in each analysis group, evaluated by the Medical Officer, are presented in Table II-3. There was no statistically significant difference with respect to the percentage of patients in each treatment group.

TABLE II-3: STUDY 356: NUMBER OF PATIENTS EVALUATED BY THE MEDICAL OFFICER INCLUDED IN PER TREATMENT GROUP		
Treatment Group for Clinical Response	Patients Included	
	Sparfloxacin 400/200 mg QD (N=395)	Ofloxacin 400 mg BID (N=403)
At Test-of-Cure		
*M.O. Clinically Evaluable	279 (70.6%)	276 (68.3%)
M.O. Bacteriologically Evaluable	253 (64.1%)	251 (62.3%)
At Late Follow-up		
*M.O. Clinically Evaluable with Sustained/Delayed Response	275 (69.6%)	270 (67.0%)
M.O. Bacteriologically Evaluable with Sustained/Delayed Response	233 (59.0%)	223 (55.3%)

*: Clinical evaluable with baseline pathogen.

The clinical response at test-of-cure of the Medical Officer clinically evaluable patients and the bacteriologic response at test-of-cure of the Medical Officer bacteriologically evaluable patients are presented in Tables II-4 and II-5, respectively. Confidence interval results showed that sparfloxacin was therapeutically equivalent to ofloxacin with respect to the cure+improvement rate of clinical response, however, they were not therapeutically equivalent with respect to the all eradicated rate of bacteriologic response.

Analyses of the clinical sustained/delayed response at late follow-up of the Medical Officer clinically evaluable patients and the bacteriologic sustained/delayed responses at late follow-up of the Medical Officer bacteriologically evaluable patients are displayed in Tables II-6 and II-7, respectively. Confidence interval results from both analyses showed that sparfloxacin was therapeutically equivalent to ofloxacin with respect to the sustained cure+delayed cure+sustained improvement rate of clinical sustained/delayed response and the sustained eradicated rate of bacteriologic sustained/delayed response.

Subset analyses by gender, age, and race as per clinical and bacteriologic response at test-of-cure in the Medical Officer evaluable patients are presented in Tables II-8 and II-9, respectively. With regard to clinical response, significant heterogeneity of treatment effects was detected between the age subgroups, and the treatment effect favored sparfloxacin in younger patients. Significant heterogeneity of treatment effects also existed between the race subgroups, and the treatment effect favored sparfloxacin in nonwhite patients. Results showed that gender did not take an effect on the clinical response at test-of-cure. Results of bacteriologic response were consistent across all subgroups except the race subgroups in which the treatment effect favored sparfloxacin in nonwhite patients.

Subset analyses by gender, age, and race as per clinical and bacteriologic sustained/delayed responses in the Medical Officer evaluable patients at the late follow-up visit are presented in Tables II-10 and II-11, respectively. With regard to clinical response, significant heterogeneity of treatment effects was detected between the age subgroups, and the treatment effect favored sparfloxacin in younger patients. Significant heterogeneity of treatment effect existed between the race subgroups for bacteriologic response, for which the treatment effect favored sparfloxacin in nonwhite patients.

TABLE II-4: STUDY 356: CLINICAL RESPONSE OF THE MEDICAL OFFICER CLINICALLY EVALUABLE PATIENTS AT TEST-OF-CURE

Clinical Response	Sparfloxacin (N=279)	Ofloxacin (N=276)	95% Confidence Interval Sparfloxacin vs Ofloxacin
Cure	171 (61.3%)	176 (63.8%)	-2.5% (-10.9%, 5.9%)
Cure+Improvement	244 (87.5%)	245 (88.8%)	-1.3% (-7.1%, 4.4%)

TABLE II-5: STUDY 356: BACTERIOLOGIC RESPONSE OF THE MEDICAL OFFICER BACTERIOLOGICALLY EVALUABLE PATIENTS AT TEST-OF-CURE

Bacteriologic Response	Sparfloxacin (N=253)	Ofloxacin (N=251)	95% Confidence Interval Sparfloxacin vs Ofloxacin
Eradicated	31 (12.3%)	37 (14.7%)	-2.5% (-8.8%, 3.9%)
All Eradicated	221 (87.4%)	231 (92.0%)	-4.7% (-10.4%, 1.0%)

TABLE II-6: STUDY 356: CLINICAL SUSTAINED/DELAYED RESPONSE OF THE MEDICAL OFFICER CLINICALLY EVALUABLE PATIENTS AT LATE FOLLOW-UP

Clinical Response	Sparfloxacin (N=275)	Ofloxacin (N=270)	95% Confidence Interval Sparfloxacin vs Ofloxacin
Sust. Cure	157 (57.1%)	160 (59.3%)	-2.2% (-10.8%, 6.5%)
Sust.Cure+Del.Cure	186 (67.6%)	188 (69.6%)	-2.0% (-10.1%, 6.2%)
Sust.Cure+Del.Cure+Sust.Impr	219 (79.6%)	214 (79.3%)	0.4% (-6.8%, 7.5%)

TABLE II-7: STUDY 356: BACTERIOLOGIC SUSTAINED/DELAYED RESPONSE OF THE MEDICAL OFFICER BACTERIOLOGICALLY EVALUABLE PATIENTS AT LATE FOLLOW-UP

Bacteriologic Response	Sparfloxacin (N=233)	Ofloxacin (N=223)	95% Confidence Interval Sparfloxacin vs Ofloxacin
Sustained Eradicated	188 (80.7%)	185 (83.0%)	-2.3% (-9.8%, 5.2%)

TABLE II-8: STUDY 356: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CURE&IMPROVEMENT RATE OF THE MEDICAL OFFICER CLINICALLY EVALUABLE PATIENTS AT TEST-OF-CURE

Subset	Sparfloxacin (N=279)	Ofloxacin (N=276)	95% C.I.	P-value Breslow-Day's
Male	124/143 (86.7%)	137/150 (91.3%)	(-12.5%, 3.2%)	0.183
Female	120/136 (88.2%)	108/126 (85.7%)	(-6.4%, 11.4%)	
<65	178/197 (90.4%)	171/195 (87.7%)	(-4.0%, 9.4%)	0.034
≥65	66/82 (80.5%)	74/81 (91.4%)	(-22.6%, 0.9%)	
White	189/221 (85.5%)	189/209 (90.4%)	(-11.5%, 1.7%)	0.013
Nonwhite	55/58 (95.6%)	56/67 (87.5%)	(-0.9%, 23.4%)	

TABLE II-9: STUDY 356: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF ALL ERADICATED RATE OF THE MEDICAL OFFICER BACTERIOLOGICALLY EVALUABLE PATIENTS AT TEST-OF-CURE

Subset	Sparfloxacin (N=253)	Ofloxacin (N=251)	95% C.I.	P-value Breslow-Day's
Male	111/129 (86.0%)	126/136 (92.6%)	(-14.8%, 1.6%)	0.480
Female	110/124 (88.7%)	105/115 (91.3%)	(-11.0%, 5.8%)	
<65	160/179 (89.4%)	162/177 (91.5%)	(-8.8%, 4.5%)	0.207
≥65	61/74 (82.4%)	69/74 (93.2%)	(-22.6%, 0.9%)	
White	171/202 (84.7%)	181/192 (94.3%)	(-16.1%, -3.2%)	0.001
Nonwhite	50/51 (97.5%)	50/59 (90.5%)	(1.5%, 25.1%)	

TABLE II-10: STUDY 356: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF SUST.CURE+DEL.CURE+SUST.IMPROVEMENT RATE OF THE MEDICAL OFFICER CLINICALLY EVALUABLE PATIENTS WITH SUSTAINED/DELAYED RESPONSE AT LATE FOLLOW-UP

Subset	Sparfloxacin (N=275)	Ofloxacin (N=270)	95% C.I.	P-value Breslow-Day's
Male	113/142 (79.6%)	120/147 (81.6%)	(-11.9%, 7.3%)	0.446
Female	106/133 (79.7%)	94/123 (76.4%)	(-7.7%, 14.2%)	
<65	162/193 (83.9%)	152/190 (80.0%)	(-4.3%, 12.2%)	0.128
≥65	57/82 (69.5%)	62/80 (77.5%)	(-22.8%, 6.8%)	
White	169/219 (77.2%)	159/203 (78.3%)	(-9.6%, 7.3%)	0.253
Nonwhite	50/56 (88.9%)	55/67 (85.4%)	(-6.7%, 21.1%)	

TABLE II-11: STUDY 356: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF SUSTAINED ERADICATED RATE OF THE MEDICAL OFFICER BACTERIOLOGICALLY EVALUABLE PATIENTS WITH SUSTAINED/DELAYED RESPONSE AT LATE FOLLOW-UP				
Subset	Sparfloxacin (N=233)	Ofloxacin (N=223)	95% C.I.	P-value Breslow-Day's
Male	92/116 (79.3%)	106/126 (84.1%)	(-15.4%, 5.8%)	0.455
Female	98/117 (82.1%)	79/97 (81.4%)	(-10.7%, 12.0%)	
<65	139/168 (83.7%)	133/156 (85.3%)	(-10.0%, 7.0%)	0.804
≥65	49/67 (73.1%)	52/67 (77.6%)	(-20.5%, 11.6%)	
White	146/188 (77.7%)	142/170 (83.5%)	(-14.6%, 2.8%)	0.029
Nonwhite	42/45 (91.9%)	43/53 (86.5%)	(-2.7%, 27.10%)	

Analyses of the by-pathogen bacteriologic response for the most frequently isolated baseline pathogens of the Medical Officer clinically evaluable patients are displayed in Table II-12, respectively. Analyses of the by-pathogen bacteriologic response for the most frequently isolated baseline pathogens of the Medical Officer bacteriologically evaluable patients are displayed in Tables II-13.

TABLE II-12: STUDY 356: BY-PATHOGEN BACTERIOLOGICAL RESPONSE FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS OF THE MEDICAL OFFICER CLINICALLY EVALUABLE PATIENTS			
Pathogen	Sparfloxacin	Ofloxacin	95% Confidence Interval Sparfloxacin vs Ofloxacin
<i>C. pneumoniae</i>	39/47 (83.0%)	41/46 (89.1%)	-6.2% (-22.3%, 10.0%)
<i>E. cloacae</i>	13/14 (92.9%)	12/15 (80.0%)	12.9% (-18.4%, 44.1%)
<i>H. influenzae</i>	57/64 (89.1%)	71/75 (94.7%)	-5.6% (-16.2%, 5.0%)
<i>H. parainfluenzae</i>	120/126 (95.2%)	103/108 (95.4%)	-0.1% (-6.4%, 6.2%)
<i>K. pneumoniae</i>	17/18 (94.4%)	16/18 (88.9%)	5.6% (-18.0%, 29.1%)
<i>M. catarrhalis</i>	38/40 (95.0%)	34/35 (97.1%)	-2.1% (-13.5%, 9.3%)
<i>P. aeruginosa</i>	9/15 (60.0%)	13/15 (86.7%)	-26.7% (-63.5%, 10.2%)
<i>S. aureus</i>	19/22 (86.4%)	13/14 (92.9%)	-6.5% (-32.0%, 19.0%)
<i>S. pneumoniae</i>	32/36 (88.9%)	22/24 (91.7%)	-2.8% (-21.3%, 15.8%)

By-pathogen bacteriologic response rate=(Number of eradicated and presumed eradicated) / (Total number of isolates)

TABLE II-13: STUDY 358: BY-PATHOGEN BACTERIOLOGICAL RESPONSE FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS OF THE MEDICAL OFFICER BACTERIOLOGICALLY EVALUABLE PATIENTS

Pathogen	Sparfloxacin	Ofloxacin	95% Confidence Interval Sparfloxacin vs Ofloxacin
<i>C. pneumoniae</i>	37/45 (82.2%)	36/40 (90.0%)	-7.8% (-24.7%, 9.1%)
<i>E. cloacae</i>	12/13 (92.3%)	12/15 (80.0%)	12.3% (-19.8%, 44.4%)
<i>H. influenzae</i>	51/57 (89.5%)	61/65 (93.8%)	-4.4% (-15.9%, 7.2%)
<i>H. parainfluenzae</i>	104/109 (95.4%)	90/95 (94.7%)	0.7% (-8.3%, 7.6%)
<i>K. pneumoniae</i>	17/17 (100.0%)	15/17 (88.2%)	11.8% (-9.4%, 33.0%)
<i>M. catarrhalis</i>	36/38 (94.7%)	33/34 (97.1%)	-2.3% (-14.2%, 9.6%)
<i>P. aeruginosa</i>	9/13 (69.2%)	9/11 (81.8%)	-12.6% (-54.9%, 29.7%)
<i>S. aureus</i>	16/19 (84.2%)	13/14 (92.9%)	-8.6% (-36.1%, 18.8%)
<i>S. pneumoniae</i>	30/34 (88.2%)	20/22 (90.9%)	-2.7% (-22.6%, 17.2%)

By-pathogen bacteriological response rate=(Number of eradicated and presumed eradicated) / (Total number of isolates)

The summaries of the adverse events: the rate of patients with adverse event, the rate of adverse events related to study medication, the rate of discontinuation due to adverse events, the rate of serious adverse events, the rate of adverse laboratory events, are presented in Table II-14. No significant differences between treatment groups were detected with respect to all these parameters. Among the most common adverse events, for both the rate of adverse event and the rate of adverse events related to study medication, the percentage of patients who experienced insomnia and nausea were significantly lower in the sparfloxacin group than in the ofloxacin groups, respectively, however, the percentages of patients who experienced photosensitivity reaction were very significantly higher in the sparfloxacin group than in the ofloxacin group. The rates of patients reporting adverse events associated with the digestive system, musculoskeletal system, and nervous system were significantly lower in the sparfloxacin group than in the ofloxacin groups, respectively.

No deaths were reported in the sparfloxacin group, however, one ofloxacin patient died during the study.

Table II-15 shows photosensitivity reaction subset by demographic aspects. Results observed in the analysis of adverse events for the frequency of photosensitivity reaction, subset by gender, age, and race, were all consistent with those observed in the overall adverse event analysis, that is, the percentage of patients who experienced photosensitivity reaction was very significantly higher in the sparfloxacin group than in the ofloxacin group.

Table II-16 shows mean changes in QT_c intervals at selected time points. A significantly greater mean change from baseline to maximum on-treatment value for QT_c interval was observed in the sparfloxacin group as compared with the ofloxacin group. Table II-17 presents a summary of mean changes from baseline in QT_c interval at selected time points, subset by gender, age, and race.

TABLE II-14: STUDY 356: CLINICAL AND LABORATORY ADVERSE EVENT RATES			
Safety Parameter	Sparfloxacin (N=395)	Ofloxacin (N=403)	Fisher's P-value
Patients with Adverse Events	215 (54.4%)	224 (55.6%)	0.776
Headache	44 (11.1%)	35 (8.7%)	0.286
Insomnia	13 (3.3%)	65 (16.1%)	<0.001
Nausea	22 (5.6%)	45 (11.2%)	0.005
Dizziness	23 (5.8%)	15 (3.7%)	0.185
Photosensitivity Reaction	33 (8.4%)	3 (0.7%)	<0.001
Digestive System	58 (14.7%)	99 (24.6%)	<0.001
Musculoskeletal System	2 (0.5%)	11 (2.7%)	0.022
Nervous System	60 (15.2%)	99 (24.6%)	0.001
Cardiovascular System	17 (4.3%)	17 (4.2%)	1.000
AE Related to Study Medication	139 (35.2%)	163 (40.4%)	0.144
Insomnia	6 (1.5%)	60 (14.9%)	<0.001
Nausea	17 (4.3%)	41 (10.2%)	0.002
Photosensitivity Reaction	32 (8.1%)	3 (0.7%)	<0.001
Discontinuation due to AE	21 (5.3%)	30 (7.4%)	0.248
Serious Adverse Events	6 (1.5%)	6 (1.5%)	1.000
Adverse Laboratory Events	25 (6.3%)	31 (7.7%)	0.490
SGOT	5 (1.3%)	4 (1.0%)	0.750
SGPT	4 (1.0%)	7 (1.7%)	0.546
WBC	7 (1.8%)	13 (3.2%)	0.258

TABLE II-15: STUDY 356: PHOTOSENSITIVITY REACTION SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=395)	Ofloxacin (N=403)	95% C.I.	P-value Fisher's Exact	P-value Breslow-Day's
Male	22/195 (11.3%)	3/218 (1.4%)	(4.7%, 15.1%)	<0.001	0.277
Female	11/200 (5.5%)	0/185 (0%)	(1.8%, 9.2%)	0.001	
<65	20/271 (7.4%)	3/281 (1.1%)	(2.6%, 10.0%)	<0.001	0.176
≥65	13/124 (10.5%)	0/122 (0%)	(4.3%, 16.7%)	<0.001	
White	33/305 (10.8%)	3/308 (1.0%)	(5.9%, 13.8%)	<0.001	NA
Nonwhite	0/90 (0%)	0/95 (0%)	NA	NA	

Safety Parameter	Sparfloxacin (N=395)	Ofloxacin (N=403)
<i>Day 4</i>		
Number of Patients	357	357
Baseline Mean	0.409	0.408
Mean Change	0.011	0.001
<i>Endpoint</i>		
Number of Patients	387	392
Baseline Mean	0.409	0.409
Mean Change	0.002	0.002
Maximum on Treatment Mean Change and Its P-value and 95% C.I.	0.012	0.001
	p<0.001, (0.007, 0.014)	

Subset	Sparfloxacin (N=395)		Ofloxacin (N=403)	
	Male	Female	Male	Female
GENDER				
<i>Day 4</i>				
Number of Patients	180	177	195	162
Baseline Mean	0.403	0.146	0.407	0.409
Mean Change	0.009	0.012	-0.001	0.003
<i>Endpoint</i>				
Number of Patients	192	195	212	180
Baseline Mean	0.404	0.414	0.407	0.411
Mean Change	0.001	0.003	0	0.005
AGE	18-64	≥65	18-64	≥65
<i>Day 4</i>				
Number of Patients	250	107	250	107
Baseline Mean	0.409	0.410	0.409	0.408
Mean Change	0.010	0.012	0.001	0.001
<i>Endpoint</i>				
Number of Patients	264	123	272	120
Baseline Mean	0.409	0.411	0.409	0.408
Mean Change	0.003	<0.001	0.002	0.002
RACE	White	Nonwhite	White	Nonwhite
<i>Day 4</i>				
Number of Patients	276	81	279	78
Baseline Mean	0.410	0.408	0.408	0.411
Mean Change	0.011	0.009	<0.001	0.005
<i>Endpoint</i>				
Number of Patients	300	87	304	88
Baseline Mean	0.410	0.408	0.409	0.410
Mean Change	0.001	0.006	0.001	0.005

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Pages 14-31

Not APPROVED
Indication

IV. COMBINED SAFETY ANALYSIS

IV.A. INTRODUCTION

This section presents an integrated summary of data relating to the safety of sparfloxacin for all Phase III clinical studies in this NDA submission. Eight Phase III clinical studies sponsored by the Applicant were conducted in the U.S.A. and Canada to evaluate the safety of sparfloxacin in patients with CAP, ABECB

In the CAP, ABECB, indications, sparfloxacin patients received a 10 days treatment course of 400 mg loading dose on the first day, followed by 200 mg daily dose. In the U-UTI study, sparfloxacin patients received 1 day treatment course of 400 mg single dose or a 3 days treatment course of 400 mg loading dose on the first day, followed by 200 mg daily dose. Details of these Phase III clinical studies are presented in Table IV-1.

In order to obtain a better understanding of the safety profile of sparfloxacin, this reviewer performed a combined safety analysis of the Applicant's eight sparfloxacin studies submitted in this NDA in the two groups, respectively, based on the sparfloxacin treatment regimen. One group (all studies includes six studies (301, 352, 356, 358, 359, and 353), and another study) includes the other two studies (355 and 363).

A total of 4510 patients was enrolled in eight Phase III clinical studies; 2916 in the first six studies and 1594 in the other two studies. Among all studies, 1585 patients were randomized to receive sparfloxacin and 1331 patients were randomized to receive comparators. In the two studies, 993 patients were randomized to receive sparfloxacin and 601 patients were randomized to receive comparators. The percentage of patients who completed study was comparable between sparfloxacin and comparators across all indications (sparfloxacin: 73.1% ~ 80.0%; comparators: 69.5% ~ 76.9%), with the exception of the studies, in which the percentage of patients completed study was lower than that of the other indications (sparfloxacin: 49.5%; comparators: 48.1%). For all studies, the sparfloxacin and the comparator groups were comparable across all indications with respect to the demographic characteristic of gender, age, and race. The majority of patients in both treatment groups across all indications were white, ranging in mean age from 34.5 years to 51.9 years. With the exception of the studies in which, per protocol, only female patients were enrolled, and the studies, in which the percentage of females was higher than that of males for both sparfloxacin and comparators, the distributions of males and females in these studies were similar across indications. The distribution of age by gender and ages by race were similar across indications for the sparfloxacin and the comparator groups.

TABLE IV-1: PHASE III CLINICAL STUDIES					
Indication	Study	Study Design	Treatment Duration	Number of Patients	
				Sparfloxacin	Comparators
CAP	301	Double-blind, Randomized, Comparative, Multicenter	10 days	219	209 (Erythromycin)
	352	Double-blind, Randomized, Comparative, Multicenter	10 days	168	162 (Cefaclor)
ABECB	356	Double-blind, Randomized, Comparative, Multicenter	10 days	395	403 (Ofloxacin)
	301	Double-blind, Randomized, Comparative, Multicenter	10 days	219	209 (Erythromycin)
	352	Double-blind, Randomized, Comparative, Multicenter	10 days	168	162 (Cefaclor)
	356	Double-blind, Randomized, Comparative, Multicenter	10 days	395	403 (Ofloxacin)
	358	Double-blind, Randomized, Comparative, Multicenter	10 days	252	252 (Clarithromycin)
	359	Open-label, Noncomparative, Multicenter	10 days	253	0 (None)
	353	Double-blind, Randomized, Comparative, Multicenter	10 days	298	305 (Ciprofloxacin)
	355	Double-blind, Randomized, Comparative, Multicenter	3 days 1 day	395 394	386 (Ciprofloxacin)
	363	Open-label, Observer-blind, Randomized, Comparative, Multicenter	3 days	204	215 (Ofloxacin)

IV.B. METHODS

In the eight Phase III clinical studies included in this analysis, three sparfloxacin treatment regimens were studied: (1) 200 mg once daily following a 400 mg loading dose given for 10 days of total treatment course, (2) a single 400 mg dose, and (3) 200 mg once daily following a 400 mg loading dose given for 3 days of total treatment course. Separate integrated safety analyses were performed for the above sparfloxacin regimen groups. Although various comparator agents were used in these trials, all the comparator agents were combined to form combined control groups correspondingly.

The rate of patients with adverse events, the rate of adverse events related to study medication, the rate of discontinuation due to adverse events, the rate of serious adverse events, the rate of adverse laboratory events, the rate of sponsor defined clinically significant laboratory adverse events, and the incidence rate of photosensitivity reaction were the safety parameters examined in this analysis. The QT_c interval of electrocardiogram was also evaluated.

All patients who received at least one dose of study medication were evaluable for safety. Treatment comparisons with respect to the safety parameters were conducted for the entire patient population and for

the following subpopulations: gender (male, female), age (<60, 65+ years), race (white, nonwhite), and indication.

The treatment comparison was made using Fisher's exact test, and the test of homogeneity of treatment effect across subgroups was performed using Breslow-Day's test. The 95% confidence interval was computed using a normal approximation method and included a continuity correction. Fisher's exact test differences in the safety parameters were considered significant at the 0.05 level. Breslow-Day's test of homogeneity of treatment effect was deemed significant at the 0.15 level. Changes in the QT_c interval were summarized with descriptive statistics for all Phase III clinical studies combined and by demographic aspects and indication.

In the discussion of subgroup results, it should be noted that in some patient subgroups, the large variation in treatment effect precluded a meaningful pooling of results across studies, or the amount of data in the individual studies was too sparse to obtain a valid estimate of the treatment effect of the study.

IV.C. RESULTS

IV.C.1. ALL STUDIES

Six studies (301, 352, 356, 358, 359, and 353) were included in this analysis. Sparfloxacin was administered by a daily oral dose of 200 mg following a loading dose of 400 mg on the first day of treatment for 10 days of total treatment course. The safety population for this regimen included a total of 1585 sparfloxacin patients and 1331 combined comparator patients. The comparators in these studies were erythromycin, cefaclor, ofloxacin, clarithromycin, and ciprofloxacin.

All Clinical Adverse Events

Safety results of the difference between sparfloxacin and the combined comparators in clinical adverse events are presented in Table IV-2. For all six studies, 53.1% of 1585 sparfloxacin patients and 55.9% of 1331 combined comparator patients experienced with adverse events. Fisher's exact p-value was 0.136, which indicated that there was no significant difference between sparfloxacin and the combined comparators with respect to the rates of adverse event. No significant differences between sparfloxacin and the combined comparators were also detected with respect to the rates of serious adverse events and the rates of adverse laboratory events. For the patients reporting adverse events related to study medication and the discontinuation due to adverse events, the rates were significantly lower in the sparfloxacin group than in the combined comparator group, respectively ($p=0.003$ and $p=0.021$). However, the sparfloxacin group had a very significantly higher incidence rate of photosensitivity reaction ($p<0.001$). Table IV-2 also summarizes the incidence of adverse events by body system. A statistically lower percentage of patients in the sparfloxacin group was reported with respect to the rates of adverse events in digestive and nervous systems as compared with the combined comparator group. The percentage of patients who experienced adverse events associated with body as a whole was significantly higher in the sparfloxacin group. The two treatments were statistically comparable for the adverse events occurred in cardiovascular, respiratory, skin and appendage, special sense, and urogenital systems. Note that the most frequently reported incidences of adverse events in both treatment groups were found in digestive system and body as a whole.

TABLE IV-2: COMBINED SAFETY ANALYSIS FOR ALL STUDIES CLINICAL AND SELECTED LABORATORY ADVERSE EVENT RATES			
Safety Parameter	Sparfloxacin (N=1585)	Comparators (N=1331)	P-value Fisher's Exact
<u>Patients with Adverse Events</u>	842 (53.1%)	744 (55.9%)	0.136
Body as a Whole	414 (26.1%)	268 (20.1%)	<0.001
Cardiovascular System	73 (4.6%)	66 (5.0%)	0.664
Digestive System	240 (15.1%)	342 (25.7%)	<0.001
Nervous System	180 (11.4%)	184 (13.8%)	0.049
Respiratory System	162 (11.5%)	144 (10.8%)	0.596
Skin and Appendage	112 (7.1%)	85 (6.4%)	0.505
Special Sense	80 (5.0%)	70 (5.3%)	0.801
Urogenital System	30 (1.9%)	37 (2.8%)	0.136
Photosensitivity Reaction	130 (8.2%)	12 (0.9%)	<0.001
<u>AE Related to Study Medication</u>	518 (32.7%)	505 (37.9%)	0.003
Body as a Whole	223 (14.1%)	117 (8.8%)	<0.001
Cardiovascular System	41 (2.6%)	38 (2.9%)	0.731
Digestive System	184 (11.6%)	274 (20.6%)	<0.001
Metabolism	10 (0.6%)	8 (0.6%)	1.000
Nervous System	121 (7.6%)	151 (11.3%)	0.001
Respiratory System	28 (1.8%)	27 (2.0%)	0.682
Skin and Appendage	70 (4.4%)	47 (3.5%)	0.256
Special Sense	43 (2.7%)	45 (3.4%)	0.328
Urogenital System	15 (0.9%)	24 (1.8%)	0.052
Photosensitivity Reaction	126 (7.9%)	12 (0.9%)	<0.001
<u>Discontinuation due to AE</u>	104 (6.6%)	118 (8.9%)	0.021
<u>Serious Adverse Events</u>	43 (2.7%)	47 (3.5%)	0.237
<u>Adverse Laboratory Events</u>	115 (7.3%)	99 (7.4%)	0.887
SGOT	32 (2.0%)	19 (1.4%)	0.258
SGPT	36 (2.3%)	28 (2.1%)	0.801
WBC	18 (1.1%)	23 (1.7%)	0.207

Patients with Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of adverse events are displayed in Table IV-3. No statistical significance was detected in age and indication subgroups. However, significantly lower rates of adverse events for sparfloxacin were observed in female patients ($p=0.012$) and in nonwhite patients ($p=0.011$).

Adverse Events Related to Study Medication

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of adverse events related to study medication are displayed in Table IV-4. Sparfloxacin had significantly lower rates of adverse events related to study medication in female patients of gender subgroup ($p < 0.001$), in <65 years patients of age subgroup ($p = 0.001$), in nonwhite patients of race subgroup ($p < 0.001$), in CAP and patients of indication subgroup ($p = 0.015$ and $p = 0.005$).

Discontinuation due to Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of discontinuation due to adverse events are displayed in Table IV-5. The results from all subgroup analyses showed that numerically lower rates of discontinuation due to adverse events were observed in the sparfloxacin patients than in the combined comparator patients. Significantly lower rates were also observed in <65 years patients of gender subgroup ($p = 0.024$), and in nonwhite patients of race subgroup ($p = 0.024$).

Serious Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of serious adverse events are displayed in Table IV-6. No statistical significance was detected among all demographic subgroups, except in patients of indication subgroup, in which sparfloxacin had a significantly lower rate than the combined comparators ($p = 0.017$).

Deaths

A total of 7 patients died in all studies. These deaths were considered by the investigators to be either unrelated or remotely related to study medication. There were 4 deaths in the sparfloxacin group and 3 deaths in the combined comparator group.

Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	842/1585 (53.1%)	744/1331 (55.9%)	(-6.5%, 0.9%)	0.136	
Male	440/819 (53.7%)	388/732 (53.0%)	(-4.4%, 5.8%)	0.799	0.038
Female	402/766 (52.5%)	356/599 (59.4%)	(-12.4%, -1.5%)	0.012	
<65	665/1274 (52.2%)	579/1034 (56.0%)	(-0.8%, 0.4%)	0.071	0.257
≥65	177/311 (56.9%)	165/297 (55.6%)	(-6.9%, 9.6%)	0.744	
White	737/1313 (56.1%)	630/1104 (57.1%)	(-5.0%, 3.1%)	0.651	0.029
Nonwhite	105/272 (38.6%)	114/227 (50.2%)	(-20.7%, -2.5%)	0.011	
CAP	220/387 (56.8%)	220/371 (59.3%)	(-9.7%, 4.8%)	0.508	0.870
ABECB	215/395 (54.4%)	224/403 (55.6%)	(-8.3%, 6.0%)	0.776	
	435/782 (55.6%)	444/774 (57.4%)	(-6.8%, 3.3%)	0.506	
	261/505 (51.7%)	146/252 (57.9%)	(-14.0%, 1.5%)	0.105	
	146/298 (49.0%)	154/305 (50.5%)	(-9.8%, 6.8%)	0.745	

**TABLE IV-4: COMBINED SAFETY ANALYSIS FOR ALL STUDIES
ADVERSE EVENTS RELATED TO STUDY MEDICATION
SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION**

Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	518/1585 (32.7%)	505/1331 (37.9%)	(-8.8%, -1.7%)	0.003	
Male	280/819 (34.2%)	265/732 (36.2%)	(-6.9%, 2.9%)	0.424	0.050
Female	238/766 (31.1%)	240/599 (40.1%)	(-14.3%, -3.7%)	<0.001	
<65	404/1274 (31.7%)	400/1034 (38.7%)	(-11.0%, -3.0%)	0.001	0.056
≥65	114/311 (36.7%)	105/297 (35.4%)	(-6.7%, 9.3%)	0.800	
White	468/1313 (35.6%)	429/1104 (38.9%)	(-7.2%, 0.7%)	0.108	0.003
Nonwhite	50/272 (18.4%)	76/227 (33.5%)	(-23.2%, -7.0%)	<0.001	
CAP	122/387 (31.5%)	149/371 (40.2%)	(-15.7%, -1.6%)	0.015	0.559
ABECB	139/395 (35.2%)	163/403 (40.4%)	(-12.2%, 1.7%)	0.144	
	261/782 (33.4%)	312/774 (40.3%)	(-11.8%, -2.0%)	0.005	
	156/505 (30.9%)	89/252 (35.3%)	(-11.9%, 3.0%)	0.248	
	101/298 (33.9%)	104/305 (34.1%)	(-8.1%, 7.7%)	1.000	

**TABLE IV-5: COMBINED SAFETY ANALYSIS FOR ALL STUDIES
DISCONTINUATION DUE TO ADVERSE EVENTS RELATED TO STUDY MEDICATION
SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION**

Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	104/1585 (6.6%)	118/1331 (8.9%)	(-4.3%, -0.3%)	0.021	
Male	51/819 (6.2%)	61/732 (8.3%)	(-4.8%, 0.6%)	0.116	0.906
Female	53/766 (6.9%)	57/599 (9.5%)	(-5.7%, 0.5%)	0.089	
<65	72/1274 (5.7%)	83/1034 (8.0%)	(-4.5%, -0.2%)	0.024	0.467
≥65	32/311 (10.3%)	35/297 (11.8%)	(-6.8%, 3.8%)	0.605	
White	98/1313 (6.7%)	91/1104 (8.2%)	(-3.7%, 0.7%)	0.161	0.131
Nonwhite	16/272 (5.9%)	27/227 (11.9%)	(-11.5%, -0.6%)	0.024	
CAP	32/387 (8.3%)	40/371 (10.8%)	(-7.0%, 1.9%)	0.265	0.934
ABECB	21/395 (5.3%)	30/403 (7.4%)	(-5.8%, 1.5%)	0.248	
	53/782 (6.8%)	70/774 (9.0%)	(-5.1%, 0.5%)	0.110	
	27/505 (5.3%)	21/252 (8.3%)	(-7.2%, 1.2%)	0.116	
	24/298 (8.1%)	27/305 (8.9%)	(-5.6%, 4.0%)	0.771	

TABLE IV-6: COMBINED SAFETY ANALYSIS FOR ALL STUDIES					SERIOUS
ADVERSE EVENTS SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION					ADVERSE EVENTS
Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	43/1585 (2.7%)	47/1331 (3.5%)	(-2.2%, 0.5%)	0.237	
Male	33/819 (4.0%)	34/732 (4.6%)	(-2.8%, 1.5%)	0.617	0.453
Female	10/766 (1.3%)	13/599 (2.2%)	(-2.4%, 0.7%)	0.289	
<65	25/1274 (2.0%)	25/1034 (2.4%)	(-1.7%, 0.8%)	0.475	0.907
≥65	18/311 (5.8%)	22/297 (7.4%)	(-5.9%, 2.7%)	0.513	
White	33/1313 (2.5%)	36/1104 (3.3%)	(-2.2%, 0.7%)	0.273	0.968
Nonwhite	10/272 (3.7%)	11/227 (4.8%)	(-5.2%, 2.8%)	0.655	
CAP	27/387 (7.0%)	24/371 (6.5%)	(-3.3%, 4.3%)	0.885	0.127
ABECB	6/395 (1.5%)	6/403 (1.5%)	(-1.9%, 2.0%)	1.000	
	33/782 (4.2%)	30/774 (3.9%)	(-1.7%, 2.4%)	0.797	
	1/506 (0.2%)	5/252 (2.0%)	(-3.8%, 0.3%)	0.017	
	9/298 (3.0%)	12/305 (3.9%)	(-4.2%, 2.3%)	0.658	

Photosensitivity Reaction

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the incidence rate of photosensitivity reaction and incidence rate of photosensitivity reaction related to study medication are displayed in Table IV-7 and Table IV-8, respectively. The results observed in the analyses subset by demographic aspects and indication were consistent with those observed in the overall analysis, that is, in all of the subgroups, sparfloxacin had a very significantly higher incidence rate of photosensitivity reaction and incidence rate of photosensitivity reaction related to study medication ($p < 0.001$ and $p < 0.001$) than the combined comparators.

The comparison results of the day of onset, duration, and number of episodes of photosensitivity reaction is presented in Table IV-9. A statistically significant difference between sparfloxacin and the combined comparators was only detected in the duration of photosensitivity reaction ($p = 0.043$).

Table IV-10 displays the results of patients experiencing photosensitivity reaction by selected classes of concomitant medication. The incidences of photosensitivity reaction by all concomitant medications, except tricyclic antidepressants, were significantly higher in the sparfloxacin group.

A summary of the outcome and action taken for photosensitivity reaction is presented in Table IV-11. There was not a statistically significant difference between the sparfloxacin patients and the combined comparator patients.

It is noteworthy that the US development program was stopped temporarily by the Applicant on Oct. 18, 1993 due to the high frequency of photosensitivity reaction in sparfloxacin studies, and the protocols were amended to provide new information regarding sparfloxacin associated photosensitivity to the investigators and to provide advice and additional precautions to patients regarding sun exposure during treatment with study medication. Upon IRB approval at each site of the Oct. 25, 1993 amendment, the studies resumed. Table IV-12 presents the incidence rates of photosensitivity reaction pre- and post- Oct. 25, 1993 Amendment. For sparfloxacin, although the rate of post-1993 was numerically decreased slightly as compared with that of pre-1993, it had always very significantly higher rates than its comparators.

TABLE IV-7: COMBINED SAFETY ANALYSIS FOR ALL STUDIES PHOTOSENSITIVITY REACTION SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION					
Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value -Breslow- Day's
All	130/1585 (8.2%)	12/1331 (0.9%)	(5.8%, 8.8%)	<0.001	
Male	74/819 (9.0%)	9/732 (1.2%)	(5.6%, 10.1%)	<0.001	0.322
Female	56/766 (7.3%)	3/599 (0.5%)	(4.7%, 8.9%)	<0.001	
<65	107/1274 (8.4%)	11/1034 (1.1%)	(5.6%, 9.1%)	<0.001	0.325
≥65	23/311 (7.4%)	1/297 (0.3%)	(3.7%, 10.4%)	<0.001	
White	128/1313 (9.7%)	12/1104 (1.1%)	(6.9%, 10.5%)	<0.001	0.679
Nonwhite	2/272 (0.7%)	0/227 (0)	(-0.7%, 2.2%)	0.503	
CAP	18/387 (4.7%)	2/371 (0.5%)	(1.6%, 6.6%)	<0.001	0.990
ABECB	33/395 (8.4%)	3/403 (0.7%)	(4.5%, 10.7%)	<0.001	
	51/782 (6.5%)	5/774 (0.6%)	(3.9%, 7.8%)	<0.001	
	44/505 (8.7%)	3/252 (1.2%)	(4.4%, 10.6%)	<0.001	
	35/298 (11.7%)	4/305 (1.3%)	(6.2%, 14.6%)	<0.001	

TABLE IV-8: COMBINED SAFETY ANALYSIS FOR ALL STUDIES PHOTOSENSITIVITY REACTION RELATED TO STUDY MEDICATION SUBSET BY DEMOGRAPHIC ASPECTS AND INDICATION					
Subset	Sparfloxacin (N=1585)	Comparators (N=1331)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
All	126/1585 (7.9%)	12/1331 (0.9%)	(5.6%, 8.5%)	<0.001	
Male	72/819 (8.8%)	9/732 (1.2%)	(5.6%, 10.1%)	<0.001	0.329
Female	54/766 (7.0%)	3/599 (0.5%)	(4.7%, 8.9%)	<0.001	
<65	103/1274 (8.1%)	11/1034 (1.1%)	(5.6%, 9.1%)	<0.001	0.304
≥65	23/311 (7.4%)	1/297 (0.3%)	(3.7%, 10.4%)	<0.001	
White	124/1313 (9.4%)	12/1104 (1.1%)	(6.9%, 10.5%)	<0.001	0.674
Nonwhite	2/272 (0.7%)	0/227 (0)	(-0.7%, 2.2%)	0.503	
CAP	17/387 (4.4%)	2/371 (0.5%)	(1.6%, 6.6%)	0.001	0.990
ABECB	32/395 (8.1%)	3/403 (0.7%)	(4.5%, 10.7%)	<0.001	
	49/782 (6.3%)	5/774 (0.6%)	(3.9%, 7.8%)	<0.001	
	43/505 (8.5%)	3/252 (1.2%)	(4.4%, 10.6%)	<0.001	
	34/298 (11.4%)	4/305 (1.3%)	(6.2%, 14.6%)	<0.001	

TABLE IV-9: COMBINED SAFETY ANALYSIS FOR ALL STUDIES THE DAY OF ONSET, DURATION, AND NUMBER OF EPISODES OF PHOTOSENSITIVITY REACTION			
Photosensitivity Reaction	Sparfloxacin (130/1585)	Comparators (12/1331)	P-value: Fisher's Exact
Day of Onset <i>Relative to the First Dose of Study Medication:</i>			
Mean ± S.D. Range	7.5 ± 5.3	9.1 ± 6.3	0.326*
<i>Relative to the Last Dose of Study Medication:</i>			
Mean ± S.D. Range	-3.5 ± 5.7	-2.8 ± 6.5	0.688*
Duration Mean ± S.D. Range	13.2 ± 11.0	6.5 ± 9.0	0.043*
Number of Episodes			
1	123 (94.6%)	12 (100.0%)	1.000
2	7 (5.4%)	0	1.000

*: P-value by two-sample t test for independent samples with equal variances.

TABLE IV-10: COMBINED SAFETY ANALYSIS FOR ALL STUDIES PHOTOSENSITIVITY REACTION BY SELECTED CLASSES OF CONCOMITANT MEDICATION			
Class of Concomitant Medication	Sparfloxacin (130/1585)	Comparators (12/1331)	P-value: Fisher's Exact
Sunscreens	18/27 (66.7%)	2/13 (15.4%)	0.006
Antihistamines	9/69 (13.0%)	0/66 (0)	0.003
Oral Contraceptives	15/156 (9.6%)	1/106 (0.9%)	0.003
Tricyclic Antidepressants	2/22 (9.1%)	0/14 (0)	0.511
NSAIDS	18/249 (7.2%)	1/208 (0.5%)	<0.001
Diuretics	12/195 (6.2%)	0/184 (0)	<0.001

TABLE IV-11: COMBINED SAFETY ANALYSIS FOR ALL STUDIES PHOTOSENSITIVITY REACTION BY OUTCOME AND ACTION TAKEN			
Outcome or Action Taken	Sparfloxacin (130/1585)	Comparators (12/1331)	P-value: Fisher's Exact
Outcome at End of Study			
Recovered	113 (86.9%)	11 (91.7%)	1.000
Recovered with Sequelae	8 (4.6%)	0	1.000
Ongoing	11 (8.5%)	1 (8.3%)	1.000
Action Taken - Study Medication			
None	114 (87.7%)	11 (91.7%)	1.000
Discontinued	16 (12.3%)	1 (8.3%)	1.000
Action Taken - Other Treatment			
None	80 (81.5%)	9 (75.0%)	0.535
Medication	36 (27.7%)	3 (25.0%)	1.000
Other	14 (10.8%)	0	0.608
Discontinued From the Study			
Yes	17 (13.1%)	1 (8.3%)	1.000
No	113 (86.9%)	11 (91.7%)	1.000

TABLE IV-12: COMBINED SAFETY ANALYSIS FOR ALL STUDIES THE INCIDENCE RATES OF PHOTOSENSITIVITY REACTION PRE- AND POST- 1993 AMENDMENT			
Study Period	Sparfloxacin	Comparators	P-value Fisher's Exact
Pre-1993	44/430 (10.2%)	2/428 (0.5%)	<0.001
Post-1993	86/1155 (7.4%)	10/903 (1.1%)	<0.001

Sponsor Defined Clinically Significant Laboratory Adverse Events

Table IV-13 summarizes the incidence of sponsor defined clinically significant laboratory adverse events. Of all variables, a statistically significant difference between the two groups was reported only in WBC, in which sparfloxacin had a significantly lower incidence rate than the combined comparators (p=0.048).

TABLE IV-13: COMBINED SAFETY ANALYSIS FOR ALL STUDIES SPONSOR DEFINED CLINICALLY SIGNIFICANT LABORATORY ADVERSE EVENT RATES			
Laboratory Values	Sparfloxacin (N=1585)	Comparators (N=1331)	P-value Fisher's Exact
Creatinine	27 (1.7%)	27 (2.0%)	0.582
Eosinophils	27 (1.7%)	28 (1.8%)	0.495
Hemoglobin	146 (9.2%)	130 (9.8%)	0.612
Platelets	5 (0.3%)	3 (0.2%)	0.734
SGOT	38 (2.4%)	33 (2.5%)	0.904
SGPT	55 (3.5%)	55 (4.1%)	0.380
Total Bilirubin	5 (0.3%)	0	0.067
WBC	9 (0.6%)	17 (1.3%)	0.048

Mean Change from Baseline in QT_c Interval

In all six studies, a total of 14 patients (11 in the sparfloxacin group and 3 in the combined comparator group) had one or more on-treatment QT_c values larger than 500 msec. Table IV-14 shows mean change in QT_c interval from baseline to maximum for on- and off-treatment value. Table IV-15 presents a summary of mean changes in QT_c interval from baseline to maximum for on- and off-treatment value, subset by gender, age, race, and indication. Summary of the mean change in QT_c interval from baseline to off-treatment value larger than 10% and QT_c interval off-treatment value larger than 400 msec is presented in Table IV-16. For all six studies as a whole, the sparfloxacin group had significantly more patients who met the level than the combined comparator group (p<0.001), so did the sparfloxacin groups for Study 353 and Study 356, respectively.

TABLE IV-14: COMBINED SAFETY ANALYSIS FOR ALL STUDIES MEAN CHANGE IN QT_c INTERVAL AT SELECTED TIME POINTS		
Safety Parameter	Sparfloxacin	Comparators
<i>On Treatment</i>		
Number of Patients	1489	1215
Baseline Mean	0.408	0.406
Mean Change	0.010±0.001	0.003±0.001
<i>Off Treatment</i>		
Number of Patients	1435	1198
Baseline Mean	0.408	0.406
Mean Change	0.001±0.001	0.004±0.001

TABLE IV-15: COMBINED SAFETY ANALYSIS FOR ALL STUDIES											MEAN	
CHANGE IN QT _c INTERVALS AT SELECTED TIME POINTS SUBSET BY DEMOGRAPHIC												
ASPECTS												
Subset	Sparfloxacin					Comparators						
GENDER	Male		Female			Male		Female				
<i>On Treatment</i> Patients	772		717			678		537				
Baseline Mean	0.402		0.413			0.402		0.411				
Mean Change	0.008±0.001		0.011±0.001			0.003±0.001		0.004±0.001				
<i>Off Treatment</i> Patients	745		690			654		544				
Baseline Mean	0.403		0.413			0.403		0.410				
Mean Change	0.001±0.001		0.001±0.001			0.002±0.001		0.007±0.001				
AGE	18-64		≥65			18-64		≥65				
<i>On Treatment</i> Patients	1202		287			952		263				
Baseline Mean	0.406		0.414			0.404		0.412				
Mean Change	0.009±0.001		0.013±0.002			0.003±0.001		0.002±0.002				
<i>Off Treatment</i> Patients	1159		276			933		265				
Baseline Mean	0.406		0.414			0.404		0.414				
Mean Change	0.001±0.001		0.002±0.002			0.004±0.001		0.004±0.002				
RACE	White		Non-White			White		Non-White				
<i>On Treatment</i> Patients	1242		247			1019		196				
Baseline Mean	0.408		0.408			0.406		0.408				
Mean Change	0.010±0.001		0.007±0.002			0.002±0.001		0.006±0.002				
<i>Off Treatment</i> Patients	1191		244			1000		198				
Baseline Mean	0.408		0.409			0.406		0.408				
Mean Change	-0.001±0.001		-0.002±0.002			0.004±0.001		0.005±0.003				
INDICATION	CAP	ABECB	LRTI	AMS	CSSSI	CAP	ABECB	LRTI	AMS	CSSI		
<i>On Treatment</i> Patients	363	365	728	482	279	334	363	697	239	279		
Baseline Mean	0.408	0.410	0.409	0.408	0.404	0.408	0.408	0.408	0.406	0.402		
Mean Change	0.008±0.001	0.012±0.001	0.010±0.001	0.008±0.001	0.012±0.001	0.004±0.001	0.001±0.001	0.002±0.001	0.003±0.002	0.006±0.002		
<i>Off Treatment</i> Patients	341	355	696	482	277	321	367	688	227	283		
Baseline Mean	0.409	0.409	0.409	0.409	0.404	0.407	0.409	0.408	0.405	0.402		
Mean Change	0.001±0.001	0.003±0.001	0.002±0.001	-0.001±0.001	0.000±0.001	0.004±0.001	0.005±0.001	0.004±0.001	0.003±0.002	0.004±0.002		

TABLE IV-16: COMBINED SAFETY ANALYSIS FOR ALL STUDIES MEAN CHANGE IN QT_c INTERVAL FROM BASELINE TO OFF- TREATMENT VALUE>10% AND QT_c INTERVAL OFF-TREATMENT VALUE>400 msec			
Study	Sparfloxacin (N=1585)	Comparators (N=1331)	P-value Fisher's Exact
All	93/1555 (6.0%)	35/1292 (2.7%)	<0.001
301	12/214 (5.6%)	6/197 (3.0%) Erythromycin	0.235
352	11/163 (6.7%)	7/158 (4.4%) Cefaclor	0.469
353	15/297 (5.1%)	6/298 (2.0%) Ciprofloxacin	0.048
356	26/387 (6.7%)	4/392 (1.0%) Ofloxacin	<0.001
358	14/247 (5.7%)	12/247 (4.9%) Clarithromycin	0.841
359	15/247 (6.1%)	NA	NA

IV.C.2. STUDIES

Two studies (355, and 363) were included in this analysis. In Study 355, sparfloxacin was administered by two treatment courses, a single dose of 400 mg, and a 400 mg loading dose on day 1 followed by 200mg on days 2-3. In Study 363, sparfloxacin was administered by a 200 mg dose following a loading dose of 400 mg on the first day of treatment for 3 days of total treatment course. The safety population for this indication included a total of 993 sparfloxacin patients and 601 combined comparator patients. The comparators in these studies were ciprofloxacin and ofloxacin. All enrolled patients were females.

All Clinical Adverse Events

Safety results from comparisons of sparfloxacin and the combined comparators in clinical adverse events are presented in Table IV-17. For the two studies, 53.2% of 993 sparfloxacin patients and 49.3% of 601 combined comparator patients experienced with adverse events. No significant differences between the sparfloxacin and the combined comparator treatment groups were detected with respect to the rates of adverse events, the rates of discontinuation due to adverse events, the rates of serious adverse events, and the rates of adverse laboratory events. For the patients reporting adverse events related to study medication, the rate was significantly higher in the sparfloxacin group than in the combined comparator group (p=0.025). The sparfloxacin group had very significantly higher incidence rate of photosensitivity reaction and incidence rate of at photosensitivity reaction related to study medication (p<0.001 and p<0.001). Table IV-17 also summarizes the incidence of adverse events by body system. A statistically higher percentage of patients in the sparfloxacin group was reported with respect to the incidence of adverse events in body as a whole, cardiovascular, respiratory, and skin and appendage systems as compared with the combined comparator groups. Note that the most frequently reported incidences of adverse events in both treatment groups were found in digestive system.

TABLE IV-17: COMBINED SAFETY ANALYSIS FOR STUDIES: CLINICAL AND SELECTED LABORATORY ADVERSE EVENT RATES			
Safety Parameter	Sparfloxacin (N=993)	Comparators (N=601)	P-value Fisher's Exact
<u>Patients with Adverse Events</u>	528 (53.2%)	296 (49.3%)	0.134
Body as a Whole	291 (29.3%)	160 (26.6%)	0.252
Cardiovascular System	24 (2.4%)	4 (0.7%)	0.010
Digestive System	177 (17.8%)	110 (18.3%)	0.840
Nervous System	112 (11.3%)	66 (11.0%)	0.870
Respiratory System	87 (8.8%)	30 (5.0%)	0.005
Skin and Appendage	67 (6.7%)	26 (4.3%)	0.047
Special Sense	22 (2.2%)	13 (2.2%)	1.000
Urogenital System	77 (7.8%)	54 (9.0%)	0.398
Photosensitivity Reaction	37 (3.7%)	3 (0.5%)	<0.001
<u>AE Related to Study Medication</u>	359 (36.2%)	184 (30.6%)	0.025
Body as a Whole	158 (15.9%)	68 (11.3%)	0.012
Cardiovascular System	14 (1.4%)	3 (0.5%)	0.129
Digestive System	129 (13.0%)	76 (12.6%)	0.877
Metabolism	7 (0.7%)	3 (0.5%)	0.751
Nervous System	93 (9.4%)	51 (8.5%)	0.589
Respiratory System	8 (0.8%)	2 (0.3%)	0.336
Skin and Appendage	51 (5.1%)	14 (2.3%)	0.006
Special Sense	16 (1.6%)	5 (0.8%)	0.257
Urogenital System	47 (4.7%)	29 (4.8%)	1.000
Photosensitivity Reaction	36 (3.6%)	3 (0.5%)	<0.001
<u>Discontinuation due to AE</u>	43 (4.3%)	18 (3.0%)	0.225
<u>Serious Adverse Events</u>	2 (0.2%)	2 (0.3%)	0.635
<u>Adverse Laboratory Events</u>	25 (2.5%)	14 (2.3%)	0.869
SGOT	5 (0.5%)	4 (0.7%)	0.736
SGPT	4 (0.4%)	4 (0.7%)	0.485
WBC	1 (0.1%)	1 (0.2%)	1.000

Because the sample size of 65+ years patients was considerably small in studies, no valid statistical conclusion was drawn from this group of patients, and therefore, the corresponding p-values and confidence intervals in the following tables were not interpreted.

Patient with Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of adverse events are displayed in Table IV-18. No statistical significance was detected in age

subgroup. In the race subgroups, a significantly higher rate of adverse events for sparfloxacin was observed in white patients ($p=0.049$).

Adverse Events Related to Study Medication

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of adverse events related to study medication are displayed in Table IV-19. The <65 years patients of age subgroup and the nonwhite patients of race subgroup had statistically higher rates of adverse events related to study medication in the sparfloxacin treatment than in the combined comparator treatment.

Discontinuation due to Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of discontinuation due to adverse events are displayed in Table IV-20. The results from all subgroup analyses showed that with respect to the rate of discontinuation due to adverse events, there was no significant difference between the sparfloxacin patients and the combined comparator patients.

Serious Adverse Events

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the rate of serious adverse events are displayed in Table IV-21. The results from all subgroup analyses showed that with respect to the rate of serious adverse events, there was no significant difference between the sparfloxacin patients and the combined comparator patients.

Deaths

No deaths were reported during these two studies.

TABLE IV-18: COMBINED SAFETY ANALYSIS FOR STUDIES: PATIENTS WITH ADVERSE EVENTS SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=993)	Comparators (N=601)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
Male	0	0	NA	NA	NA
Female	528/993 (53.2%)	296/601 (49.3%)	(-1.3%, 9.1%)	0.134	
<65	526/990 (53.1%)	293/597 (49.1%)	(-1.2%, 9.3%)	0.120	0.735
≥65	2/3 (66.7%)	3/4 (75.0%)	(-105.7%89.1%)	1.000	
White	465/849 (54.8%)	249/506 (49.2%)	(-0.1%, 11.2%)	0.049	0.115
Nonwhite	63/144 (43.8%)	47/95 (49.5%)	(-19.5%, 8.1%)	0.427	

TABLE IV-19: COMBINED SAFETY ANALYSIS FOR ADVERSE EVENTS RELATED TO STUDY MEDICATION SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=993)	Comparators (N=601)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
Male	0	0	NA	NA	NA
Female	359/993 (36.2%)	184/601 (30.6%)	(0.7%, 10.4%)	0.025	
<65	358/990 (36.2%)	181/597 (30.3%)	(1.0%, 10.7%)	0.019	0.202
≥65	1/3 (33.3%)	3/4 (75.0%)	(-139.0% 55.7%)	0.486	
White	309/849 (36.4%)	153/506 (30.2%)	(0.9%, 11.5%)	0.021	0.546
Nonwhite	50/144 (34.7%)	31/95 (32.6%)	(-11.0%, 15.2%)	0.781	

TABLE IV-20: COMBINED SAFETY ANALYSIS FOR DISCONTINUATION DUE TO ADVERSE EVENTS RELATED TO STUDY MEDICATION SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=993)	Comparators (N=601)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
Male	0	0	(-0.7%, 3.3%)	NA	NA
Female	43/993 (4.3%)	18/601 (3.0%)	(-0.5%, 3.5%)	0.225	
<65	43/990 (4.3%)	17/597 (2.8%)	(-96.6%, 46.6%)	0.137	0.263
≥65	0/3 (0)	1/4 (25.0%)	(-1.4%, 3.1%)	1.000	
White	36/849 (4.2%)	17/506 (3.4%)	(-1.4%, 3.1%)	0.471	0.210
Nonwhite	7/144 (4.9%)	1/95 (1.1%)	(-1.1%, 8.8%)	0.150	

TABLE IV-21: COMBINED SAFETY ANALYSIS FOR SERIOUS ADVERSE EVENTS SUBSET BY DEMOGRAPHIC ASPECTS					
Subset	Sparfloxacin (N=993)	Comparators (N=601)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
Male	0	0	0	NA	NA
Female	2/993 (0.2%)	2/601 (0.3%)	(-0.8%, 0.5%)	0.635	
<65	2/990 (0.2%)	2/597 (0.3%)	(-0.8%, 0.5%)	0.634	NA
≥65	0/3 (0)	0/4 (0)	NA	NA	
White	2/849 (0.2%)	2/506 (0.4%)	(-1.0%, 0.6%)	0.632	NA
Nonwhite	0/144 (0)	0/95 (0)	NA	NA	

Photosensitivity Reaction

P-values and confidence interval results from comparisons of sparfloxacin and the combined comparators in the incidence rate of photosensitivity reaction and incidence rate of photosensitivity reaction related to study medication are displayed in Table IV-22 and Table IV-23, respectively. The results observed in the analyses subset by demographic aspects and indication were consistent with those observed in the overall analysis.

that is, in all of the subgroups, sparfloxacin had very significantly higher incidence rate of photosensitivity reaction and incidence rate of photosensitivity reaction related to study medication ($p < 0.001$ and $p < 0.001$).

The comparison results of the day of onset, duration, and number of episodes of photosensitivity reaction is presented in Table IV-24. A statistically significant difference between sparfloxacin and the combined comparators was only detected in the duration of photosensitivity reaction ($p = 0.001$).

Table IV-25 displays the results of patients experiencing photosensitivity reaction by selected classes of concomitant medication. Among the four classes of concomitant medication which were available to be evaluated, the incidences of photosensitivity reaction, except antihistamines, were significantly higher in the sparfloxacin group.

A summary of the outcome and action taken for photosensitivity reaction is presented in Table IV-26. There was not a statistically significant difference between the sparfloxacin patients and the combined comparator patients.

**TABLE IV-22: COMBINED SAFETY ANALYSIS FOR PHOTSENSITIVITY REACTION
SUBSET BY DEMOGRAPHIC ASPECTS**

Subset	Sparfloxacin (N=993)	Comparators (N=601)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
Male	0	0	NA	NA	NA
Female	37/993 (3.7%)	3/601 (0.5%)	(1.8%, 4.7%)	<0.001	NA
<65	37/990 (3.7%)	3/597 (0.5%)	(1.8%, 4.7%)	<0.001	NA
≥65	0/3 (0)	0/4 (0)	NA	NA	NA
White	37/849 (4.4%)	3/506 (0.6%)	(2.1%, 5.5%)	<0.001	NA
Nonwhite	0/144 (0)	0/95 (0)	NA	NA	NA

**TABLE IV-23: COMBINED SAFETY ANALYSIS FOR PHOTSENSITIVITY REACTION
RELATED TO STUDY MEDICATION SUBSET BY DEMOGRAPHIC ASPECTS**

Subset	Sparfloxacin (N=993)	Comparators (N=601)	95% C.I.	P-value Fisher's Exact	P-value Breslow- Day's
Male	0	0	NA	NA	NA
Female	36/993 (3.6%)	3/601 (0.5%)	(1.8%, 4.7%)	<0.001	NA
<65	36/990 (3.6%)	3/597 (0.5%)	(1.8%, 4.7%)	<0.001	NA
≥65	0/3 (0)	0/4 (0)	NA	NA	NA
White	36/849 (4.2%)	3/506 (0.6%)	(2.1%, 5.5%)	<0.001	NA
Nonwhite	0/144 (0)	0/95 (0)	NA	NA	NA

TABLE IV-24: COMBINED SAFETY ANALYSIS FOR THE DAY OF ONSET, DURATION, AND NUMBER OF EPISODES OF PHOTSENSITIVITY REACTION			
Photosensitivity Reaction	Sparfloxacin (37/993)	Comparators (3/601)	P-value: Fisher's Exact
Day of Onset <i>Relative to the First Dose of Study Medication:</i>			
Mean ± S.D. Range	4.3 ± 5.5	9.7 ± 5.8	0.111*
<i>Relative to the Last Dose of Study Medication:</i>			
Mean ± S.D. Range	-1.9 ± 5.7	3.3 ± 3.8	0.131*
Duration			
Mean ± S.D. Range	9.2 ± 11.0	2.7 ± 0.6	0.001**
Number of Episodes			
1	34 (91.9%)	3 (100.0%)	1.000
2	3 (8.1%)	0	1.000
* : P-value by two-sample t test for independent samples with equal variances.			
** : P-value by two-sample t test for independent samples with unequal variances.			

TABLE IV-25: COMBINED SAFETY ANALYSIS FOR PHOTSENSITIVITY REACTION BY SELECTED CLASSES OF CONCOMITANT MEDICATION			
Class of Concomitant Medication	Sparfloxacin (37/993)	Comparators (3/601)	P-value: Fisher's Exact
Sunscreens	19/79 (24.1%)	2/43 (4.7%)	0.006
Antihistamines	1/30 (3.3%)	0/19 (0)	1.000
Oral Contraceptives	16/413 (3.9%)	2/219 (0.9)	0.042
Tricyclic Antidepressants	0	0	NA
NSAIDS	8/178 (4.5%)	0/98 (0)	0.054
Diuretics	0	0	NA

TABLE IV-26: COMBINED SAFETY ANALYSIS FOR PHOTOTOXICITY REACTION BY OUTCOME AND ACTION TAKEN			
Outcome or Action Taken	Sparfloxacin (37/993)	Comparators (3/601)	P-value: Fisher's Exact
<u>Outcome at End of Study</u>			
Recovered	37 (100%)	3 (100.0%)	NA
Recovered with Sequelae	0	0	NA
Ongoing	0	0	NA
<u>Action Taken - Study</u>			
None	35 (94.6%)	3 (100.0%)	1.000
Discontinued	2 (5.4%)	0	1.000
<u>Action Taken - Other</u>			
None	23 (62.6%)	1 (33.3%)	0.553
Medication	12 (32.4%)	1 (33.3%)	1.000
Other	2 (5.4%)	1 (33.3%)	0.214
<u>Discontinued From the Study</u>			
Yes	2 (5.4%)	0	1.000
No	35 (94.6%)	3 (100.0%)	1.000

V. SUMMARY AND CONCLUSIONS **(Which May be Conveyed to the Sponsor)**

ACUTE BACTERIAL EXACERBATIONS OF CHRONIC BRONCHITIS

Study 356 was conducted to demonstrate the efficacy and safety of sparfloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis.

Statistical evaluation of efficacy was based upon the two-sided 95% confidence interval of sparfloxacin minus its comparator (ofloxacin) in clinical and bacteriologic rates at the test-of-cure and the late follow-up visits. The Medical Officer's clinically and bacteriologically evaluable populations were used in the analyses.

Statistical evaluation of safety was based upon the comparison of the adverse event rates between sparfloxacin and ofloxacin in all patients receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval of cure+improvement rate of clinical response at test-of-cure was $_{244, 245} (-7.1\%, 4.4\%)$ $_{87.5\%, 88.8\%}$. At the late follow-up visit, the 95% confidence interval of sustained cure+delayed cure+sustained improvement rate of clinical sustained/delayed response was $_{218, 214} (-6.8\%, 7.8\%)$ $_{79.8\%, 79.3\%}$, and the 95% confidence interval of sustained eradicated rate of bacteriologic sustained/delayed response was $_{188, 185} (-9.8\%, 5.2\%)$ $_{80.7\%, 83.0\%}$. These results demonstrated that sparfloxacin was therapeutically equivalent in efficacy to ofloxacin in the treatment of acute bacteria exacerbations of chronic bronchitis except with respect to all eradicated (eradicated+presumed eradicated) rate of bacteriologic response at test-of-cure, of which the 95% confidence interval was $_{221, 231} (-10.4\%, 1.0\%)$ $_{87.4\%, 92.0\%}$.

2. Significance heterogeneity of the treatment effect was observed between the race subgroup (except the clinical sustained/delayed response). The treatment effect favored sparfloxacin in nonwhite patients.

3. The rate of patients with adverse events was 54.4% (215/395) for sparfloxacin and 55.6% (224/403) for ofloxacin (Fisher's exact p-value=0.776). However, the incidence rate of photosensitivity reaction was significantly higher in the sparfloxacin group (8.4%, 33/395) than the ofloxacin group (0.7%, 3/403) (Fisher's exact p-value<0.001).

From an efficacy standpoint, Study 356 provided evidence that sparfloxacin was therapeutically equivalent to ofloxacin with respect to clinical responses in the treatment of acute bacterial exacerbations of chronic bronchitis, however, it should be pointed out they were not therapeutically equivalent with respect to bacteriologic response at test-of-cure. The study demonstrated that the safety profile of sparfloxacin in photosensitivity reaction was considerably poorer than that of ofloxacin, although sparfloxacin therapy was as safe as ofloxacin in the other safety parameters.

COMBINED SAFETY ANALYSIS

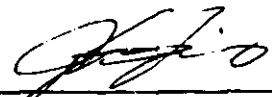
The following statements pertain to six Phase III clinical studies regarding the CAP, ABECB, indications:

The combined safety analyses demonstrated that sparfloxacin of 10 days treatment had a significantly higher incidence frequency of photosensitivity reaction than the combined comparator treatment. For the other safety parameters, sparfloxacin and the combined comparators yielded comparable safety results.

Results observed in the safety analysis subset by demographic aspects and indication generally agreed with each other and were consistent with those observed in the overall safety analysis. Some contradictions among subgroup results were expected due to the large number of subgroup analyses that were performed or the paucity of subsample size. However, the results by all subgroups always showed that sparfloxacin had a significantly higher incidence rate of photosensitivity reaction than the combined comparators, as shown by the overall population.

The following statements pertain to two studies:

The combined safety analyses demonstrated that sparfloxacin of 1 or 3 days treatment had a significantly higher incidence frequency of photosensitivity reaction than the combined comparator treatment. Compared with the combined comparators, sparfloxacin had a significantly higher frequency of adverse events related to study medication, as it had in body as a whole, cardiovascular, respiratory, and skin and appendage systems. This result failed to provide evidence that sparfloxacin could offer safety advantage compared with the combined comparators in the treatment of _____ moreover, in some aspects, sparfloxacin was not comparable in safety to its combined comparators. The clinical relevance of this finding need to be evaluated by the Medical Officer.

 10/29/96

Joel Jiang, Ph.D.
Statistician, DBIV

Concur:

 10/29/96

Daphne Lin, Ph.D.
Acting Team Leader, DBIV

 10/29/96

Ralph Harkins, Ph.D.
Division Director, DBIV

cc:

Archival: NDA 20-677

HFD-520

HFD-520/Feigal

HFD-520/Albueme

HFD-520/Moledina

HFD-520/LeSane

HFD-725/Harkins

HFD-725/Lin

HFD-725/Bail

HFD-725/Jiang

HFD-344/Thomas

Chron.

This review contains 53 pages

WordPerfect 6.1/NDA20677.wpd/10/29/96

STATISTICAL REVIEW AND EVALUATION

NDA: 20-677
Generic Drug Name: sparfloxacin
Drug Trade Name: ZAGAM®
Formulation: oral tablets
Drug Class: 1S
Applicant: Rhône-Poulenc Rorer Pharmaceuticals, Inc.

OCT 18 1996

Indications: 1. Community Acquired Pneumonia (CAP)

User Fee Data: December 27, 1996

Documents Reviewed: NDA Volumes 1.263, 1.264, 1.265, 1.274, 1.275, 1.276, 1.277, 1.283, 1.284.
SAS datasets dated March 4, 1996 provided by the applicant on diskettes.
Electronic data obtained from the Medical Officer's CANDAs on June 25, 1996.

Type of Review: Clinical

Medical Officer: Nasim Moledina, M.D., HFD-520
Statistical Reviewer: B. Sue Bell, Ph.D., HFD-725
Project Manager: Frances LeSane, HFD-520

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I. COMMUNITY ACQUIRED PNEUMONIA

I.A. INTRODUCTION

The applicant has submitted two pivotal studies in support of its application for sparfloxacin to be approved for the treatment of community acquired pneumonia (CAP). "Improvements over currently available quinolones include better *in vitro* activity against gram-positive aerobic organisms and an increased half-life which allows for once daily administration." [page 8-137-13 of volume 1.263] Both studies were undertaken to evaluate the efficacy and safety of sparfloxacin compared with approved agents in the treatment of CAP. Protocol 301 employed erythromycin as the comparator while protocol 352 employed cefaclor as the comparator. Sparfloxacin was administered orally for 10 consecutive days in the treatment of patients with CAP.

1.5. METHODS

Both studies were conducted as double-blind, double-dummy, randomized, comparative, multicenter trials of sparfloxacin versus a comparator in patients with CAP. Patients were randomly assigned in a 1:1 ratio to receive either sparfloxacin (400 mg loading dose followed by 200 mg once a day) for 10 days or the comparator treatment for 10 days. The comparator for protocol 301 was erythromycin delayed release (500 mg every 6 hours), and the comparator for protocol 352 was cefaclor (500 mg every 8 hours). Study visits were scheduled for baseline (Visit 1), Day 4 ± 1 of treatment (Visit 2), Day 20 ± 3 (10 days post-treatment; Visit 3 [Test-of-Cure]), and Day 38 ± 7 (28 days post-treatment; Visit 4). The study period for protocol 301 was May 1, 1992, through February 2, 1995, and for protocol 352 was June 1, 1992, through March 4, 1995.

The applicant's biostatistics department generated consecutive allocation numbers and divided them among the requesting centers in blocks of four. Each patient who qualified for the study was assigned the next available allocation number and received the treatment regimen associated with that allocation number.

Enrollees were male and female patients 18 years of age or older with presumed community-acquired bacterial pneumonia, as confirmed by a chest x-ray showing pulmonary findings consistent with pneumonia and new (or worsened from premonitory state) cough and sputum production. Excluded were female patients with childbearing potential. Protocol 301 excluded patients with a known hypersensitivity to quinolones or erythromycin while protocol 352 excluded patients with a hypersensitivity to quinolones, penicillins, or cephalosporins. Also excluded were patients from acute-care hospital or nursing home settings with presumed nosocomial pneumonia. Refer to the medical officer's report for additional details on inclusion and exclusion criteria.

An assessment of the patient's response to study drug treatment was to be made at Visit 3 (or Premature Discontinuation before Visit 3). An assessment of recurrence of infection was to be determined at Visit 4 (or Premature Discontinuation after Visit 3).

To ensure patient safety and appropriate efficacy with regards to sparfloxacin and the comparator, patients were to be given specific instructions. To ensure optimal absorption of sparfloxacin, patients were to be told to take the study medication 2 hours before or after taking ferrous sulfate, zinc supplements, or multivitamins containing zinc. To ensure optimal absorption of erythromycin, patients were to be told to take the study medication at least ½ hour and preferably 2 hours before or after a meal. Cefaclor-treated patients were told to take the study medication on an empty stomach, whenever possible. Investigators were expected to review each patient's concomitant medications to identify potential drug interactions. Both study protocols were amended October 25, 1993, to enhance the instructions to the patient regarding sparfloxacin-associated photosensitivity.

REVIEWER COMMENT: *It is unclear to this reviewer how the blind was maintained if different instructions were given for taking each study medication with respect to food and vitamins.*

REVIEWER COMMENT: *Confidence intervals calculated by this reviewer will be based on the normal approximation to the binomial distribution with a continuity correction.*

I.C. RESULTS**IC.1. PROTOCOL 301****IC.1.1. EFFICACY EVALUATION**

Applicant: The primary efficacy parameter was the clinical response rate in the clinically evaluable patient population based on the clinical response as determined by the investigator at the Test-of-Cure Visit. The investigator was to classify each patient's response as: Cure, Improvement, Failure or indeterminate. Clinical response and clinical recurrence were both based on the investigator's clinical evaluation of signs and symptoms of pneumonia and chest x-ray results.

Secondary efficacy parameters included clinical response (all-treated and bacteriologically evaluable patient populations); clinical recurrence (all-treated, clinically evaluable, and bacteriologically evaluable patient populations); and by patient bacteriologic response, by-pathogen bacteriologic response, bacteriologic relapse-reinfection and overall response (all-treated with a baseline pathogen and bacteriologically evaluable patient populations).

Table 1 is the applicant's summary of the primary and secondary efficacy results for the clinically and bacteriologically evaluable patients at test of cure that was at the third visit at 7-13 days post-treatment.

Table 1: Applicant's summary of efficacy results for protocol 301

Efficacy Parameter (Population, Time Point)	Number (%) of Patients		
	Sparfloxacin 400*/200 mg QD	Erythromycin 500 mg q 6h	95% CI
Clinical Response Rate - Cured + Improved** Clinical Cure Rate (clinically evaluable, at TOC)	153/177 (86.4) 85/177 (48.0)	130/161 (80.7) 65/161 (40.4)	-2.2, 13.1 -2.9, 18.2
Clinical Recurrence Rate (clinically evaluable, at late follow-up)	2/134 (1.5)	2/109 (1.8)	ND
By-Pathogen Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	61/65 (93.8)	48/52 (92.3)	ND
By-Patient Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	46/49 (93.9)	35/38 (92.1)	-9.1, 12.7
Bacteriologic Relapse Rate	0/29 (0.0)	1/19 (5.3)	ND
Reinfection Rate	0/29 (0.0)	0/19 (0.0)	ND
Relapse + Reinfection Rate (bacteriologically evaluable, at late follow-up)	0/29 (0.0)	0/19 (0.0)	ND
Overall Response Rate - Cured or Improved and Eradicated or Presumed Eradicated (bacteriologically evaluable, at TOC)	43/49 (87.8)	35/38 (92.1)	-16.9, 8.2

CI = confidence interval; TOC = Test-of-Cure; ND = not done.

* Loading Dose

** Primary efficacy parameter

REVIEWER COMMENT: The statistical reviewer was able to recreate the results reported above using the SAS datasets provided by the applicant and the electronic dataset produced from the CANDA.

After making the continuity correction, the 95% confidence interval for the clinical response rate for cured and improved is 177,161 [-2.8% , 14.2%] ^{95%, 91%} and the 95% confidence interval for the clinical cure rate is 177,161 [-3.5% , 18.8%] ^{95%, 40%}. Since the lower bounds are greater than -10%, these confidence intervals meet the DA:DP's Points to Consider document's usual requirement for establishing equivalence.

By-pathogen and by-patient bacteriologic responses were derived from sputum, throat culture, or serology results and the clinical evaluation of signs and symptoms, bacteriologic relapse/reinfection was derived from the by-patient bacteriologic response, and overall response was derived from the clinical response and the by-patient bacteriologic response. Table 2 presents the applicant's clinical response rate by baseline pathogen.

Table 2: Applicant's clinical response rate by baseline pathogen^a (bacteriologically evaluable population) for protocol 301.

Infection Type	Number (%) of Patients	
	Sparfloxacin 400 [*] /200 mg QD	Erythromycin 500 q 6h
Population Response Rate	44/49 (89.8)	35/38 (92.1)
<i>M. pneumoniae</i> ^b	15/16 (93.8)	15/15 (100)
<i>S. pneumoniae</i>	15/17 (88.2)	10/11 (90.9)

* Loading Dose

a Isolated in ≥ 10 patients in either treatment group.

b Results obtained by serology. *S. pneumoniae* isolated from sputum.

Ref.: Appendix B.6.3.1

REVIEWER COMMENT: In Table 3, subgroup analysis conducted by the statistical reviewer is presented. Based upon Breslow-Day's test for homogeneity, no statistical difference in the proportions cured was found among subgroups.. In addition to the subgroups presented, no statistically significant difference was found when gender by age-group was analyzed.

Table 3: Protocol 301's clinical response rate based upon applicant's patient evaluation by demographic variable and treatment group for the clinically evaluable population at the test of cure visit at Day 10 ± 3 days posttreatment.						
	Sparfloxacin 400*/200 mg QD		Erythromycin 500 mg q 6h			
	Cured or Improved / Evaluable	% Cured or Improved	Cured or Improved / Evaluable	% Cured or Improved	95% CI of Difference in %'s Cured	p-value Breslow-Day Test
Population Response Rate	153 / 177	(86.4%)	130 / 161	(80.7%)	(-2.8%, 14%)	
Age (years)						0.613
< 45	74 / 81	(91.4%)	64 / 76	(84.2%)	(-4.4%, 18.7%)	
45-65	53 / 62	(85.5%)	45 / 58	(77.6%)	(-7.6%, 23.4%)	
> 65	26 / 34	(76.5%)	21 / 27	(77.8%)	(-25%, 23%)	
Gender						0.677
Male	97 / 110	(88.2%)	94 / 112	(83.9%)	(-5.7%, 14.2%)	
Female	56 / 67	(83.6%)	36 / 49	(73.5%)	(-6.8%, 27.1%)	
Race						0.302
Caucasian	129 / 150	(86.0%)	114 / 138	(82.6%)	(-5.7%, 12.5%)	
Black	14 / 15	(93.3%)	10 / 14	(71.4%)	(-1.3%, 56%)	
Hispanic	8 / 9	(88.9%)	5 / 8	(62.5%)	ND	
Oriental	1 / 1	(100%)	1 / 1	(100%)	ND	
Other	1 / 2	(50.0%)	0 / 0	(0%)	ND	
* Loading Dose ND - not done						

Medical Officer: The evaluable population considered by the medical officer was composed of the clinically evaluable patients with a baseline pathogen. The primary outcome was clinical response as determined by the investigator at the Test-of-Cure Visit. If a patient was a clinical failure at the test of cure visit, then the patient was considered a clinical failure at follow-up.

The medical officer determined that 72 of 149 (48%) and 55 of 130 (42%) clinically evaluable patients with a baseline pathogen were cured by sparfloxacin and erythromycin, respectively, with a 95% confidence interval of the difference in the percents cured of $_{149,130} [-6.4\% , 18.4\%]_{48\%,42\%}$. When cured or improved are considered successful outcomes, then 129 of 149 (87%) and 107 of 130 (82%) clinically evaluable patients with a baseline pathogen were cured or improved by sparfloxacin and erythromycin, respectively, with a 95% confidence interval of the difference in the percents cured or improved of $_{149,130} [-5\% , 13.5\%]_{87\%,82\%}$.

For sparfloxacin, the medical officer determined that 65 of 136 (48%) had sustained cure and 96 of 136 (70.6%) had sustained cure or sustained improvement. For erythromycin, 48 of 114 (42%) had sustained cure and 75 of 114 (65.8%) had sustained cure or sustained improvement. The 95% confidence interval of the difference in the treatment percents for sustained cure is $_{136,114} [-7.5\% , 18.8\%]_{48\%,42\%}$, and the 95% confidence interval of the difference in treatment percents for sustained cure or sustained improvement is $_{136,114} [-7.6\% , 17.2\%]_{71\%,66\%}$.

I.C.1.b. SAFETY EVALUATION

Applicant: Table 4 summarizes adverse clinical events and adverse laboratory events for protocol 301. Note that the percentage of patients who experienced a photosensitivity reaction was statistically significantly higher ($p=0.001$; generalized Cochrane-Mantel-Haenszel Test) in the sparfloxacin group (6.4%, 14/219) as compared with the erythromycin group (0.5%, 1/209). In contrast, the percentage of patients who experienced an adverse event related to the digestive system was statistically significantly lower ($p=0.001$; generalized Cochrane-Mantel-Haenszel Test) in the sparfloxacin group (21.9%, 48/219) as compared with the erythromycin group (44.5%, 93/219).

For further analysis on the safety of sparfloxacin, refer to the separate review of the integrated summary of safety for this NDA.

Table 4: Applicant's summary of safety for protocol 301.

Safety Parameter	Number (%) Patients		
	Sparfloxacin (N=219)	Erythromycin (N=209)	p-value
Adverse Event ^a	136 (62.1)	140 (67.0)	ND
Most Common ^b			
Nausea	13 (5.9)	43 (20.6)	ND
Diarrhea	15 (6.8)	38 (18.2)	ND
Vomiting	12 (5.5)	25 (12.0)	ND
Abdominal Pain	9 (4.1)	24 (11.5)	ND
Headache	16 (7.3)	14 (6.7)	ND
Photosensitivity Reaction	14 (6.4)	1 (0.5)	<0.001
Digestive System	48 (21.9)	93 (44.5)	<0.001
Musculoskeletal System	6 (2.7)	7 (3.3)	ND
Nervous System	28 (12.8)	24 (11.5)	0.494
Cardiovascular System	19 (8.7)	16 (7.7)	0.661
Adverse Events Related to Study Drug	85 (38.8)	108 (51.7)	ND
Most Common ^b			
Diarrhea	14 (6.4)	36 (17.2)	ND
Nausea	9 (4.1)	35 (16.7)	ND
Abdominal Pain	4 (1.8)	22 (10.5)	ND
Vomiting	8 (3.7)	17 (8.1)	ND
Photosensitivity Reaction	13 (5.9)	1 (0.5)	ND
Adverse Events Leading to Discontinuation	21 (10.0)	31 (14.8)	ND
Most Common ^c			
Nausea	2 (1.0)	9 (4.3)	ND
Vomiting	1 (0.5)	9 (4.3)	ND
Pneumonia	2 (1.0)	5 (2.4)	ND
Abdominal Pain	0	6 (2.8)	ND
Serious Adverse Events	16 (7.3)	16 (7.7)	ND
Adverse Laboratory Events	30 (13.7)	28 (13.4)	ND
Most Common ^c			
SGPT	12 (5.5)	9 (4.3)	ND
SGOT	9 (4.1)	6 (2.9)	ND
Neutrophils	5 (2.3)	5 (2.4)	ND
White Blood Cell Count	7 (3.2)	5 (2.4)	ND
Platelets	5 (2.3)	2 (1.0)	ND
ND = not done			
a The majority of adverse events were of mild or moderate severity.			
b Reported by 5% of patients in either treatment group.			
c Reported by 2% of patients in either treatment group.			

LC.2. PROTOCOL 352**LC.2.a. EFFICACY EVALUATION**

Applicant: The primary efficacy parameter was the clinical response rate in the clinically evaluable patient population based on the clinical response as determined by the investigator at the Test-of-Cure Visit. The investigator was to classify each patient's response as: Cure, Improvement, Failure or Indeterminate. Clinical response and clinical recurrence were both based on the investigator's clinical evaluation of signs and symptoms of pneumonia and chest x-ray results.

Secondary efficacy parameters included clinical response (all-treated and bacteriologically evaluable patient populations); clinical recurrence (all-treated, clinically evaluable, and bacteriologically evaluable patient populations); and by patient bacteriologic response, by-pathogen bacteriologic response, bacteriologic relapse-reinfection and overall response (all-treated with a baseline pathogen and bacteriologically evaluable patient populations).

Table 5 is the applicant's summary of the primary and secondary efficacy results for the clinically and bacteriologically evaluable patients at test of cure that was at the third visit at 7-13 days posttreatment.

Table 5: Applicant's summary of primary efficacy results for protocol 352

Efficacy Parameter (Population, Time Point)	Number (%) of Patients		
	Sparfloxacin 400*/200 mg QD	Cefaclor 500 mg q 8h	95% CI
Clinical Response Rate - Cured + Improved**	116/134 (86.6)	108/128 (84.4)	-6.3, 10.7
Clinical Cure Rate (clinically evaluable, at TOC)	59/134 (44.0)	50/128 (39.1)	-7, 16.9
Clinical Recurrence Rate (clinically evaluable, at late follow-up)	3/99 (3.0)	1/99 (1.0)	ND
By-Pathogen Bacteriologic Response Rate - Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	159/173 (91.9)	119/142 (83.8)	ND
By-Patient Bacteriologic Response Rate- Eradicated + Presumed Eradicated (bacteriologically evaluable, at TOC)	97/109 (89.0)	79/100 (79.0)	0.1, 19.9
Bacteriologic Relapse Rate	0/81 (0.0)	1/72 (1.4)	ND
Reinfection Rate	0/81 (0.0)	0/72 (0.0)	ND
Relapse + Reinfection Rate (bacteriologically evaluable, at late follow-up)	0/81 (0.0)	0/72 (0.0)	ND
Overall Response Rate - Cured or Improved and Eradicated or Presumed Eradicated (bacteriologically evaluable, at TOC)	95/109 (87.2)	79/100 (79.0)	-2, 18.3

CI=confidence interval; TOC=Test-of-Cure; ND=not done.

* Loading Dose

** Primary efficacy parameter

Ref.: Appendices B.6.1, B.6.1.2, B.7.1.1., B.7.1.4, B.7.1.5, B.8.1.

REVIEWER COMMENT: The statistical reviewer was able to essentially recreate the results reported above using the SAS datasets provided by the applicant and the SAS dataset produced from the CANDA. In the dataset produced from the CANDA there was one less clinically evaluable patient in the cefaclor treated group.

After making the continuity correction, the 95% confidence interval for the clinical response rate for cured and improved is $134,128 [-7.1\%, 11.5\%]$ $67\%, 84\%$, and the 95% confidence interval for the clinical cure rate is $134,128 [-7.7\%, 17.7\%]$ $44\%, 39\%$. Since the lower bounds are greater than -10%, these confidence intervals meet the DAIDP's Points to Consider document's usual requirement for establishing equivalence.

By-pathogen and by-patient bacteriologic responses were derived from sputum, throat culture, or serology results and the clinical evaluation of signs and symptoms, bacteriologic relapse/reinfection was derived from the by-patient bacteriologic response, and overall response was derived from the clinical response and the by-patient bacteriologic response. Table 6 presents the applicant's clinical response rate by baseline pathogen.

Table 6: Applicant's clinical response rate by baseline pathogen* (bacteriologically evaluable population) for protocol 352.

Infection Type	Number (%) of Patients	
	Sparfloxacin 400*/200 mg QD	Cefaclor 500 mg q 8 h
Population Response Rate	98/109 (89.9)	87/100 (87.0)
<i>H. parainfluenzae</i>	51/55 (92.7)	35/41 (85.4)
<i>M. pneumoniae</i> ^b	21/23 (91.3)	20/24 (83.3)
<i>H. influenzae</i>	19/24 (79.2)	27/31 (87.1)
<i>S. pneumoniae</i>	24/24 (100)	17/17 (100)
<i>C. pneumoniae</i> ^b	10/13 (76.9)	5/5 (100)

* Loading Dose

a Isolated in ≥ 10 patients in either treatment group.

b Results obtained by serology.

Ref.: Appendix B.6.3.1

REVIEWER COMMENT: In Table 7, subgroup analysis conducted by the statistical reviewer is presented. Based upon Breslow-Day's test for homogeneity, no statistical difference in the proportions cured was found among subgroups. In addition to the subgroups presented, no statistically significant difference was found when gender by age-group was analyzed.

Table 7: Protocol 352's clinical response rate based upon applicant's patient evaluation by demographic variable and treatment group for the clinically evaluable population at the test of cure visit at Day 10 ± 3 days post treatment.

	Sparfloxacin 400*/200 mg QD		Cefactor 500 mg q 8h		95% CI of Difference in %'s Cured	p-value Breslow-Day Test
	Cured or Improved / Evaluable	% Cured or Improved	Cured or Improved / Evaluable	% Cured or Improved		
Population Response Rate	116 / 134	(86.6%)	107 / 127 ¹	(84.37%)	(-7%, 11.7%)	
Age (years)						0.544
< 45	53 / 62	(85.5%)	45 / 53	(84.9%)	(-14%, 15%)	
45-65	40 / 47	(85.1%)	37 / 43	(86.1%)	(-18%, 16%)	
> 65	23 / 25	(92%)	25 / 31	(80.7%)	(-9.7%, 32%)	
Gender						0.963
Male	65 / 74	(87.8%)	66 / 77	(85.7%)	(-10%, 14%)	
Female	51 / 60	(83.6%)	41 / 50	(82.0%)	(-13%, 19%)	
Race						0.383
Caucasian	93 / 109	(85.3%)	82 / 100	(82.0%)	(-7.7%, 14%)	
Black	20 / 21	(95.2%)	18 / 20	(90.0%)	(-16%, 26%)	
Hispanic	3 / 4	(75.0%)	5 / 5	(100%)	ND	
Oriental	0 / 0		2 / 2	(100%)	ND	

* Loading Dose

ND - not done

¹ Applicant reported 108/128 in volume 1.275 page 8-149-57; but the CANDA dataset supported 107/127.

Medical Officer: The evaluable population considered by the medical officer was composed of the clinically evaluable patients with a baseline pathogen. The primary outcome was clinical response as determined by the investigator at the Test-of-Cure Visit. If a patient was a clinical failure at the test of cure visit, then the patient was considered a clinical failure at follow-up.

The medical officer determined that 55 of 124 (44%) and 48 of 119 (40%) clinically evaluable patients with a baseline pathogen were cured by sparfloxacin and cefaclor, respectively, with a 95% confidence interval of the difference in the percents cured of $_{124,119} [-9.2\% , 17.2\%]$ 44%,40%. When cured or improved are considered successful outcomes, then 108 of 124 (87%) and 101 of 119 (85%) clinically evaluable patients with a baseline pathogen were cured or improved by sparfloxacin and cefaclor, respectively, with a 95% confidence interval of the difference in the percents cured or improved of $_{124,119} [-7.3\% , 11.8\%]$ 87%,85%.

For sparfloxacin, the medical officer determined that 47 of 109 (43.1%) had sustained cure and 64 of 109 (58.7%) had sustained cure or sustained improvement. For cefaclor, 44 of 110 (40%) had sustained cure and 55 of 110 (50%) had sustained cure or sustained improvement. The 95% confidence intervals for the difference in the treatment percents for sustained cure is $_{109,110} [-10.8\% , 17.1\%]$ 43%,40%, and the 95% confidence interval for the difference in treatment percents for sustained cure or sustained improvement is $_{109,110} [-5.3\% , 22.8\%]$ 59%,50%.

1.C.1.b. SAFETY EVALUATION

Applicant: Table 8 summarizes adverse clinical events and adverse laboratory events for protocol 352. Note that sparfloxacin is not statistically significantly worse than cefaclor with respect to any of the reported adverse events.

Table 8: Applicant's summary of safety for protocol 352

Safety Parameter	Number (%) Patients		
	Sparfloxacin (n= 168)	Cefaclor (n= 162)	p-value
Adverse Event ^a	84(50.0)	80(49.4)	ND
Most Common ^b			
Headache	18(10.7)	14 (8.6)	ND
Rhinitis	10 (6.0)	11 (6.8)	ND
Diarrhea	7 (4.2)	10 (6.2)	ND
Digestive System	24 (14.3)	21 (13.0)	0.846
Musculoskeletal System	3 (1.8)	3 (1.9)	ND
Nervous System	16 (9.5)	14 (8.6)	0.924
Cardiovascular System	12 (7.1)	8 (4.9)	0.446
Photosensitivity Reaction	4 (2.4)	1 (0.6)	0.177
Adverse Events Related to Study Drug	37 (22.0)	41 (25.3)	ND
Adverse Events Leading to Discontinuation ^c	11(6.5)	9 (5.6)	ND
Most Common ^d			
Pneumonia	1 (0.6)	4 (2.5)	ND
Serious Adverse Events	11 (6.5)	8 (4.9)	ND
Adverse Laboratory Events	18 (10.7)	14 (8.6)	ND
Most Common ^d			
SGPT	9 (5.4)	6 (3.7)	ND
SGOT	8 (4.8)	5 (3.1)	ND
Blood Glucose	4 (2.4)	1 (0.6)	ND

ND=not done

- a The majority of adverse events were of mild or moderate severity.
- b Reported by 5% of patients in either treatment group
- c One additional patient in the cefaclor group experienced an adverse event that led to discontinuation from the study by the investigator; however, the investigator classified the reason for discontinuation for this patient as test drug ineffective in the disposition section of the case report form.
- d Reported by 2% of patients in either treatment group.

Ref.: B.11.1, B.11.1.2, B.11.2., B.12.4, and Appendix E.

LC.3. COMBINED BACTERIOLOGICAL PATHOGEN ANALYSIS

Applicant: The applicant is requesting labeling for the following specific microorganisms associated with CAP: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Table 9 combines the bacteriologic results from protocol 301 and protocol 352.

Table 9: Applicant's assessment of bacteriologic response by baseline pathogen at test of cure combined for protocol 301 and protocol 352 in the bacteriologically evaluable patients.						
Microorganisms requested for labeling	(n of isolates eradicated or presumed eradicated) / (total N of isolates)					
	Sparfloxacin		Erythromycin		Cefaclor	
	n/N	%	n/N	%	n/N	%
<i>Streptococcus pneumoniae</i>	39/41	95.1%	17/17	100%	10/11	90.9%
<i>Haemophilus influenzae</i>	19/24	79.2%			27/31	87.1%
<i>Haemophilus parainfluenzae</i>	51/55	92.7%			35/41	85.4%
<i>Moraxella catarrhalis</i>	7/8	87.5%	4/4	100%	5/6	83.3%
<i>Chlamydia pneumoniae</i>	10/13	76.9%			5/5	100%
<i>Mycoplasma pneumoniae</i>	36/39	92.3%	15/15	100%	20/24	83.3%

REVIEWER COMMENT: DAIDP's Points to Consider document requires at least 10 cases of the clinically and microbiologically evaluable cases be successfully treated with the investigative agent for the microorganism to be specifically included in the INDICATIONS AND USAGE section of the product labeling. Note that *Moraxella catarrhalis* does not meet this guideline.

I.D. SUMMARY AND CONCLUSIONS

Under protocol 301 for the treatment of community acquired pneumonia, sparfloxacin administered orally for 10 days with a 400 mg loading dose followed by 200 mg once a day met DAIDP's guideline for comparability with erythromycin administered orally for 10 days at 500 mg every 6 hours. Based upon the medical officer's review of clinically evaluable patients with a baseline pathogen, the 95% confidence interval for the difference in percent cured or improved by sparfloxacin and the percent cured or improved by erythromycin is 149,130 [-5% , 13.5%] 87%,82%.

Under protocol 352 for the treatment of community acquired pneumonia, sparfloxacin administered orally for 10 days with a 400 mg loading dose followed by 200 mg once a day met DAIDP's guideline for comparability with cefaclor administered orally for 10 days at 500 mg every 8 hours. Based upon the medical officer's review of clinically evaluable patients with a baseline pathogen, the 95% confidence interval for the difference in percent cured or improved by sparfloxacin and the percent cured or improved by cefaclor is 124,119 [-7.3% , 11.8%] 87%,85%.

Sparfloxacin-treated patients under protocol 301 experienced a statistically higher adverse event rate for photosensitivity reaction than erythromycin-treated patients (p-value < 0.001). For protocol 352 the difference was not statistically significant (p-value = 0.18).

After pooling the bacteriological results from the two protocols, *Moraxella catarrhalis* does not meet the guideline specified in DAIDP's Points to Consider for inclusion in the INDICATIONS AND USAGE section of the product labeling. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* do meet the guideline for inclusion in the label.

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This review contains 14 pages
WordPerfect 6.1/nda20677.wpd

SEP - 3 1996

Statistical Review and Evaluation

NDA/IND #: 20-677/36-888 (rat carcinogenicity study)
Applicant: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Name of Drug: Zagam (Sparfloxacin)
Types of Review: Animal Carcinogenicity

Documents Reviewed:

1. NDA submission volume 1 of 6, "A 104-week Carcinogenicity Study of AT-4140 in Rats", Study number P-1821.
2. Pharmacology Review written by Dr. Kenneth Seethaler, received August 13, 1996.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. Dr. Kenneth Seethaler, HFD-520, who is the reviewing pharmacologist of the rat study of this NDA has requested the Division of Biometrics IV to check the histopathological findings in the rat study. Note that the sponsor did not submit the tumor data in computer readable media. The following analyses are based on the summary tables included in the submission.

II. The Rat Study

II. a. Design

In this study, AT-4140 (sparfloxacin) was administered orally in the diet to groups of 50 male and 50 female Wistar rats at the dose levels of 50, 100, 200, and 300 mg/kg/day for 103-104 weeks. Two control groups of 50 rats/sex received a standard diet alone. Because of excessive toxicity observed during the first few months, male rats at 300 mg/kg/day were terminated at the end of week 38 and excluded from the study. Histopathological examinations were performed for animals in all groups (excluding the males at 300 mg/kg/day).

II. b. Reviewer's Analyses

The intercurrent mortality rates for both male and female rats (see Appendix 1 - the sponsor's Tables 1-1 and 1-2) are tested for linear trend according to the Peto death rate method using the

time intervals 0-52, 53-78, and 79-104 weeks. The following analyses combine the data of two control groups and exclude the male dose group of 300 mg/kg/day. The actual dose levels 0, 50, 100, and 200 mg/kg/day are the scores assigned to the controls, low, medium, and high dose groups for males, respectively, and 0, 50, 100, 200, and 300 mg/kg/day for the controls, low, medium, high-1, and high-2 dose groups for females, respectively. The results of the analyses show that there are significant (at 0.05 level) linear trends in the intercurrent mortality rate in male ($p = 0.0189$) and female rats ($p < 0.0001$).

Since the individual tumor data are not available in computer readable media, based on the sponsor's summary tables, two approaches are applied to test the linear trend in the tumor data. First, the time-unadjusted exact permutation trend test is used to test each of the tumor data as shown in Appendix 2 (the sponsor's Tables 13-1 to 13-4). Second, the time-adjusted exact permutation trend test is used to test the adrenal pheochromocytoma. The results of the first analysis show that there is a significant (at 0.05 level) positive linear trend in the following tumor type:

<u>Tumor/organ</u>	<u>Incidence of Tumors</u>					<u>P-value</u>
Females:						
Adrenal Gland:						
Pheochromocytoma, benign	0/100	2/50	0/50	1/50	3/50	0.0318

The results of the second analysis show that there are significant positive linear trends in the adrenal gland pheochromocytoma (benign) ($p < 0.015$) and adrenal gland pheochromocytoma (benign+malignant) ($p < 0.008$) in female rats. These results are consistent with the sponsor's finding (see Appendix 3; the sponsor's Tables 15-4 to 15-6).

Since there are significant linear trends in the intercurrent mortality rate in male and female rats, the time-adjusted exact permutation trend test should be used to test the linear trend in the tumor data. Hence, the p-values from the time-adjusted exact permutation trend test (second analysis) in the adrenal pheochromocytoma are more accurate than those of first analysis.

In order to reduce the overall false positive rate, the following decision rule is used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor. On the basis of above adjustment rule, the adrenal gland pheochromocytoma (benign) and adrenal gland pheochromocytoma (benign+malignant) in female rats

is considered to be statistically significant.

III. Conclusion

Applying Peto's method to test the positive linear trend in intercurrent mortality rates, the results of the analyses show that there are significant (at 0.05 level) linear trends in the intercurrent mortality rate in male ($p = 0.0189$) and female rats ($p < 0.0001$).

The individual tumor data are not available in computer readable media, hence, two approaches are applied to test the linear trend in the tumor data. First, the time-unadjusted exact permutation trend test is used to test each of the tumor data. Second, the time-adjusted exact permutation trend test is used to test the adrenal pheochromocytoma. Results of the above tumor data analyses showed that there are significant positive linear trends in adrenal gland pheochromocytoma (benign) ($p < 0.015$) and adrenal gland pheochromocytoma (benign+malignant) ($p < 0.008$) in female rats. These findings are based on the assumption of treating adrenal gland pheochromocytoma (benign or/and malignant) in female rats as a rare tumor. If it is a common tumor, then the adrenal gland pheochromocytoma (benign or/and malignant) in female rats is not considered to be statistically significant.

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8/24/96

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This review contains ³12 pages and 9 Tables.

Appendix I (two pages)

D-1821

Table I-1 A 104-week carcinogenicity study of AT-4140 in rats
Mortality / survivor
Male

Week	Dose (mg/kg)	0-1	0-2	50	100	200	300
	No. of animals	50	50	50	50	50	50
1- 26		a) b) 0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	2 (96)
27- 52		1 (98)	1 (98)	2 (96)	0 (100)	1 (98)	32 (32)d)
53- 78		7 (84)	6 (86)	6 (84)	10 (80)	10 (78)	-
79-104		25 (34)	21 (44)	20 (44)	26 (28)	27 (24)c)	-
After 104		0	0	0	1	-	-
Total		33	28	28	37	38	34
Mean survival time (weeks)		91.2 ±13.6	93.2 ±14.5	92.6 ±14.6	90.2 ±13.6	88.6 ±14.2	84.4 ±4.1**

a) : No. of dead or sacrificed animals
b) : Percentage of survivors at end of indicated period (week)
c) : Terminal sacrifice at Week 104 of administration
d) : Terminal sacrifice after 38 weeks administration
** : p<0.01 (Significant difference from control : 0-1)

Appendix I (continued)

D-1821

Table 1-2 A 104-week carcinogenicity study of AT-4140 in rats
Mortality / survivor
Female

Week	Dose (mg/kg) No. of animals	0-1	0-2	50	100	200	300
		50	50	50	50	50	50
1- 26		a) 0 (100) b)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)
27- 52		1 (98)	3 (94)	2 (96)	0 (100)	1 (98)	2 (96)
53- 78		4 (90)	2 (90)	3 (90)	3 (94)	3 (92)	11 (74)
79-104		11 (68)	9 (72)	5 (80)	12 (70)	14 (64)	24 (28)c)
After 104		1	0	2	0	1	-
Total		17	14	12	15	19	37
Mean survival time (weeks)		97.2 ±14.3	97.3 ±15.3	98.3 ±15.2	99.0 ±9.8	98.4 ±12.8	88.4 ±17.3**

a) : No. of dead or sacrificed animals
b) : Percentage of survivors at end of indicated period (week)
c) : Terminal sacrifice at Week 104 of administration
** : p<0.01 (Significant difference from control : 0-1)

Table 13-1 A 104-week Carcinogenicity Study of AT-4140 in Rats
 Histopathological findings / Neoplastic lesions
 Male

Organ : Findings	Group Dose (ug/kg)	C I 0	C II 0	AT-4140		
				50	100	200
Haematopoietic system :		(50)	(50)	(50)	(50)	(50)
Lymphoma		1	3	2	2	0
Heart :		(50)	(50)	(50)	(50)	(50)
Endocardial schwannoma		0	2	0	1	1
Thymus :		(49)	(50)	(48)	(47)	(49)
Thymoma		0	0	1	3	0
Oral cavity :		(1)	(0)	(1)	(0)	(2)
Squamous cell papilloma		1	-	0	-	0
Fibrosarcoma		0	-	1	-	1
Osteosarcoma		0	-	0	-	1
Tongue :		(50)	(50)	(50)	(50)	(50)
Squamous cell papilloma		0	1	0	0	0
Salivary gland :		(50)	(50)	(50)	(50)	(50)
Schwannoma		0	1	0	0	0
Forestomach :		(50)	(49)	(50)	(49)	(50)
Squamous cell papilloma		1	0	0	0	0
Sarcoma NOS		0	1	0	0	0
Jejunum :		(49)	(47)	(47)	(42)	(47)
Adenocarcinoma		2	0	0	0	1
Caecum :		(50)	(48)	(49)	(44)	(42)
Adenocarcinoma		0	0	0	0	1
Liver :		(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma		0	0	1	1	0
Hepatocellular carcinoma		1	0	0	0	0
Cholangioma		0	0	0	1	0
Pancreas :		(50)	(49)	(50)	(50)	(50)
Acinar cell adenoma		7	7	4	5	3
Acinar cell carcinoma		0	1	1	1	0
Islet cell adenoma		3	2	4	0	0
Nasal cavity :		(49)	(49)	(49)	(48)	(50)
Squamous cell carcinoma		1	0	0	0	0
Lung :		(50)	(50)	(50)	(50)	(50)
Adenoma		0	1	0	0	0
Kidney :		(50)	(50)	(50)	(50)	(50)
Tubular cell adenoma		0	5	2	2	2
Tubular cell carcinoma		1	0	0	0	0
Lipoma		0	0	0	3	1
Testis :		(50)	(50)	(50)	(50)	(50)
Interstitial cell tumor		5	6	7	2	2
Prostate :		(50)	(50)	(50)	(49)	(50)
Adenoma		1	1	3	3	1
Pituitary gland :		(48)	(50)	(50)	(50)	(50)
Adenoma		20	16	11	12	11
Thyroid gland :		(50)	(49)	(50)	(50)	(50)
Follicular cell adenoma		1	1	4	2	3
Follicular cell carcinoma		1	1	0	1	0
C-cell adenoma		1	5	4	1	0
C-cell carcinoma		0	0	1	0	0
Parathyroid gland :		(49)	(48)	(47)	(50)	(49)
Adenoma		1	1	1	3	1

C I : Control I, C II : Control II
 () : Total number examined, - : Not examined

Table 13-2 A 104-week Carcinogenicity Study of AT-4140 in Rats
 Histopathological findings / Neoplastic lesions
 Male

Organ : Findings	Group Dose (mg/kg)	C1	C2	AT-4140		
				50	100	200
Adrenal gland :		(50)	(50)	(50)	(50)	(50)
Cortical adenoma		0	0	0	1	0
Pheochromocytoma, benign		5	3	3	5	7
Pheochromocytoma, malignant		1	2	3	3	1
Skin & subcutis :		(49)	(50)	(50)	(50)	(50)
Keratoacanthoma		0	3	2	0	2
Squamous cell papilloma		2	3	2	0	0
Squamous cell carcinoma		2	2	1	0	0
Sebaceous adenoma		1	1	0	0	0
Basal cell adenoma		0	0	0	1	0
Fibroma		2	3	3	2	3
Fibrosarcoma		0	0	1	0	0
Neuroma		1	0	0	0	0
Neuangioma		2	0	0	0	0
Neuangioma		1	0	0	0	0
Neural crest tumor		0	0	0	1	0
Malignant schwannoma		1	1	1	1	1
Histiocytic sarcoma		0	0	0	1	1
Fibrous histiocytoma		0	0	0	1	0
Malignant fibrous histiocytoma		0	0	0	0	1
Mammary gland :		(45)	(50)	(50)	(46)	(47)
Adenocarcinoma		0	1	1	0	0
Fibroadenoma		0	0	0	0	1
Eye :		(50)	(50)	(50)	(50)	(50)
Schwannoma		1	0	0	0	0
Harderian gland :		(50)	(50)	(50)	(50)	(50)
Adenoma		1	0	0	0	0
Auricle :		(1)	(1)	(2)	(1)	(3)
Squamous cell papilloma		0	0	1	1	0
Malignant fibrous histiocytoma		0	1	0	0	0
Brain :		(50)	(50)	(50)	(50)	(50)
Astrocytoma		0	2	0	1	0
Oligodendroglioma		0	1	0	0	0
Granular cell tumor		0	1	3	2	0
Meningioma		0	0	1	0	0
Spinal cord :		(50)	(50)	(50)	(50)	(50)
Schwannoma		0	0	1	0	0
Body cavity :		(0)	(6)	(2)	(1)	(2)
Neuroma		-	1	0	0	0
Mesothelioma		-	1	0	1	0
Fibrosarcoma		-	1	0	0	0
Malignant schwannoma		-	1	0	0	0
Histiocytic sarcoma		-	1	0	0	0

C1 : Control I, C2 : Control II
 (): Total number examined, -: Not examined

$P = 0.0155$

Table 13-3 A 104-week Carcinogenicity Study of AT-4140 in Rats
 Histoathological findings / Neoplastic lesions
 Female

Organ : Findings	Group Dose (ug/kg)	C I	C II	AT-4140			
				0	50	100	200
Hematopoietic system:		(50)	(50)	(50)	(50)	(50)	(50)
Lymphoma		0	0	1	0	0	1
Mesenteric lymph node :		(50)	(50)	(50)	(50)	(50)	(50)
Neuangioma		0	1	0	0	0	0
Thymus :		(50)	(48)	(50)	(50)	(50)	(50)
Thymoma		2	1	0	3	2	2
Spleen :		(50)	(50)	(50)	(50)	(50)	(48)
Neuangioma		0	1	0	0	0	0
Tongue :		(50)	(50)	(50)	(50)	(50)	(50)
Squamous cell papilloma		1	0	0	0	0	0
Forestomach :		(50)	(50)	(50)	(50)	(50)	(50)
Squamous cell papilloma		1	1	0	0	0	0
Glandular stomach :		(49)	(50)	(49)	(50)	(50)	(50)
Lipomyosarcoma		0	0	0	0	1	0
Jejunum :		(48)	(47)	(49)	(47)	(47)	(49)
Adenocarcinoma		0	0	0	0	1	0
Lipomyoma		0	0	0	0	1	0
Liver :		(50)	(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma		0	1	3	2	0	1
Hepatocellular carcinoma		0	0	0	0	0	1
Pancreas :		(50)	(50)	(50)	(50)	(50)	(50)
Acinar cell adenoma		0	0	1	0	0	1
Acinar cell carcinoma		0	0	0	0	1	0
Islet cell adenoma		1	1	0	2	0	0
Islet cell carcinoma		0	1	0	0	0	0
Nasal cavity :		(50)	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma		0	1	0	0	0	0
Kidney :		(50)	(50)	(50)	(50)	(50)	(50)
Tubular cell adenoma		0	0	1	0	1	0
Nephroblastoma		0	0	1	0	0	0
Lipoma		1	1	0	0	0	0
Liposarcoma		0	0	1	0	0	1
Ovary :		(50)	(50)	(50)	(50)	(50)	(49)
Granulosa cell tumor, malignant		0	0	1	0	0	0
Sertoli cell tumor		0	1	0	0	0	2
Tubular adenoma		0	0	0	1	0	0
Uterus :		(49)	(50)	(50)	(50)	(50)	(50)
Endometrial stromal polyp		11	10	5	2	10	3
Endometrial stromal sarcoma		1	1	1	2	3	1
Granular cell tumor		1	1	1	3	1	3
Lipomyoma		0	0	1	0	0	0
Neuangioma		0	0	0	0	1	0
Neuangiomasarcoma		0	0	0	0	0	1
Malignant schwannoma		0	0	0	0	1	0
Vagina :		(50)	(49)	(50)	(50)	(50)	(49)
Endometrial stromal polyp		0	0	1	0	0	0
Granular cell tumor		1	0	3	2	2	2

C I : Control I, C II : Control II
 (): Total number examined

✓ 0.1193

Table 13-4 A 104-week Carcinogenicity Study of AT-4140 in Rats
 Histopathological findings / Neoplastic lesions
 Female

Organ : Findings	Group	CI	CH	AT-4140			
				Dose (ng/kg)			
		0	0	50	100	200	300
Pituitary gland :		(50)	(50)	(50)	(50)	(50)	(50)
Adenoma		24	20	21	20	21	10
Thyroid gland :		(50)	(50)	(50)	(50)	(50)	(50)
Follicular cell adenoma		0	1	0	1	1	1
Follicular cell carcinoma		0	1	0	0	0	0
C-cell adenoma		2	0	3	1	1	1
C-cell carcinoma		1	0	0	0	0	0
Adrenal gland :		(50)	(50)	(50)	(50)	(50)	(50)
Cortical adenoma		0	0	0	0	1	1
Pheochromocytoma, benign		0	0	2	0	1	3
Pheochromocytoma, malignant		0	0	1	1	0	1
Skin & subcutis :		(50)	(50)	(50)	(50)	(50)	(50)
Keratoacanthoma		0	0	0	1	1	0
Squamous cell carcinoma		1	1	0	0	0	1
Sebaceous adenoma		0	0	0	0	1	0
Sebaceous squamous cell carcinoma		0	0	1	0	0	0
Basal cell carcinoma		1	1	1	0	0	0
Fibrosarcoma		0	2	0	0	0	0
Lipoma		0	0	0	0	0	1
Hemangiosarcoma		1	0	0	0	0	0
Histiocytic sarcoma		0	0	0	1	0	0
Malignant fibrous histiocytoma		1	0	0	0	0	1
Mammary gland :		(50)	(50)	(50)	(50)	(50)	(50)
Adenoma		4	1	2	3	2	2
Adenolipoma		0	0	1	0	0	0
Adenocarcinoma		4	3	3	2	6	4
Fibroadenoma		13	15	10	11	11	10
Fibroma		1	1	0	1	2	1
Auricle :		(1)	(0)	(3)	(3)	(1)	(0)
Neural crest tumor		0	-	1	0	0	-
Brain :		(50)	(50)	(50)	(50)	(50)	(50)
Astrocytoma		0	0	0	0	0	1
Granular cell tumor		0	1	0	0	1	1
Body cavity :		(0)	(4)	(2)	(1)	(2)	(3)
Hemangiosarcoma		-	1	0	0	0	0
Malignant schwannoma		-	0	0	0	1	0
Lipoma		-	2	0	0	0	0
Histiocytic sarcoma		-	0	1	1	0	0
Osteosarcoma		-	0	0	0	0	1

✓ P = 0.0718

CI : Control I, CH : Control II
 (): Total number examined, - : Not examined

Appendix III (three pages)

Table 15-4

A 104-week carcinogenicity study of AT-4140 in rats

B-1821

Statistical analysis of incidence of tumors

Adrenal pheochromocytoma (benign) / female

Week	Control (I+II)		50		100		200		300		T ³⁾	V ⁴⁾	Z ⁵⁾	p ⁶⁾
	O/R ¹⁾	E ²⁾	O/R	E	O/R	E	O/R	E	O/R	E				
	<u>Animals bearing INCIDENTAL tumor</u>													
1-104	0/30	0.545455	0/10	0.181818	0/15	0.272727	1/18	0.327273	1/37	0.672727	196.364	30438.8		
Terminal	0/70	1.47368	2/40	0.842105	0/35	0.736842	0/32	0.673684	2/13	0.273684	367.368	32861.7		
Total											563.732	63300.5	2.24062	1P:0.015<Z<1P:0.010

¹⁾ Number observed / number at risk

²⁾ Number expected

³⁾ Trend = $\sum \text{Dose} \times (\text{number observed} - \text{number expected})$

⁴⁾ Variance

⁵⁾ Z-value = $T / \text{SQR}(V)$

⁶⁾ P-value (one-sided)

Appendix III (continued)

Table 15-5

A 104-week carcinogenicity study of AT-4140 in rats

B-1821

Statistical analysis of incidence of tumors

Adrenal pheochromocytoma (malignant) / female

Week	Control (I+II)		50		100		200		300		T ³⁾	V ⁴⁾	Z ⁵⁾	P ⁶⁾	
	O/R ¹⁾	E ²⁾	O/R	E	O/R	E	O/R	E	O/R	E					
	<u>Animals bearing FATAL tumor</u>														
91	0/82	0.340249	0/45	0.186722	1/41	0.170124	0/44	0.182573	0/29	0.120332	1.03735	10507.2 ¹			
100	0/78	0.739337	1/40	0.379147	0/37	0.350711	0/36	0.341232	1/20	0.189573	170.853	19028.0			
Total											171.890	29535.3	1.00019	1P:0.20<Z<1P:0.1	

¹⁾ Number observed / number at risk

²⁾ Number expected

³⁾ Trend = Σ Dose X (number observed - number expected)

⁴⁾ Variance

⁵⁾ Z-value = $T / \text{SQR}(V)$

⁶⁾ P-value (one-sided)

Appendix III (continued)

Table 15-6

A 104-week carcinogenicity study of AT-4140 in rats

B-1821

Statistical analysis of incidence of tumors

Adrenal pheochromocytoma (benign + malignant) / female

Week	Control (I+II)		50		100		200		300		T ³⁾	V ⁴⁾	Z ⁵⁾	p ⁶⁾
	O/R ¹⁾	E ²⁾	O/R	E	O/R	E	O/R	E	O/R	E				
	<u>Animals bearing FATAL tumor</u>													
91	0/82	0.340249	0/45	0.186722	1/41	0.170124	0/44	0.182573	0/29	0.120332	1.03735	10507.2 ⁵⁾		
100	0/78	0.739337	1/40	0.379147	0/37	0.350711	0/36	0.341232	1/20	0.189573	170.853	19028.0		
	<u>Animals bearing INCIDENTAL tumor</u>													
1-104	0/30	0.545455	0/10	0.181818	0/15	0.272727	1/18	0.327273	1/37	0.672727	196.364	30438.8		
Terminal	0/70	1.47368	2/40	0.842105	0/35	0.736842	0/32	0.673684	2/13	0.273684	367.368	32861.7		
Total											735.622	92835.7	2.41433	1P:0.008<Z<1P:0.007

¹⁾ Number observed / number at risk

²⁾ Number expected

³⁾ Trend = Σ Dose $\times$ (number observed - number expected)

⁴⁾ Variance

⁵⁾ Z-value = T / SQR(V)

⁶⁾ P-value (one-sided)

Statistical Review and Evaluation

AUG 17 1996

NDA/IND #: 20-677/36-888 (mouse carcinogenicity study)

Applicant: Rhone-Poulenc Rorer Pharmaceuticals, Inc.

Name of Drug: Zagam (Sparfloxacin)

Types of Review: Animal Carcinogenicity

Documents Reviewed:

1. NDA submission volume 1 of 6, " 104-week Carcinogenicity Study of AT-4140 in Mice ", Study number B-1822.
2. Pharmacology Review written by Dr. Amy Ellis, received August 9, 1996.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. Dr. Amy Ellis, HFD-520, who is the reviewing pharmacologist of the mouse study of this NDA has requested the Division of Biometrics IV to check the histopathological findings in the mouse study. Note that the sponsor did not submit the tumor data in computer readable media. The following analyses are based on the summary tables included in the submission.

II. The Mouse Study

II. a. Design

In this study, AT-4140 (sparfloxacin) was administered orally in the diet to groups of 50 male and 50 female :B6C3F1 mice for 104 weeks. Initially, AT-4140 was administered to three treatment groups at the dose level of 125, 250, and 500 mg/kg/day while two control groups of 50 mice/sex received a standard diet alone. Because excessive toxicity was observed during the first month at 500 mg/kg/day, the following dose groups were added to the study: 31.25 mg/kg/day (50 males and no females) and 62.5 mg/kg/day (50 males and 50 females). A third control group of 50 mice/sex was introduced at the same time. Animals at 500 mg/kg/day were terminated early and excluded from the main study because this dose exceeded the maximum tolerated dose. Histopathological examinations were performed for animals in all groups (excluding the group at 500 mg/kg/day).

II. b. Reviewer's Analyses

The intercurrent mortality rates for both male and female mice (see Appendix 1 - the sponsor's Tables 1-1 and 1-2) are tested for linear trend according to the Peto death rate method using the time intervals 0-52, 53-78, and 79-104 weeks. The following analyses combine the data of three control groups and exclude the animals at a dose of 500 mg/kg/day. The actual dose levels 0, 31.25, 62.5, 125, and 250 mg/kg/day are the scores assigned to the controls, low, medium, high-1 and high-2 dose groups for males, respectively, and 0, 62.5, 125, and 250 mg/kg/day for females, respectively. The results of the analyses show that there is no significant (at 0.05 level) linear trend in the intercurrent mortality rate in both sexes (male: $p = 0.2230$; female: $p = 0.4702$).

Since there is no significant (at 0.05 level) linear trend in the intercurrent mortality rate in both male and female mice, the time-unadjusted exact permutation trend test is used to test the linear trend in the tumor data as shown in Appendix 2 (the sponsor's Tables 13-1 to 13-4). The results of the above analyses show that there is a significant (at 0.05 level) positive linear trend in the following tumor type:

<u>Tumor/organ</u>	<u>Incidence of Tumors</u>				<u>P-value</u>
Females:					
Thyroid					
Follicular cell adenoma	1/150	0/50	0/50	3/50	0.02*

In order to reduce the overall false positive rate, the following decision rule is used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor. On the basis of above adjustment rule, the thyroid follicular cell adenoma in female mice is considered to be statistically significant. Note that there is a marginally significant positive linear trend in lung adenocarcinoma in female mice ($p = 0.0615$). The incidence rates of this tumor are 4/150, 1/50, 2/50, and 4/50.

III. Conclusion

The time-unadjusted exact permutation trend test is used to test the linear trend in the mouse tumor data. Results of tumor data

analyses showed that there is a significant positive linear trend in thyroid follicular cell adenoma in female mice ($p = 0.02$). This finding is based on the assumption of treating thyroid follicular cell adenoma in female mice as a rare tumor. If it is a common tumor, then the thyroid follicular cell adenoma in female mice is not considered to be statistically significant.

Daphne Lin 8/16/96

Daphne Lin, Ph.D.
Acting Team Leader, Biometrics IV

Concur: Ralph Harkins 8/17/96
Ralph Harkins, Ph.D.
Division Director, Biometrics IV

✓ cc: Archival: NDA 20-677

HFD-520/Dr. Ellis

HFD-520/Dr. Osterberg

HFD-520/Ms. LeSane

HFD-725/Dr. Harkins

HFD-725/Dr. Daphne Lin

Chron.

This review contains ³/₉ pages and 6 Tables.

Appendix 1

B-1822

Table 1-1 A 104-week carcinogenicity study of AT-4140 in mice
Mortality / survivor
Male

Week	Dose (mg/kg)	0-1	0-2	125	250	500	0-3	31.25	62.5
	No. of animals	50	50	50	50	50	50	50	50
1- 26		a) b) 0 (100)	0 (100)	0 (100)	2 (96)	16 (68)c)	0 (100)	0 (100)	0 (100)
27- 62		1 (98)	0 (100)	0 (100)	0 (96)	-	1 (98)	0 (100)	0 (100)
63- 78		3 (92)	1 (98)	2 (96)	1 (94)	-	1 (96)	4 (92)	0 (100)
79-104		4 (84)	9 (80)	6 (84)	2 (90)	-	3 (90)	4 (84)	5 (90)
After 104		0	0	0	0	-	0	0	0
Total		8	10	8	5	16	5	8	5
Mean survival time (weeks)		100.5 ±11.3	101.0 ±8.1	100.8 ±9.5	98.9 ±20.4	11.1 ±3.3**	101.6 ±9.1	100.6 ±9.2	103.0 ±3.1

a) : No. of dead or sacrificed animals
b) : Percentage of survivors at end of indicated period (week)
c) : Terminal sacrifice after 13 weeks administration
** : p<0.01 (Significant difference from control : 0-1)

Appendix 1 (continued)

H-1822

Table 1-2 A 104-week carcinogenicity study of AT-4140 in mice
Mortality / survivor
Female

Week	Dose (mg/kg)	0-1		0-2	125	250	500	0-3	62.5
		No. of animals							
		a)	b)						
1- 26		0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	17 (66)**	0 (100)	0 (100)
27- 52		0 (100)	0 (100)	0 (100)	0 (100)	2 (96)	3 (60)**	0 (100)	0 (100)
53- 78		1 (98)	1 (98)	0 (100)	0 (100)	3 (90)	12 (36)c)	3 (94)	3 (94)
79-104		14 (75)	8 (82)	7 (86)	7 (76)	-	8 (78)	10 (74)	
After 104		1	0	0	1	-	0	1	
Total		16	9	7	13	32	11	14	
Mean survival time (weeks)		100.4 ±7.7	101.8 ±5.7	102.2 ±5.6	97.2 ±16.8	51.2 ±28.5**	100.1 ±9.9	99.0 ±10.5	

a) : No. of dead or sacrificed animals
b) : Percentage of survivors at end of indicated period (week)
c) : Terminal sacrifice after 77 weeks administration
** : p<0.01 (Significant difference from control : 0-1)

Table 12-1 A 104-week Carcinogenicity Study of AT-4140 in Mice

Histopathological findings / Neoplastic lesions

Male

Organ : Findings	Group Dose (ng/kg)	C I	C II	C III	AT-4140			
					31.25	62.5	125	250
Hematopoietic system : Malignant lymphoma Myelogenous leukemia Histiocytic sarcoma		(50) 7 0 0	(50) 2 0 1	(50) 4 0 0	(50) 4 1 3	(50) 2 0 1	(50) 3 0 0	(50) 1 0 0
Circulatory system : Hemangioma Hemangiosarcoma		(50) 1 6	(50) 0 4	(50) 3 4	(50) 1 6	(50) 3 6	(50) 0 4	(50) 4 7
Salivary gland : Myoepithelioma		(50) 0	(50) 0	(50) 0	(50) 0	(50) 2	(50) 0	(50) 0
Fore stomach : Squamous cell papilloma		(48) 1	(47) 1	(49) 0	(50) 0	(50) 0	(49) 1	(49) 1
Glandular stomach : Carcinoid tumor		(49) 0	(47) 1	(48) 0	(50) 0	(49) 0	(49) 0	(49) 0
Duodenum : Adenoma		(47) 0	(46) 0	(48) 0	(50) 0	(48) 0	(46) 0	(50) 1
Jejunum : Adenocarcinoma		(47) 0	(46) 0	(47) 0	(49) 0	(48) 0	(46) 0	(50) 1
Ileum : Leiomyoma		(47) 0	(46) 0	(47) 1	(49) 0	(48) 0	(46) 0	(49) 0
Cecum : Signet-ring cell carcinoma		(48) 0	(46) 0	(47) 0	(49) 1	(47) 0	(47) 0	(49) 0
Liver : Hepatocellular adenoma Hepatocellular carcinoma		(50) 4 14	(50) 0 15	(50) 4 12	(50) 0 11	(50) 0 11	(50) 6 11	(50) 2 11
Lung : Adenoma Adenocarcinoma		(50) 4 6	(50) 5 3	(50) 4 5	(50) 0 2	(50) 0 5	(50) 2 0	(50) 2 7
Kidney : Tubular cell adenoma Mesenchymal cell tumor		(50) 1 0	(50) 0 1	(50) 0 0	(50) 0 0	(50) 0 0	(50) 0 0	(50) 0 0
Epididymis : Leydig cell tumor		(50) 0	(50) 1	(50) 1	(50) 4	(50) 0	(50) 2	(50) 1
Sexual vesicle : Adenoma		(50) 1	(50) 0	(50) 0	(50) 0	(50) 0	(50) 0	(50) 0
Thyroid : Follicular cell adenoma C-cell carcinoma		(50) 1 0	(50) 1 1	(50) 0 0	(50) 1 0	(50) 0 0	(50) 0 0	(50) 1 0
Adrenal gland : Cortical adenoma Pheochromocytoma, benign Pheochromocytoma, malignant		(50) 1 1 0	(50) 2 0 0	(50) 0 1 0	(50) 0 0 0	(50) 0 0 0	(50) 0 1 1	(50) 2 0 0

C I : Control I, C II : Control II, C III : Control III
 (): Total number examined, -: Not examined

NDA 20-677

6 OF 8

Table 13-2 A 104-week Carcinogenicity Study of AT-4140 in Mice
 Histopathological findings / Neoplastic lesions
 Male

Organ : Findings	Group	C I	C II	C III	AT-4140			
					Dose (mg/kg)	0	31.25	62.5
Skin & subcutis :		(50)	(50)	(50)	(50)	(50)	(50)	(50)
Sebaceous adenoma		0	1	0	0	0	0	0
Malignant fibrous histiocytoma		1	1	0	0	0	0	0
Sarcoma NOS		1	0	0	0	0	0	0
Brain :		(50)	(50)	(50)	(50)	(50)	(50)	(50)
Lipoma		0	0	0	0	0	1	0
Harderian gland :		(50)	(50)	(50)	(50)	(50)	(50)	(50)
Adenoma		1	5	5	1	7	7	3
Adenocarcinoma		0	0	0	0	0	2	0
Body cavity :		(0)	(0)	(0)	(3)	(0)	(2)	(0)
Malignant mesothelioma		-	-	-	1	-	0	-
Osteoma		-	-	-	1	-	0	-
Tail :		(0)	(0)	(2)	(0)	(0)	(0)	(0)
Chordoma		-	-	1	-	-	-	-

CI : Control I, CII : Control II, CIII : Control III
 () : Total number examined, - : Not examined

Table 13-3 A 104-week Carcinogenicity Study of AT-4140 in Mice
 Histopathological findings / Neoplastic lesions
 Female

Organ : Findings	Group Dose (µg/kg)	C I	C II	C III	AT-4140		
					62.5	125	250
Haematopoietic system :		(50)	(50)	(50)	(50)	(50)	(50)
Malignant lymphoma		15	12	12	10	12	13
Myelogenous leukemia		0	0	1	0	1	0
Histiocytic sarcoma		4	3	2	5	3	2
Circulatory system :		(50)	(50)	(50)	(50)	(50)	(50)
Hemangioma		0	0	0	0	4	1
Hemangiosarcoma		1	6	9	6	6	4
Forestomach :		(50)	(50)	(50)	(50)	(50)	(50)
Squamous cell papilloma		3	5	0	0	1	2
Cecum :		(48)	(46)	(46)	(45)	(46)	(49)
Leiomyoma		0	0	0	1	0	0
Liver :		(50)	(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma		2	2	1	2	2	3
Hepatocellular carcinoma		2	2	6	1	1	1
Nasal cavity		(49)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma		0	0	0	1	0	0
Lung :		(50)	(50)	(50)	(50)	(50)	(50)
Adenoma		2	1	3	1	2	1
Adenocarcinoma		1	2	1	1	2	4
Kidney :		(50)	(50)	(50)	(50)	(50)	(50)
Tubular cell carcinoma		0	0	0	0	1	0
Ovary :		(50)	(50)	(50)	(50)	(50)	(50)
Granulosa cell tumor		0	0	1	1	0	1
Luteoma		2	2	2	2	2	1
Tubular adenoma		0	0	1	0	1	1
Teratoma		0	0	0	0	1	0
Theciocarcinoma		0	0	1	0	0	0
Uterus :		(50)	(50)	(50)	(50)	(50)	(50)
Endometrial stromal polyp		0	5	2	5	2	3
Endometrial stromal sarcoma		1	0	2	2	2	0
Adenoma		1	0	2	0	0	0
Adenocarcinoma		3	1	0	0	0	0
Leiomyoma		0	0	0	0	1	1
Leiomyosarcoma		1	1	0	0	0	0
Pituitary :		(49)	(49)	(50)	(50)	(49)	(50)
Adenoma		5	8	9	11	11	8
Thyroid :		(50)	(50)	(50)	(50)	(50)	(50)
Follicular cell adenoma		0	1	0	0	0	3
Adrenal gland :		(50)	(50)	(49)	(50)	(50)	(50)
Cortical adenoma		1	0	0	0	1	1
Pheochromocytoma, benign		0	0	2	0	0	0

C I : Control I, C II : Control II, C III : Control III
 () : Total number examined

Table 13-4 A 104-week Carcinogenicity Study of AT-4140 in Mice
 Histopathological findings / Neoplastic lesions
 Female

Organ : Findings	Group Dose (mg/kg)	C I 0	C II 0	C III 0	AT-4140		
					62.5	125	250
Skin & subcutis :		(50)	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma		1	0	0	0	0	0
Sebaceous adenoma		0	0	0	0	0	-1
Fibrosarcoma		0	0	1	1	0	1
Lipoma		1	0	0	0	0	0
Malignant fibrous histiocytoma		1	0	0	0	0	0
Mammary gland :		(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma		0	2	1	0	5	1
Lumbar vertebrae :		(0)	(0)	(1)	(0)	(0)	(0)
Osteosarcoma		-	-	1	-	-	-
Harderian gland :		(50)	(50)	(50)	(50)	(50)	(50)
Adenoma		1	5	3	6	4	0
Auricle :		(1)	(2)	(0)	(0)	(0)	(1)
Amelanotic melanoma		0	1	-	-	-	0
Leiomyosarcoma		0	0	-	-	-	1

C I : Control I, C II : Control II, C III : Control III
 (): Total number examined, -: Not examined

HPD 520
LESINE

OCT 12 1996

DIVISION OF ANTJ-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA# 20-677: CHEM. REVIEW#: 1 REVIEW DATE: 1/13/96
Revision: 9/23/96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL SUBMISSION	12/27/95	12/28/95	1/3/96

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer
Pharmaceuticals Inc.
500 Arcola Road,
Collegville, PA 19426

DRUG PRODUCT NAME

Proprietary: ZAGAM
Nonproprietary/USAN: S-sparfloxacin
Code Names/#'S: RP64206
Chemical Type/
Therapeutic Class: 1-S

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Antibacterial

DOSAGE FORM: Tablets

STRENGTHS: 200 mg

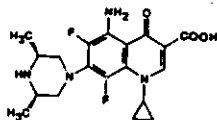
ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Names and Chemical Formula

ZAGAM



Molecular Formula and Weight

C₁₇H₂₀F₂N₂O₃ = 392.41

Chemical Name

5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolincarboxylic acid

Therapeutic Code Numbers

AT-4140 (CI-978, PD 131501, RP 64206)

Proprietary Name

Sparfloxacin (INN)

Physical and Chemical Properties

Appearance

Flow crystals or crystalline powder. It is odorless and has a bitter taste.

SUPPORTING DOCUMENTS:

The firm refers to the following INDS:

IND
IND
IND

RELATED DOCUMENTS (if applicable):

For drug substance; refer to DMF

The DMF is reviewed separately for the drug substance.

CONSULTS:

1. The EA review has been completed. FONSI has been recommended by Dr. Vincents' s. group.
2. The trade name, ZAGAM has been submitted on January 31, 96 to the labeling and nomenclature committee for their approval. Requested again on 7/17/96. *Approved 8/22/96.*

REMARKS/COMMENTS:

Sparfloxacin is a quinolone derivative anti-infective which acts by inhibiting the bacterial DNA-gyrase enzyme. It is a base which is converted to a zwitterion in the presence of water. The conversion may occur during formulation, resulting in changes in the physical properties of the bulk drug. The drug will be used for the treatment of patients with community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis

CONCLUSION & RECOMMENDATIONS:

The application is APPROVABLE for manufacturing and controls under section 505 of the Act. Specific items which are not approvable are identified under the following headings: Drug Product: Sampling and assay, Methods Validation, and Establishment Inspections *being inspected again.*

Methods Validation completed. Not acceptable; deficiencies addressed by firm.
Note: DMF has been reviewed and deficiencies in the new drug substance has been noted.

Fonsi issued.

BV Shetty 9/23/96

Vithal Shetty, Ph.D.
Review Chemist

cc: Orig NDA 20-677
HFD-520/Div File
HFD-520/MO/Moledina
HFD-520/CHEM/Shetty
HFD-520/PHARM/Ellis
HFD-520/TLCHEM (Acting)/BBDunn *BBDunn*
HFD-520/MICRO/Dionne *10-12-96*
HFD-520/BIOPHARM/Sun
HFD-520/PM/LeSane
HFD-830/DD/Sheinin

Micro

NOV 7 1995

Division of Anti-Infective Drug Products
Clinical Microbiological Review

NDA #: 20-677 **MICRO.REVIEW #:** 1 **REVIEW DATE:** 09-MAY-96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL NDA	27-DEC-95	27-DEC-95	19-JAN-96

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

CONTACT PERSON: John J. Savarese, M.D., Ph.D.
Phone Number: (610) 454-5471

DRUG PRODUCT NAME

<u>Proprietary:</u>	ZAGAM® Tablets
<u>Nonproprietary/USAN:</u>	Sparfloxacin tablets
<u>Code Names/#'s:</u>	RP 64206; CI-978
<u>Chemical Type/</u>	fluoroquinolone
<u>Therapeutic Class:</u>	1 S

ANDA Suitability Petition/DESI/Patent Status:

US Patent No. 4,795,751 (expires 10/28/2006) Dainippon Pharmaceutical Co., Ltd.

PHARMACOLOGICAL CATEGORY/INDICATION:

Fluoroquinolone/community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis

DOSE FORM:

Tablets

STRENGTHS:

200 mg/tablet

ROUTE OF ADMINISTRATION:

Oral

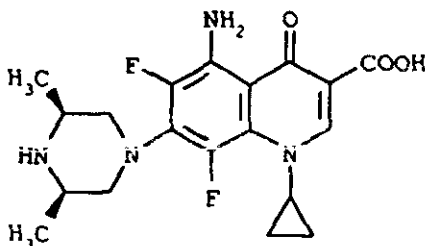
DISPENSED:

Rx OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:**

CHEMICAL NAME: 5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

Chemical Structure:



Molecular Formula: C₁₉H₂₂F₂N₄O₃

Molecular Weight: 392.41

SUPPORTING DOCUMENTS:

INDs: -Rhone-Poulenc Rorer for treatment of mycobacterium avium
IND -Rhone-Poulenc Rorer treatment of community acquired infections
IND
DMFs:

RELATED DOCUMENTS (if applicable): NONE

CONSULTS: NONE

REMARKS/COMMENTS:

This application is for a fluoroquinolone, sparfloxacin. The application is for the treatment of patients with community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY section of the package insert. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 152-158.

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INTRODUCTION

Sparfloxacin is a synthetic, broad spectrum, fluoroquinolone for oral administration. Sparfloxacin demonstrates excellent activity against the predominant gram-negative aerobic pathogens associated with community-acquired respiratory tract infections (i.e. *Haemophilus influenzae* and *Moraxella catarrhalis*). It shows better activity relative to most approved quinolones against gram-positive aerobic respiratory tract pathogens (i.e. *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*). It also has good *in vitro* activity against *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*. Sparfloxacin has a low spontaneous mutation frequency, relative to ciprofloxacin, in *in vitro* tests. This is especially true for aerobic gram-positive cocci.

After oral administration of a 400 mg loading dose and then 200 mg daily doses, sparfloxacin achieves a maximum plasma concentration of 1.3 $\mu\text{g/mL}$ in about 4 hours. The absolute oral bioavailability is approximately 90% and steady-state concentrations are achieved by the second or third dose. The C_{max} of sparfloxacin in respiratory tissues is approximately 3 to 15 times greater than C_{max} in plasma. The $\text{AUC}_{0-\infty}$ for sparfloxacin following a single 400 mg dose is 34 $\mu\text{g}\cdot\text{h/mL}$.

PRECLINICAL EFFICACY (IN VITRO)

MECHANISM OF ACTION

Sparfloxacin, like other fluoroquinolones exert their antibacterial action on bacteria by entering the bacterial cell and interacting with bacterial DNA gyrase. This is a two subunit (gyr A + gyr B) bacterial enzyme responsible for the coordinated breaking and resealing of double stranded DNA. This interaction of fluoroquinolones with this enzyme results in interference with the vital supercoiling of the DNA, and hence inhibition of DNA synthesis and rapid cell death.

The inhibitory effects of sparfloxacin on DNA synthesis and/or DNA supercoiling activity of purified DNA gyrase from fluoroquinolone susceptible and resistant *E. coli*, other Enterobacteriaceae, *Pseudomonas aeruginosa*, *S. aureus*, and *Streptococcus pneumoniae* have been determined in numerous studies (1,2,3,4). The concentrations of sparfloxacin and ciprofloxacin which inhibited DNA synthesis and DNA supercoiling by 50% are shown in TABLE 1 along with the MICs for the test strains.

TABLE 1
 Correlation of inhibition of DNA supercoiling and DNA synthesis by
 Sparfloxacin with MICs of Sparfloxacin.

Organism	Sparfloxacin ($\mu\text{g/mL}$)			Ciprofloxacin ($\mu\text{g/mL}$)			Reference
	MIC	ISuC ₅₀ ^a	ISyC ₅₀ ^b	MIC	ISuC ₅₀	ISyC ₅₀	
<i>E. coli</i>	0.02	10	0.04	0.02	6	0.01	1
	0.5	--	0.39	0.5	80	0.35	1
	0.01	0.39	--	--	--	--	2
	0.2	3.13	--	--	--	--	2
<i>K. pneumoniae</i>	0.06	--	0.08	0.03	--	0.04	1
	32	--	25	32	--	200	1
<i>P. aeruginosa</i>	1	--	20	0.25	--	25	1
	32	--	200	32	--	200	1
<i>S. pneumoniae</i>	0.5	--	0.6	1	--	2.4	3
	1.25	--	1.63	16	--	25.6	3
<i>S. aureus</i>	0.05	10.5	--	0.39	19.4	--	4
	12.5	>800	--	400	>800	--	4
	0.06	--	0.03	0.5	--	0.2	3
	0.25	--	0.85	4	--	0.9	3

^a concentration inhibiting DNA supercoiling by 50%

^b concentration inhibiting DNA synthesis by 50%

As can be seen in this table the amount of drug needed to inhibit supercoiling activity and DNA synthesis is correlated with the MIC of the organism. The higher the MIC value the more drug is needed to inhibit supercoiling and DNA synthesis.

Other studies also support the role of DNA gyrase as a target for fluoroquinolones. Heisig and Tschorny (5) using *Escherichia coli* and Ito et al (6) using *Staphylococcus aureus* showed that fluoroquinolone resistant mutants can be transformed to susceptible with wild-type gyrase genes. In Ito's study the MICs of sparfloxacin for a sparfloxacin-susceptible isolate, a sparfloxacin-

resistant mutant, and the sparfloxacin-resistant mutant transformed with a wild-type *gryA* gene were 0.1, 12.5 and 0.39 $\mu\text{g/mL}$, respectively.

Most mutations in DNA gyrase which cause significant increases in MICs of fluoroquinolone have been related to amino acid substitutions in the *gryA* protein, which is coded by the chromosomal gene, *gryA* (2,5,6). Mutations have also been seen in the *gryB* gene which codes for the B subunit of the gyrase, but they seem to cause less significant increases in MICs than do mutations in the *gryA* gene.

Alangaden et al (7) showed that substitution of the Asp residue at position 87 by Asn or Ala or the substitution of Ala-83 by Val in the A subunit of DNA gyrase led to fluoroquinolone-resistant mutants of *Mycobacterium tuberculosis*. Heisig and Tschorny (5) showed that resistant mutants in *E. coli* had a Ser-83 substituted by Leu or a double mutation, Ser-83 by Leu and Asp-87 by Gly. Ito et al (6) studied mutations in the gyrase of *Staphylococcus aureus* and found five groups of mutations. Group 1 had Ser-84 substituted by Leu in Gyr A; Group 2 had Ser-84 substituted by Ala, Ser-85 by Pro, and Glu-88 by Lys; Group 3 had Asp-437 substituted by Asn in Gyr B; Group 4 had Arg-458 going to Gln; and Group 5 had Ser-85 going to Pro in Gyr A and Asp-437 going to Asn in Gry B. These authors found that mutations of Ser-84 to Ala; Ser-85 to Pro, and Glu-88 to Lys only led to low level sparfloxacin resistance. Only the mutation of Ser-84 to Leu led to high level sparfloxacin resistance. These authors postulated a pocket model for the mechanism of action of quinolones. The drugs bind to a gyrase-DNA complex and the quinolone binding affinities for the complex are determined by both the GryA and GryB subunits. The existence of double mutations in the *gryA* and *gryB* genes may mean that the region around Ser-84 to Glu-88 in GryA polypeptide is in close proximity to Asp-437 and Arg-458 in GryB polypeptide. This region is important for quinolone activity. Mutations in this region seem to prevent quinolones from getting into the pocket or from interacting with the DNA gyrase-DNA complex within the pocket. All these studies show that the region around amino acid 83 to 88 in the Gry A subunit is important for quinolone activity.

Since quinolones act on an intracellular enzyme, uptake and intracellular accumulation of fluoroquinolones are needed in order to achieve and maintain intracellular concentrations required for inhibition of DNA gyrase activity. In gram-negative bacteria, the uptake of these drugs has been related to transport mechanisms involving specific outer membrane proteins (porins) which form channels through which fluoroquinolones gain entry into the cell. The physical properties of the drug such as molecular weight, molecular charge, and relative hydrophobicity and charge can be important factors in drug uptake. In general, high molecular weight, bulky size, negative charge and increasing hydrophobicity decrease transport into gram-negative organisms. Gram-positive bacteria do not

have these porins and fluoroquinolones gain entry by a process of passive diffusion regardless of molecular weight or size, and greater hydrophobicity enhances drug entry.

Bazile et al (8) measured the intracellular accumulation of 11 fluoroquinolones in *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. They also determined the hydrophobicities of these compounds and the compounds MICs against these organisms. They also determined the minimal effective dose (MED) for all the drugs in a supercoiling assay with *E. coli* DNA gyrase. The hydrophobicities were measured as log D which is the logarithm of the ratio of the concentration of the drug in the organic phase (1-octanol) to the concentration in the aqueous phase. The higher the Log D value the more hydrophobic the drug is. TABLE 2 shows the correlation between hydrophobicity, accumulation of drug, MIC and MED.

Table 2 shows that for *S. aureus* there was a direct correlation between accumulation and hydrophobicity ($r=0.71$). For *S. aureus*, the size of the molecule is not a limiting factor, since in the case of the compounds BMY 40062 and BMY 40397, the more bulky and hydrophobic BMY 40397 entered the cell more easily. In the case of *E. coli*, there was an inverse correlation between accumulation and hydrophobicity ($r=0.73$). For *P. aeruginosa*, there was an inverse relationship between accumulation and log D, not taking into account compound BMY 40062 ($r=0.64$). Compound BMY 40062 was accumulated to the highest degree by the two gram-negative organisms. This compound has a piperazine ring that probably modifies its basic properties and increases the role of the charge factor in determining its accumulation by active transport systems in gram-negative cells. The accumulation in *P. aeruginosa* is lower than in *E. coli*. It may be that the principal porin in *P. aeruginosa* is smaller than those in other gram-negative organisms. *Pseudomonas aeruginosa* seems to be more resistant to drugs that must get through its cell wall than most other organisms.

Table 2 shows that there is no direct relationship between antibacterial activity and drug accumulation with the three microorganisms tested. There is a direct correlation between MICs and MED for gyrase in most cases. In cases where a low MIC is associated with a high MED, the accumulation of the drug may help explain this. BMY 42230 and BMY 40062 have high MEDs (10 and 0.6 $\mu\text{g}/\text{mL}$, respectively) and low MICs (0.22 and 0.03 $\mu\text{g}/\text{mL}$, respectively), but have good accumulation by *E. coli* (104 and 120 $\text{ng}/10^9$ cells, respectively).

The data in this experiment suggest that both activity against DNA gyrase and the degree of accumulation are important factors governing the activity of fluoroquinolones. The activity against gyrase appears to be most important. With regard to intracellular accumulation, hydrophobicity appears to be a major factor for both gram-negative and gram-positive bacteria. High molecular weight is a limiting factor only in gram-negative bacteria, especially in *P. aeruginosa*.

TABLE 2
 Antibacterial activities and intracellular accumulation of fluoroquinolones
 for *S. aureus*, *E. coli*, and *P. aeruginosa*

Compound	Hydrophobicity Log D	<i>S. aureus</i> GAB S		<i>P. aeruginosa</i> S 678		<i>E. coli</i> K-12 J53		
		MIC ($\mu\text{g/mL}$)	Accumulation (ng/ 10^9 cells)	MIC ($\mu\text{g/mL}$)	Accumulation (ng/ 10^9 cells)	MIC ($\mu\text{g/mL}$)	Accumulation (ng/ 10^9 cells)	MED ($\mu\text{g/mL}$)
BMY 33315	-0.33	0.15	262	1.6	48	0.11	78	1
BMY 42230	-0.68	0.60	158	3.2	41	0.22	104	10
BMY 43261	-1.18	24	108	30	36	3.5	90	40
BMY 45706	0.61	0.15	290	1.6	19	0.45	44	1.2
BMY 40062	-0.41	0.25	220	0.25	111	0.03	120	0.6
BMY 40397	1.05	0.06	340	60	19	1.75	40	1.2
BMY 41429	0.42	0.25	134	1	11	0.11	42	0.4
BMY 40124	0.04	0.25	224	2	31	0.30	108	0.4
CIPRO	-0.70	0.25	54	0.5	36	0.05	100	0.1
PEFLOX	0.25	1	224	4	15	0.20	89	1
SPARFLOX	0.08	0.06	170	1	48	0.05	80	0.2

CIPRO= ciprofloxacin; PEFLOX = pefloxacin; SPARFLOX = sparfloxacin

Denis and Moreau (1) study the accumulation of sparfloxacin and three other fluoroquinolones of decreasing hydrophobicity, pefloxacin, ofloxacin, and ciprofloxacin into fluoroquinolone-sensitive and -resistant clinical isolates of bacteria (four Enterobacteriaceae, one *Pseudomonas aeruginosa* and one *Staphylococcus aureus*). They found that sparfloxacin was accumulated in *S. aureus* to a higher concentration than the other quinolones, followed by pefloxacin and ofloxacin, and ciprofloxacin accumulated least. For the gram-negative species, sparfloxacin accumulated poorly, while ciprofloxacin was accumulated the most (except for the sensitive *Enterobacter* spp.), followed by pefloxacin and ofloxacin. Their results are shown in TABLE 3.

TABLE 3
 Uptake of fluoroquinolones by sensitive isolates (ng/10⁹ bacteria)

Organism	Ciprofloxacin	Ofloxacin	Pefloxacin	Sparfloxacin
<i>S. aureus</i>	75	120	195	225
<i>E. coli</i>	170	105	120	25
<i>K. pneumoniae</i>	215	135	145	60
<i>E. cloacae</i>	80	65	135	20
<i>S. marcescens</i>	80	45	70	25
<i>P. aeruginosa</i>	75	40	70	25

They also performed the experiment in resistant strains. These results can be seen in TABLE 4.

TABLE 4
 Uptake of fluoroquinolones by resistant isolates (ng/10⁹ bacteria)

Organism	Ciprofloxacin	Ofloxacin	Pefloxacin	Sparfloxacin
<i>S. aureus</i>	75	105	175	210
<i>E. coli</i>	125	25	100	20
<i>K. pneumoniae</i>	100	50	100	45
<i>E. cloacae</i>	30	20	30	15
<i>S. marcescens</i>	35	20	30	10
<i>P. aeruginosa</i>	70	40	50	20

When the data for the sensitive and resistant strains are compared, three observations are made. Firstly, for *S. aureus* and *P. aeruginosa* the resistant strain accumulated as much drug as the sensitive one, regardless of the fluoroquinolone. This indicates that resistance is probably due to a mutation affecting DNA gyrase. Secondly, for *E. coli* there was no difference in the uptake of sparfloxacin and pefloxacin, but ciprofloxacin and ofloxacin were accumulated less by the resistant strain. This indicates that sparfloxacin and pefloxacin have a different mechanism by which they enter the cell. These are the two most hydrophobic agents and may get into the cell by passive transport. The other two more hydrophilic compounds need to get into the cell via the porin-mediated route and the resistant strain has an altered porin which prevents these agents from entering via this mechanism. Since this strain was resistant to all the quinolones tested, porin mutations only explain resistance partially and a gyrase mutation is probably the cause of resistance. Thirdly, for *K. pneumoniae*, *S. marcescens*, and *E. cloacae*, there was less accumulation of the four quinolones by the resistant strain compared to the sensitive one. When the authors examined the OMPs (outer membrane porin proteins) of the gram-negative strains using electrophoresis they found differences between those in the sensitive strains and resistant strains of *K. pneumoniae*, *S. marcescens*, and *E. cloacae*. This difference indicates that these resistant strains may have accumulated less drug due to differences in these porin proteins and that these OMPs may play a part in resistance to fluoroquinolones in these species. This study shows that the more hydrophobic a drug is, the more it enters gram-positive cells. This confirms the finding in the Bazile et al study. For gram-negative bacteria the concentration of accumulated drug did not exactly correlate with the hydrophobicity value, although ciprofloxacin, the most hydrophilic drug did accumulate most (except by *E. cloacae*). As suggested in the Bazile study gram-positive bacteria use a passive system to get fluoroquinolones into the cell and the more hydrophobic a compound is the more easily it gets into the cell. Gram-negative bacteria use an active transport system with porin proteins that favors more hydrophilic agents in most cases but size of the compound and charge may also play a part.

All these studies show that the quinolones act by first entering the cell and then interfering with DNA gyrase activity. This blocks DNA synthesis and the cell is killed.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The sponsor conducted a program of studies both in North America and in foreign countries to assess the activity of sparfloxacin and comparator agents. These studies were conducted using standardized and controlled *in vitro* susceptibility test methods against more than 26,000 strains in over 55 centers. The comparators used were ciprofloxacin, ofloxacin, and vancomycin for gram-positive aerobes; ciprofloxacin, ofloxacin, and ceftazidime for gram-negative aerobes; ciprofloxacin, clindamycin, and metronidazole against anaerobes; and ofloxacin, tetracycline, and erythromycin against intracellular organisms. An MIC₉₀ range is usually given for each organism (TABLES 8, 10, 12, 13, 14).

In addition to the MIC₉₀ data, single antimicrobial MIC₅₀ and MIC₉₀ values are given for selected gram-positive and gram-negative aerobic pathogens from seven specific North American investigators. These studies were performed between 1989-1995 (TABLES 9, 11). In these tables MIC data was retrospectively collected and summarized. Due to the elapsed time between their initial report and the submission of data, many of these investigators tested additional strains. The number of strains and consequently the MIC₉₀ range or MIC₅₀ and MIC₉₀ value for certain pathogens in these tables may vary from that in TABLES 8 and 10.

Minimum inhibitory concentrations (MICs) were determined by a dilution method, most commonly using Mueller-Hinton (MH) broth for aerobes, supplemented as required and Wilkins-Chalgren (WC) agar for anaerobes. For investigators using broth microdilution methods an inoculum of about 10⁵ CFU per milliliter was used in almost all studies. For investigators using agar dilution an inoculum of about 10⁴ CFU per spot for aerobes and 10⁵ CFU per spot for anaerobes was used in almost all studies. Tests for aerobes were read after overnight incubation at 37 °C, but some anaerobes required up to 48 hours incubation. These agar and inocula are those recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

The investigators (TABLE 5) performed their investigations using agreed upon protocols which required the use of established methodology and reference strains as controls. TABLE 6 shows the media and inoculum used by each investigator. TABLE 7 shows the number of isolates tested totally and by country. Some species had only a few isolates (10-30) isolates tested, but most had over a 100 isolates tested in a number of centers. The applicant has taken the data and combined all of the North American studies and all of the foreign studies into tables showing the activity of sparfloxacin and comparators. These data are presented as the MIC₉₀ range for the North American centers and the MIC₉₀ range for the foreign centers for sparfloxacin and its comparators (see TABLES 8, 10, 12, 13, 14). Tables are also presented for certain aerobic

pathogens from seven North American centers showing the MIC₅₀ and MIC₉₀ values for all the isolates from the centers that participated for each organism and an MIC range (see TABLES 9, 11). Tables are presented for gram-positive aerobes, gram-negative aerobes, anaerobes, intracellular pathogens, and resistant organisms. Most of the investigators have published their data.

There are 31 USA investigators, 1 Belgium, 3 Canadian, 5 French, 2 German, 1 Greek, 3 Japanese, 1 Dutch, 1 Saudia Arabian, 3 Spanish, 1 Swede, 2 Swiss, and 4 United Kingdom.

Since the NDA holders letter of January 1993 suggested that at least 100 isolates from each species should be tested, only species with around 100 isolates will be considered for inclusion in the package insert. If all the species listed in each table were discussed many species with only a few isolates from one study center would have MIC data presented and discussion below would never end. The NDA holders letter states that in order to be included in the label a microorganism should be a significant (not anecdotal) pathogen at the body site(s) or in the infection(s) for which clinical effectiveness for other pathogens has been established. Since the sponsor is requesting only lower respiratory tract infections and sinusitis, only microorganisms usually found at these sites that may be a pathogen for these diseases will be included in the label.

The proposed susceptibility breakpoint for sparfloxacin is 1.0 µg/mL, therefore, in order to be allowed in the *in vitro* list in the label the MIC₉₀ value for an organism must be ≤ 1.0 µg/mL.

The labeling submitted by the sponsor includes the following organisms in the efficacy list:

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TABLE 5
Investigators, centers, and bacterial groups studied

Country	Investigator	Center	Gram+ve aerobes	Gram-ve aerobes	Anaerobes	Intracellular organisms
USA	<u>Barry</u>	Tualatin, OR	X	X	X	
	<u>Kenny</u>	Seattle, WA				X
	<u>Doebbeling</u>	Iowa City, IA		X		
	<u>Jones</u>	Iowa City, IA	X	X		X
	<u>Chin</u>	New York, NY	X	X	X	
	<u>Appelbaum</u>	Hershey, PA	X			
	<u>Vartivarian</u>	Houston, TX		X		
	<u>Rolston</u>	Houston, TX	X	X		
	<u>North</u>	Denver, CO	X	X		
	<u>Barrett</u>	Iowa City, IA				X
	<u>Akinaro</u>	Irvine, CA	X	X		
	<u>Fuchs</u>	Portland, OR	X	X		
	<u>Edelstein</u>	Phila., PA				X
	<u>Murray</u>	St. Louis, MO	X			
	<u>Rudrik</u>	Asheville, NC	X	X		
	<u>Aldridge</u>	New Orleans, LA			X	
	<u>Eliopoulos</u>	Boston, MA	X	X	X	X
	<u>Klopman</u>	Cleveland, OH				X
	<u>Forstall</u>	Cleveland, OH	X			
	<u>Chaudhry</u>	Cleveland, OH	X			
	<u>Goldstein</u>	Los Angeles, CA	X	X	X	
	<u>Hammerschlag</u>	Brooklyn, NY				X
	<u>Waites</u>	Birmingham, AL				X
	<u>Louie</u>	Albany, NY	X	X		
	<u>Cohen</u>	Ann Arbor, MI	X	X	X	
	<u>Yaiko</u>	San Francisco, CA				X
	<u>Wexler</u>	Los Angeles, CA			X	
	<u>Hindler</u>	Los Angeles, CA		X		
<u>Spangler</u>	Hershey, PA	X				
<u>Perr</u>	Royal Oak, MI	X				
<u>Roblin</u>	Brooklyn, NY				X	
Belgium	<u>Verbist</u>	Leuven	X	X		
Canada	<u>Rotstein</u>	Hamilton	X			

TABLE 5 (cont)
Investigators, centers and bacterial groups studied

Country	Investigator	Center	Gram+ve aerobes	Gram-ve aerobes	Anaerobes	Intracellular organisms
	<u>Simor</u>	Toronto	X	X		
	<u>Loo</u>	Montreal	X			
France	<u>Lefevre</u>	Toulouse		X		
	<u>Truffot-Pernot</u>	Paris				X
	<u>Dabernat</u>	Toulouse		X		
	<u>Laurans</u>	Amiens		X		
	<u>Renaudin</u>	Cedex				X
Germany	<u>Bauernfeind</u>	Munich	X	X	X	
	<u>Wiedemann</u>	Bonn	X	X		
Greece	<u>Voutsinas</u>	Athens	X	X		
Japan	<u>Sato</u>	Tokyo	X	X	X	
	<u>Koizima</u>	Maebashi	X	X	X	X
	<u>Saito</u>	Izumo				X
Netherlands	<u>Visser</u>	Holland	X	X	X	X
Saudia Arabia	<u>Hussain</u>	Riyadh	X	X		
Spain	<u>Garcia-Rodriguez</u>	Salamanca	X	X	X	
	<u>Canton</u>	Valencia	X	X		
	<u>Loza</u>	Madrid	X			
Sweden	<u>Malmberg</u>	Huddinge	X	X		
Switzerland	<u>Rohner</u>	Geneva	X	X		
	<u>Bille</u>	Lausanne	X	X		
United Kingdom	<u>Cooper</u>	Birmingham	X	X	X	X
	<u>Wise</u>	Birmingham	X	X	X	
	<u>John Jr.</u>	London		X		
	<u>Gransden</u>	London		X		

TABLE 6
Types of medium and inoculum (cfu/spot or /mL) used.

Country	Investigator	Aerobes	Anaerobes
USA	Barry	MH (10 ⁴)	WC/BR (10 ⁵)
	Doebbeling	MHB (10 ⁵)	NT
	Barrett	7H9 (10 ⁴)	NT
	Jones	MHB (10 ⁵)	NT
	Chin	MH (10 ⁴)	BR (10 ⁵)
	Kenney	H agar (10 ⁴)	NT
	Appelbaum	MH (10 ⁴)	NT
	Vartivarian	MHB (10 ⁵)	NT
	Rolston	MHB (10 ⁵)	NT
	North	MHB (10 ⁵)	NT
	Akinaro	MHB (10 ⁵)	NT
	Fuchs	MHB (10 ⁵)	NT
	Edelstein	BCYE (10 ⁴)	NT
	Murray	MHB (10 ⁵)	NT
	Rudrik	MH (10 ⁵)	NT
	Aldridge	NT	WC (10 ⁵)
	Eliopoulos	MH (10 ⁴)	WC (10 ⁵)
	Klopman	7H II (10 ⁵)	NT
	Forstall	MHB (10 ⁵)	NT
	Chaudhry	MHB (10 ⁵)	NT
	Goldstein	MH (10 ⁴)	BR (10 ⁵)
	Hammerschlag	HeLa 229 (10 ⁴)	NT
	Waites	SP-4 (10 ⁴)	NT
	Louie	MH (10 ⁴)	NT
	Cohen	MHB (10 ⁵)	WC/BR5 (10 ⁴)
	Wexler	NT	BR (10 ⁵)
	Yajko	7HSF (10 ⁵)	NT
	Hindler	MHB (10 ⁵)	NT
	Spangler	MH (10 ⁴)	NT
	Perri	MHB (10 ⁵)	NT
Roblin	HEP2 (10 ⁴)	NT	
Belgium	Verbist	MH (10 ⁴)	NT
Canada	Rotstein	MHB (10 ⁵)	NT
	Simor	MHB (10 ⁵)	NT
	Loo	MHB (10 ⁵)	NT
France	Lefevre	MH (10 ⁴)	NT
	Truffot-Pernot	7H 11 (10 ⁴)	NT
	Dabernat	MH (10 ⁴)	NT
	Laurans	MH (10 ⁴)	NT
	Renaudin	HAY (10 ⁴)	NT
Germany	Bauernfeind	MH (10 ⁴)	WC (10 ⁵)
	Wiedemann	MH (10 ⁴)	NT
Greece	Voutsinas	MH (10 ⁴)	NT

TABLE 6 (cont.)
Types of medium and inoculum (cfu/spot or /mL) used.

Country	Investigator	Aerobes		Anaerobes
Japan	Sato	MH	(10 ³)	GAM (10 ³)
	Kojima	SDA	(10 ³)	GAM (10 ³)
	Saito	7H10	(10 ⁴)	NT
Netherlands	Visser	ISA	(10 ⁴)	WC (10 ⁴)-
Saudia Arabia	Hussain	MH	(10 ⁴)	NT
Spain	Garcia-Rodriguez	MH	(10 ⁴)	WC (10 ⁵)
	Canton	MH	(10 ⁴)	NT
	Loza	MH	(10 ⁵)	NT
Sweden	Malmborg	ISA/MH	(10 ⁷)	NT
Switzerland	Rohner	MH	(10 ⁴)	NT
	Bille	MHB	(10 ⁴)	NT
United Kingdom	Cooper	ISA	(10 ⁴)	WC (10 ⁴)
	Wise	ISA	(10 ⁴)	WC (10 ⁴)
	John, Jr.	MH	(10 ⁴)	NT
	Gransden	MH	(10 ⁴)	NT

Footnotes and Abbreviations:

7H 9 = Broth for Testing *Mycobacterium* spp.
 7H 10 = 7H10 Agar for Testing *Mycobacterium* spp.
 7H 11 = Broth for Testing *Mycobacterium* spp.
 7H SF = 7HSF Broth for Testing *Mycobacterium* spp.
 BCYE = Buffered Charcoal Yeast Extract Agar for Testing *Legionella* spp.
 BR = Brucella Agar
 GAM = GAM Agar
 H Agar = Agar for Testing *Mycoplasma* spp.
 HAY = Hayflick Media for Testing *Mycoplasma* spp.
 HeLa 229 = HeLa Cells for Testing *Chlamydia* spp.
 HEP2 = HEP-2 Cells for Testing *Chlamydia* spp.
 ISA = Iso Sensitest Agar
 MH = Mueller-Hinton Agar
 MHB = Mueller-Hinton Broth
 NT = Not Tested
 SDA = Sensitivity Disk Agar-N
 SP-4 = Broth for Testing *Mycoplasma* spp.
 WC = Wilkens Chalgren Agar

TABLE 7
List of bacterial species and associated numbers tested by country

Organism	Total No. strains	USA	Canada	Greece	Saudia Arabia	Nether -lands	Japan	France	Switz -erland	Germany	Spain	Sweden	Belgium	UK
<i>Acinetobacter anitratus</i>	159	99		60										
<i>Acinetobacter lwoffii</i>	51	28								23				
<i>Acinetobacter spp.</i>	279	29			51	50	35		28		52			34
<i>Aeromonas hydrophila</i>	99	70				10				19				
<i>Alcaligenes denitrificans</i> ss <i>xylosoxidans</i>	24	14								10				
<i>Bacillus cereus</i>	15	15												
<i>Bacillus spp.</i>	10	10												
<i>Bacteroides distasonis</i>	24	24												
<i>Bacteroides fragilis</i>	456	313					58				31			54
<i>Bacteroides ovatus</i>	34	34												
<i>Bacteroides thetaiotaomicron</i>	71	51									20			
<i>Bacteroides uniformis</i>	13	13												
<i>Bacteroides vulgatus</i>	28	28												
<i>Campylobacter jejuni</i>	35	10				25								
CDC group EF-4	13	13												
<i>Chlamydia pneumoniae</i>	19	18							1					
<i>Citrobacter amalonaticus</i>	21	21												
<i>Citrobacter diversus</i>	154	122								32				
<i>Citrobacter freundii</i>	400	164				35	96			75	30			
<i>Clostridium perfringens</i>	47	21				10	16							
<i>Clostridium spp.</i>	34	23												11
<i>Corynebacterium jeikeium</i>		49	49											
<i>Eikenella corrodens</i>	22	22												
<i>Enterobacter aerogenes</i>	274	201				12	10			51				
<i>Enterobacter agglomerans</i>	58	46								12				
<i>Enterobacter cloacae</i>	687	322		42		50	155			107				11
<i>Enterobacter sakazakii</i>	37	19								18				
<i>Enterococcus faecalis</i>	1152	707				40	152		45	131	52			25
<i>Enterococcus faecium</i>	236	97					88		34	17				
<i>Enterococcus avium</i>	34	34												
<i>Escherichia coli</i>	2341	1457			186	70	253		30	156	68			121
<i>Eubacterium spp.</i>	18	18												
<i>Fusobacterium spp.</i>	33	33												
<i>Haemophilus influenzae</i>	412	64					133	102	26	52				35

TABLE 7 (cont.)
List of bacterial species and associated numbers tested by country

Organism	Total No. strains	USA	Canada	Greece	Saudia Arabia	Nether-lands	Japan	France	Switz-erland	Germany	Spain	Sweden	Belgium	UK
<i>Haemophilus influenzae</i> (β lac +)	483	270	100				20					22	71	
<i>Haemophilus influenzae</i> (β lac -)	715	530	100				40					21	25	
<i>Haemophilus parainfluenzae</i>	60	60												
<i>Hafnia alvei</i>	53	32								21				
<i>Helicobacter pylori</i>	50	25				16				9				
<i>Klebsiella oxytoca</i>	540	169			31	41	156			112	31			
<i>Klebsiella pneumoniae</i>	938	424		37	64	69	158			155	31			
<i>Legionella pneumophila</i>	113	98				15								
<i>Legionella spp.</i>	21	21												
<i>Listeria monocytogenes</i>	141	70				10			22		39			
<i>Morganella morganii</i>	568	183				20	158			80	87			40
<i>Moraxella catarrhalis</i>	585	99				60	71	128	17	20	32	19	91	48
<i>Moraxella catarrhalis</i> (β lac +)	698	549	149											
<i>Moraxella catarrhalis</i> (β lac -)	98	47	51											
<i>Mycobacterium avium-intracellulare</i>	147	134						13						
<i>Mycoplasma tuberculosis</i>	42						25	17						
<i>Mycoplasma pneumoniae</i>	90	69						21						
<i>Neisseria gonorrhoeae</i>	194	43					40			34				77
<i>Neisseria gonorrhoeae</i> (β lac +)	130	97				13		20						
<i>Neisseria gonorrhoeae</i> (β lac -)	308	257				11		40						
<i>Neisseria meningitidis</i>	157	110				10			29					8
<i>Pasteurella multocida</i>	34	34												
<i>Peptostreptococcus spp.</i>	135	74					24			8				30
<i>Porphyromonas asaccharolytica</i>	10	10												
<i>Prevotella bivia</i>	23	23												
<i>Prevotella disiens</i>	10	10												
<i>Proteus mirabilis</i>	755	282				40	153		25	126	60			69

TABLE 7 (cont.)
List of bacterial species and associated numbers tested by country

Organism	Total No. strains	USA	Canada	Greece	Saudia Arabia	Nether-lands	Japan	France	Switz-erland	Germany	Spain	Sweden	Belgium	UK
<i>Proteus vulgaris</i>	362	121				21	75			49	71			25
<i>Providencia rettgeri</i>	150	76					50				17			7
<i>Providencia stuartii</i>	197	69					75			29				24
<i>Pseudomonas aeruginosa</i>	1489	779		37	98	70	157		32	136	100			80
<i>Pseudomonas cepacia</i>	120	20					51			25	24			
<i>Pseudomonas fluorescens</i>	52	32								20				
<i>Pseudomonas putida</i>	38	20								18				
<i>Salmonella spp.</i>	613	274			47	40	108		25	60	44			15
<i>Serratia liquefaciens</i>	70	20				20				30				
<i>Serratia marcescens</i>	551	233			40	30	170			78				
<i>Shigella spp.</i>	367	27			29	30	72			22	70			117
<i>Staphylococcus aureus</i>	1365	1019			128					100	65	23		30
<i>Staphylococcus aureus (MR)</i>	843	284	211	50		34	135		46	23	60			
<i>Staphylococcus aureus (MS)</i>	954	279	266	27		40	175		45	49	73			
<i>Staphylococcus epidermidis</i>	194	60		23							64			47
<i>Staphylococcus epidermidis (MR)401</i>		89	25			35	113		25	18	96			
<i>Staphylococcus epidermidis (MS)771</i>		390	22			25	146		24	24	140			
<i>Staphylococcus haemolyticus</i>	15													
<i>Staphylococcus haemolyticus (MR)115</i>			115											
<i>Staphylococcus haemolyticus (MS)29</i>			13							16				
<i>Staphylococcus hominis</i>	50	40								10				
<i>Staphylococcus hominis (MR)</i>	11		11											
<i>Staphylococcus saprophyticus</i> 220		22	100			30			10	8				50
<i>Staphylococcus saprophyticus (MR)18</i>			18											
<i>Staphylococcus saprophyticus (MS)22</i>			22											
<i>Staphylococcus simulans</i>	28	14								14				
<i>Staphylococcus spp. (coagulase neg)</i>	599	457			122						20			
<i>Streptococcus agalactiae</i>	281	192				20			33		21			15
<i>Streptococcus group G</i>	41	41												
<i>Streptococcus pneumoniae</i>	279												279	
<i>Streptococcus pneumoniae (PenS)626</i>		626												
<i>Streptococcus pneumoniae (PenI)154</i>		154												
<i>Streptococcus pneumoniae (PenR)152</i>		152												

TABLE 7 (cont.)
List of bacterial species and associated numbers tested by country

Organism	Total No. strains	USA	Canada	Greece	Saudia Arabia	Nether-lands	Japan	France	Switz-erland	Germany	Spain	Sweden	Belgium	UK
<i>Streptococcus pneumoniae</i> (ERY S)31	31													
<i>Streptococcus pneumoniae</i> (ERYR) 93	50							43						
<i>Streptococcus pyogenes</i>	562	134	200			38	125		34			21		10
<i>Veillonella parvula</i>	10	120												
Viridans group streptococci	110	46								25		39		
<i>Xanthomonas maltophilia</i>	515	301			31	17	74		14	50	28			
<i>Yersinia enterocolitica</i>	125	51				10				16	48			

β lac + = Beta-lactamase positive

β lac - = Beta- lactamase negative

ERY S = Erythromycin-sensitive ($\leq 0.5 \mu\text{g/mL}$)

ERY R = Erythromycin-resistant ($\geq 4 \mu\text{g/mL}$)

MR = Methicillin (oxacillin)-resistant ($\geq 4 \mu\text{g/mL}$)

MS = Methicillin (oxacillin)-sensitive ($\leq 2 \mu\text{g/mL}$)

PEN R = Penicillin-resistant ($\geq 2 \mu\text{g/mL}$)

PEN S = Penicillin-sensitive ($\leq 0.06 \mu\text{g/mL}$)

PEN I = Penicillin-intermediate (0.1-1 $\mu\text{g/mL}$)

TABLE 8
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-positive aerobes determined in 37 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Bacillus cereus</i>	Sparfloxacin	15 (1) ^b			
	Ciprofloxacin	15			
<i>Bacillus species</i>	Sparfloxacin	10 (1)			
	Ciprofloxacin	10			
<i>Corynebacterium jeikeium</i>	Sparfloxacin	49 (4)			
	Ciprofloxacin	39			
	Ofloxacin	11			
	Erythromycin	11			
	Vancomycin	11			
<i>Enterococcus avium</i>	Sparfloxacin	34 (2)			
	Ciprofloxacin	10			
	Ofloxacin	-			
	Vancomycin	10			
<i>Enterococcus faecalis</i>	Sparfloxacin	586 (11)		445	
	Ciprofloxacin	586		445	
	Ofloxacin	300		287	
	Vancomycin	132		15	
	Ampicillin	38			
	Erythromycin	64		15	
<i>Enterococcus faecium</i>	Sparfloxacin	97 (5)		139	
	Ciprofloxacin	97		139	
	Ofloxacin	20		95	
	Vancomycin	20		-	
<i>Listeria monocytogenes</i>	Sparfloxacin	70 (5)		71	
	Ciprofloxacin	57		71	
	Ofloxacin	22		27	
	Vancomycin	10		-	
<i>Staphylococcus aureus</i> ^c	Sparfloxacin	1019 (2)		346	
	Ciprofloxacin	1019		346	
	Ofloxacin	-		188	
	Vancomycin	-		30	
<i>Staphylococcus aureus (MR)</i>	Sparfloxacin	322 (6)		128	
	Ciprofloxacin	322		128	
	Ofloxacin	287		64	
	Vancomycin	216		-	
	Erythromycin	41		-	

TABLE 8 (cont.)
 Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against
 gram-positive aerobes determined in 37 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Staphylococcus aureus</i> (MS)	Sparfloxacin	545 (11)		409	
	Ciprofloxacin	545		409	--
	Ofloxacin	490		300	
	Vancomycin	378		-	
	Erythromycin	59		-	
<i>Staphylococcus epidermidis</i> ^c	Sparfloxacin	60 (2)		134	
	Ciprofloxacin	60		134	
	Ofloxacin	-		23	
	Vancomycin	-		27	
<i>Staphylococcus epidermidis</i> (MR)	Sparfloxacin	89 (3)		235	
	Ciprofloxacin	89		235	
	Ofloxacin	74		193	
	Vancomycin	15		-	
<i>Staphylococcus epidermidis</i> (MS)	Sparfloxacin	95 (3)		359	
	Ciprofloxacin	95		359	
	Ofloxacin	80		310	
	Vancomycin	15		-	
<i>Staphylococcus haemolyticus</i> ^c	Sparfloxacin	15 (1)			
	Ciprofloxacin	15			
<i>Staphylococcus haemolyticus</i> (MS)	Sparfloxacin	13 (1)		16	
	Ciprofloxacin	13		16	
	Ofloxacin	13		-	
	Vancomycin	13		-	
<i>Staphylococcus haemolyticus</i> (MR)	Sparfloxacin	100 (1)			
	Ciprofloxacin	100			
	Ofloxacin	100			
	Vancomycin	100			
<i>Staphylococcus hominis</i> ^c	Sparfloxacin	40 (2)		10	
	Ciprofloxacin	40		10	
<i>Staphylococcus hominis</i> (MR)	Sparfloxacin	11 (1)			
	Ciprofloxacin	11			
	Ofloxacin	11			
	Vancomycin	11			
<i>Staphylococcus saprophyticus</i> ^c	Sparfloxacin	122 (3)		98	
	Ciprofloxacin	122		98	
	Ofloxacin	100		10	
	Vancomycin	100		30	

TABLE 8 (cont.)
 Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against
 gram-positive aerobes determined in 37 worldwide centers
 North American Foreign

Organism	Drug	No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Staphylococcus saprophyticus</i> (MS)	Sparfloxacin	22 (1)			
	Ciprofloxacin	22			
	Ofloxacin	22			
	Vancomycin	22			
<i>Staphylococcus saprophyticus</i> (MR)	Sparfloxacin	18 (1)			
	Ciprofloxacin	18			
	Ofloxacin	18			
	Vancomycin	18			
<i>Staphylococcus simulans</i> ^c	Sparfloxacin	14 (1)		14	
	Ciprofloxacin	14		14	
<i>Staphylococcus spp. (coagulase neg.)</i> ^c	Sparfloxacin	85 (2)		20	
	Ciprofloxacin	85		20	
	Ofloxacin	85		20	
	Vancomycin	40		-	
	Erythromycin	40		-	
<i>Streptococcus agalactiae</i>	Sparfloxacin	192 (7)		89	
	Ciprofloxacin	192		89	
	Ofloxacin	30		32	
	Vancomycin	43		15	
	Erythromycin	43		15	
<i>Streptococcus group G</i>	Sparfloxacin	41 (2)			
	Ciprofloxacin	15			
<i>Streptococcus pneumoniae</i>	Sparfloxacin			279	
	Ciprofloxacin			-	
	Ofloxacin			279	
	Cefuroxime			279	
<i>Streptococcus pneumoniae</i> (PENS)	Sparfloxacin	626 (4)			
	Ciprofloxacin	626			
	Ofloxacin	59			
	Cefuroxime	47			
<i>Streptococcus pneumoniae</i> (PENI)	Sparfloxacin	154 (3)			
	Ciprofloxacin	154			
	Cefuroxime	71			
<i>Streptococcus pneumoniae</i> (PENR)	Sparfloxacin	152 (4)			
	Ciprofloxacin	152			
	Ofloxacin	59			
	Cefuroxime	19			

TABLE 8 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-positive aerobes determined in 37 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Streptococcus pneumoniae</i> (ERY S)	Sparfloxacin	31 (1)			
	Ciprofloxacin	31			
	Ofloxacin	31			
	Cefuroxime	31			
	Erythromycin	31			
<i>Streptococcus pneumoniae</i> (ERY R)	Sparfloxacin	50 (1)			
	Ciprofloxacin	50			
	Ofloxacin	50			
	Penicillin	50			
<i>Streptococcus pyogenes</i>	Sparfloxacin	334 (8)		228	
	Ciprofloxacin	334		228	
	Ofloxacin	261		158	
	Vancomycin	54		10	
	Erythromycin	74		10	
Viridans group streptococci	Sparfloxacin	46 (3)		64	
	Ciprofloxacin	36		64	
	Ofloxacin	16		25	
	Vancomycin	20		39	

Footnotes:

a = Twenty-one North American and 16 foreign study centers tested isolates, MIC₉₀ if only one center tested or if an MIC frequency distribution could be obtained.

b = Number of North American centers that tested sparfloxacin are indicated in Parentheses, but number of centers testing comparator drugs may be less.

c = Methicillin susceptibility not specified.

Abbreviations:

ERY S = Erythromycin-sensitive ($\leq 0.5\mu\text{g/mL}$)
 ERY R = Erythromycin-resistant ($\geq 4\mu\text{g/mL}$)
 MR = Methicillin (oxacillin)-resistant ($\geq 4\mu\text{g/mL}$)
 MS = Methicillin (oxacillin)-sensitive ($\leq 2\mu\text{g/mL}$)
 PEN R = Penicillin-resistant ($\geq 2\mu\text{g/mL}$)
 PEN S = Penicillin-sensitive ($\leq 0.06\mu\text{g/mL}$)
 PEN I = Penicillin-intermediate (0.1-1 $\mu\text{g/mL}$)

Antimicrobial activity (MIC₉₀ range) of Sparfloxacin, Ciprofloxacin, Ofloxacin and comparators against selected gram-positive aerobes determined in 71 American centers

Organism	Drug	No. of centers	No. of isolates	MIC (μg/mL)		Range
				MIC ₅₀	MIC ₉₀	
<i>Bacillus species</i>	Sparfloxacin	2	12	0.03	0.25	--
	Ciprofloxacin	2	12	0.03	0.5	
<i>Corynebacterium jeikeium</i>	Sparfloxacin	2	20	0.25	0.25	
	Ciprofloxacin	1	10	0.25	0.5	
	Vancomycin	1	10	1	1	
<i>Enterococcus avium</i>	Sparfloxacin	1	10	1	2	
	Ciprofloxacin	1	10	1	1	
	Vancomycin	1	10	1	-	
<i>Enterococcus faecalis</i>	Sparfloxacin	5	25	0.5	1	
	Ciprofloxacin	5	25	0.5	2	
	Ofloxacin	4	20	0.5	4	
	Vancomycin	4	20	1	4	
	Ampicillin	1	10	1	2	
	Erythromycin	2	10	1	>512	
<i>Enterococcus faecium</i>	Sparfloxacin	4	20	0.5	2	
	Ciprofloxacin	4	20	0.5	>4	
	Ofloxacin	3	15	0.5	>8	
	Vancomycin	3	15	1	4	
<i>Listeria monocytogenes</i>	Sparfloxacin	4	20	0.5	1	
	Ciprofloxacin	4	20	0.5	2	
	Ofloxacin	3	15	0.5	4	
<i>Staphylococcus aureus</i>	Sparfloxacin	6	30	0.03	0.25	
	Ciprofloxacin	6	30	0.03	1	
	Ofloxacin	5	25	0.5	1	
	Vancomycin	4	20	1	2	
	Erythromycin	3	15	0.5	>512	
<i>Staphylococcus aureus (MR)</i>	Sparfloxacin	5	25	0.06	0.25	
	Ciprofloxacin	5	25	0.5	0.5	
	Ofloxacin	5	25	0.5	2	
	Vancomycin	3	15	1	2	
	Erythromycin	2	10	>512	>512	
<i>Staphylococcus aureus (MS)</i>	Sparfloxacin	4	20	0.125	0.25	
	Ciprofloxacin	4	20	0.5	0.5	
	Ofloxacin	4	20	1	1	
	Vancomycin	4	20	1	2	
	Erythromycin	3	15	0.5	8	

TABLE 9 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against selected gram-positive aerobes determined in 7 North American centers

Organism	Drug	No. of centers	No. of strains	MIC (μg/mL)		Range
				MIC ₅₀	MIC ₉₀	
<i>Staphylococcus epidermidis</i>	Sparfloxacin	5	219	0.125	0.25	--
	Ciprofloxacin	5	219	0.25	0.5	
	Ofloxacin	4	198	0.25	0.5	
	Vancomycin	3	60	2	4	
<i>Staphylococcus epidermidis</i> (MR)	Sparfloxacin	3	150	0.125	0.25	
	Ciprofloxacin	3	150	0.25	0.5	
	Ofloxacin	2	139	0.25	0.5	
	Vancomycin	1	23	2	4	
<i>Staphylococcus epidermidis</i> (MS)	Sparfloxacin	2	29	0.25	0.25	
	Ciprofloxacin	2	29	0.25	0.5	
	Ofloxacin	1	16	0.5	1	
	Vancomycin	2	31	2	4	
<i>Staphylococcus haemolyticus</i>	Sparfloxacin	4	38	0.125	0.25	
	Ciprofloxacin	4	38	0.25	0.5	
	Ofloxacin	3	23	0.25	1	
<i>Staphylococcus hominis</i>	Sparfloxacin	3	26	0.125	0.25	
	Ciprofloxacin	3	26	0.25	0.25	
	Ofloxacin	2	14	0.25	0.5	
	Vancomycin	2	12	2	2	
<i>Staphylococcus saprophyticus</i>	Sparfloxacin	3	25	0.03	0.125	
	Ciprofloxacin	3	25	0.25	0.5	
	Ofloxacin	3	25	1	1	
<i>Staphylococcus simulans</i>	Sparfloxacin	2	8	0.06	-	
	Ciprofloxacin	2	8	<0.125	-	
	Ofloxacin	2	8	0.25	-	
<i>Streptococcus agalactiae</i>	Sparfloxacin	5	94	0.5	0.5	
	Ciprofloxacin	5	94	1	1	
	Ofloxacin	3	63	2	2	
	Vancomycin	2	20	0.125	0.25	
	Erythromycin	3	43	<0.03	1	
<i>Streptococcus group G</i>	Sparfloxacin	1	6	0.125	-	
	Ciprofloxacin	1	6	0.25	-	
<i>Streptococcus pneumoniae</i> (PENS)	Sparfloxacin	4	626	0.25	0.5	
	Ciprofloxacin	4	626	1	2	
	Ofloxacin	1	59	2	2	
	Cefuroxime	1	47	0.016	0.125	

TABLE 9 (cont.)

Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against selected gram-positive aerobes determined in 7 North American centers

Organism	Drug	No. of centers	No. of strains	MIC ($\mu\text{g/mL}$)		Range
				MIC ₅₀	MIC ₉₀	
<i>Streptococcus pneumoniae</i> (PENI)	Sparfloxacin	3	154	0.25	0.5	--
	Ciprofloxacin	3	154	1	4	
	Cefuroxime	1	71	0.5	4	
<i>Streptococcus pneumoniae</i> (PENR)	Sparfloxacin	4	152	0.25	0.5	
	Ciprofloxacin	4	152	1	4	
	Ofloxacin	1	59	4	8	
	Cefuroxime	1	19	2	2	
<i>Streptococcus pneumoniae</i> (ERYS)	Sparfloxacin	1	31	0.125	0.125	
	Ciprofloxacin	1	31	0.25	0.25	
	Ofloxacin	1	31	2	2	
	Cefuroxime	1	31	0.016	0.016	
	Erythromycin	1	31	0.03	0.06	
<i>Streptococcus pneumoniae</i> (ERYR)	Sparfloxacin	1	50	0.5	1	
	Ciprofloxacin	1	50	2	4	
	Ofloxacin	1	50	1.5	4	
	Penicillin	1	50	0.75	2	
	Cefotaxime	1	50	0.5	1.5	
<i>Streptococcus pyogenes</i>	Sparfloxacin	6	753	0.5	1	
	Ciprofloxacin	5	739	0.5	1	
	Ofloxacin	3	539	1	2	
	Vancomycin	2	44	0.5	1	
	Erythromycin	2	54	0.06	0.06	
<i>Viridans group streptococci</i>	Sparfloxacin	1	30	0.5	1	
	Ciprofloxacin	1	30	1	4	
	Vancomycin	1	30	0.5	1	

Abbreviations:

ERY S = Erythromycin-sensitive ($\leq 0.5 \mu\text{g/mL}$)
 ERY R = Erythromycin-resistant ($\geq 4 \mu\text{g/mL}$)
 MR = Methicillin (oxacillin)-resistant ($\geq 4 \mu\text{g/mL}$)
 MS = Methicillin (oxacillin)-sensitive ($\leq 2 \mu\text{g/mL}$)
 PEN R = Penicillin-resistant ($\geq 2 \mu\text{g/mL}$)
 PEN S = Penicillin-sensitive ($\leq 0.06 \mu\text{g/mL}$)
 PEN I = Penicillin-intermediate (0.1-1 $\mu\text{g/mL}$)

TABLE 10
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-negative aerobes determined in 36 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Acinetobacter anitratus</i>	Sparfloxacin	99 (5) ^b		127	
	Ciprofloxacin	99		60	
	Ofloxacin	10		60	
<i>Acinetobacter lwoffii</i>	Sparfloxacin	28 (2)		23	
	Ciprofloxacin	20		23	
<i>Acinetobacter</i> species	Sparfloxacin	29 (2)		250	
	Ciprofloxacin	29		250	
	Ofloxacin	29		55	
	Ceftazidime	14		50	
<i>Aeromonas hydrophila</i>	Sparfloxacin	70 (4)		29	
	Ciprofloxacin	45		29	
	Ofloxacin	15		-	
	Ceftazidime	-		10	
<i>Alcaligenes denitrificans</i> ss. <i>xylosoxidans</i>	Sparfloxacin	14 (1)		10	
	Ciprofloxacin	14		10	
<i>Campylobacter jejuni</i>	Sparfloxacin	10 (1)		25	
	Ciprofloxacin	10		25	
CDC group EF-4	Sparfloxacin	13 (1)		-	
	Ciprofloxacin	13			
	Ofloxacin	13			
<i>Citrobacter amalonaticus</i>	Sparfloxacin	21 (2)			
	Ciprofloxacin	14			
<i>Citrobacter diversus</i>	Sparfloxacin	122 (4)		32	
	Ciprofloxacin	90		32	
	Ofloxacin	23		18	
<i>Citrobacter freundii</i>	Sparfloxacin	164 (5)		236	
	Ciprofloxacin	164		236	
	Ofloxacin	35		168	
	Ceftazidime	-		35-	
<i>Eikenella corrodens</i>	Sparfloxacin	22 (2)			
	Ciprofloxacin	16			
	Ofloxacin	-			

TABLE 10 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-negative aerobes determined in 36 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Enterobacter aerogenes</i>	Sparfloxacin	173 (4)		73	
	Ciprofloxacin	173		73	
	Ofloxacin	35		32	
	Ceftazidime	-		12	
<i>Enterobacter agglomerans</i>	Sparfloxacin	74 (4)		12	
	Ciprofloxacin	46		12	
	Ofloxacin	10		-	
<i>Enterobacter cloacae</i>	Sparfloxacin	322 (5)		365	
	Ciprofloxacin	322		365	
	Ofloxacin	40		248	
	Ceftazidime	18		50	
	Tobramycin	18			
<i>Enterobacter sakazakii</i>	Sparfloxacin	19 (1)		18	
	Ciprofloxacin	11		18	
<i>Escherichia coli</i>	Sparfloxacin	1457 (8)		884	
	Ciprofloxacin	1457		884	
	Ofloxacin	60		387	
	Ceftazidime	76		70	
	Tobramycin	66		-	
<i>Haemophilus influenzae</i>	Sparfloxacin	64 (3)		348	
	Ciprofloxacin	64		348	
	Ofloxacin	10		235	
	Ampicillin	50		-	
<i>Haemophilus influenzae</i> (β lac +)	Sparfloxacin	370 (5)		113	
	Ciprofloxacin	370		42	
	Ofloxacin	338		93	
	Ampicillin	132		-	
	Erythromycin	10		71	
<i>Haemophilus influenzae</i> (β lac-)	Sparfloxacin	630 (4)		86	
	Ciprofloxacin	630		61	
	Ofloxacin	582		46	
	Ampicillin	148		-	
	Erythromycin	10		25	
<i>Haemophilus parainfluenzae</i>	Sparfloxacin	60 (2)			
	Ciprofloxacin	10			
	Ampicillin	10			
	Erythromycin	10			

TABLE 10 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-negative aerobes determined in 36 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Haflnia alvei</i>	Sparfloxacin	32 (2)		21	
	Ciprofloxacin	15		21	--
	Ofloxacin	15		-	
<i>Helicobacter pylori</i>	Sparfloxacin	25 (1)		25	
	Ciprofloxacin	25		25	
<i>Klebsiella oxytoca</i>	Sparfloxacin	169 (4)		371	
	Ciprofloxacin	169		371	
	Ofloxacin	20		164	
	Ceftazidime	13		41	
	Tobramycin	13		-	
<i>Klebsiella pneumoniae</i>	Sparfloxacin	424 (6)		514	
	Ciprofloxacin	424		514	
	Ofloxacin	25		289	
	Ceftazidime	32		69	
	Tobramycin	32		-	
<i>Moraxella catarrhalis</i>	Sparfloxacin	99 (3)		486	
	Ciprofloxacin	99		395	
	Ofloxacin	20		309	
	Ceftazidime	34		60	
<i>Moraxella catarrhalis</i> (β lac +)	Sparfloxacin	698(2)			
	Ciprofloxacin	698			
	Ofloxacin	698			
<i>Moraxella catarrhalis</i> (β lac -)	Sparfloxacin	98 (2)			
	Ciprofloxacin	98			
	Ofloxacin	98			
<i>Morganella morganii</i>	Sparfloxacin	183 (4)		385	
	Ciprofloxacin	76		385	
	Ofloxacin	25		264	
	Ceftazidime	-		20	
<i>Neisseria gonorrhoeae</i>	Sparfloxacin	43 (2)		151	
	Ciprofloxacin	12		151	
	Ofloxacin	12		96	
	Erythromycin	12		-	
<i>Neisseria gonorrhoeae</i> (β lac +)	Sparfloxacin	97 (2)		33	
	Ciprofloxacin	10		13	
	Ofloxacin	10		20	
	Erythromycin	-		20	

TABLE 10 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-negative aerobes determined in 36 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Neisseria gonorrhoeae</i> (β-lac-)	Sparfloxacin	257 (1)		51	
	Ciprofloxacin	-		11	--
	Ofloxacin	-		40	
	Erythromycin	-		40	
<i>Neisseria meningitidis</i>	Sparfloxacin	110 (2)		47	
	Ciprofloxacin	10		47	
<i>Pasteurella multocida</i>	Sparfloxacin	24 (2)			
	Ciprofloxacin	24			
	Ofloxacin	16			
<i>Proteus mirabilis</i>	Sparfloxacin	282 (6)		473	
	Ciprofloxacin	282		473	
	Ofloxacin	45		291	
	Ceftazidime	22		40	
	Tobramycin	12		-	
<i>Proteus vulgaris</i>	Sparfloxacin	121 (4)		241	
	Ciprofloxacin	57		241	
	Ofloxacin	25		218	
	Ceftazidime	-		21	
<i>Providencia rettgeri</i>	Sparfloxacin	76 (3)		131	
	Ciprofloxacin	36		74	
	Ofloxacin	25		50	
<i>Providencia stuartii</i>	Sparfloxacin	69 (2)		128	
	Ciprofloxacin	25		128	
	Ofloxacin	25		86	
<i>Pseudomonas aeruginosa</i>	Sparfloxacin	755 (12)		710	
	Ciprofloxacin	755		710	
	Ofloxacin	266		358	
	Ceftazidime	141		70	
	Tobramycin	49		-	
<i>Pseudomonas cepacia</i>	Sparfloxacin	20 (2)		100	
	Ciprofloxacin	20		100	
	Ofloxacin	10		61	
	Ceftazidime	10		-	
<i>Pseudomonas fluorescens</i>	Sparfloxacin	32 (2)		20	
	Ciprofloxacin	32		20	
	Ofloxacin	12		-	
	Ceftazidime	12		-	

TABLE 10 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against gram-negative aerobes determined in 36 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Pseudomonas putida</i>	Sparfloxacin	20 (1)		18	
	Ciprofloxacin	20		18	
<i>Salmonella</i> species	Sparfloxacin	274 (4)		339	
	Ciprofloxacin	52		339	
	Ofloxacin	25		171	
	Ceftazidime	13		40	
	Tobramycin	13		-	
<i>Serratia liquefaciens</i>	Sparfloxacin	20 (2)		50	
	Ciprofloxacin	10		50	
	Ofloxacin	-		15	
	Ceftazidime	-		20	
<i>Serratia marcescens</i>	Sparfloxacin	233 (8)		318	
	Ciprofloxacin	233		318	
	Ofloxacin	66		198	
	Ceftazidime	46		30	
	Tobramycin	26		-	
<i>Shigella</i> species	Sparfloxacin	27 (2)		340	
	Ciprofloxacin	27		340	
	Ofloxacin	27		112	
	Ceftazidime	12		30	
	Tobramycin	12		-	
<i>Xanthomonas maltophilia</i>	Sparfloxacin	301 (9)		214	
	Ciprofloxacin	301		214	
	Ofloxacin	52		102	
	Ceftazidime	145		17	
<i>Yersinia enterocolitica</i>	Sparfloxacin	51 (2)		74	
	Ciprofloxacin	16		74	
	Ofloxacin	16		17	
	Ceftazidime	-		10	

Footnotes:

a = Sixteen North American and 20 foreign study centers tested isolates; MIC₉₀ if only one center tested.

b = Number of North American centers that tested sparfloxacin are indicated in parentheses, but number of centers testing comparator drugs may be less.

Abbreviations:

β lac + = Beta-lactamase positive.

β lac - = Beta-lactamase negative.

TABLE 11
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against selected gram-negative aerobes determined in 7 North American centers

Organism	Drug	No. of centers	No. of strains	MIC ($\mu\text{g/mL}$)		Range
				MIC ₅₀	MIC ₉₀	
<i>Acinetobacter anitratus</i>	Sparfloxacin	2	20	0.06	0.125	--
	Ciprofloxacin	2	20	0.5	1	
	Ofloxacin	2	10	0.5	2	
<i>Acinetobacter Iwoffii</i>	Sparfloxacin	1	4	-	-	
	Ciprofloxacin	1	4	-	-	
<i>Aeromonas hydrophila</i>	Sparfloxacin	3	14	0.06	0.25	
	Ciprofloxacin	3	14	0.03	0.06	
<i>Campylobacter jejuni</i>	Sparfloxacin	1	10	0.06	0.25	
	Ciprofloxacin	1	10	0.25	1	
<i>Citrobacter diversus</i>	Sparfloxacin	3	25	<0.015	<0.03	
	Ciprofloxacin	3	25	<0.008	0.016	
	Ofloxacin	3	25	0.06	0.125	
<i>Citrobacter freundii</i>	Sparfloxacin	4	65	0.06	1	
	Ciprofloxacin	4	65	0.06	0.125	
	Ofloxacin	3	45	0.125	0.5	
<i>Enterobacter aerogenes</i>	Sparfloxacin	4	53	0.06	0.125	
	Ciprofloxacin	4	53	0.03	0.06	
	Ofloxacin	3	43	0.125	0.25	
<i>Enterobacter agglomerans</i>	Sparfloxacin	3	24	0.03	0.25	
	Ciprofloxacin	3	24	0.015	0.125	
	Ofloxacin	3	24	0.125	0.25	
<i>Enterobacter cloacae</i>	Sparfloxacin	4	65	0.06	0.125	
	Ciprofloxacin	4	65	0.03	0.06	
	Ofloxacin	3	45	0.125	0.5	
<i>Escherichia coli</i>	Sparfloxacin	5	132	0.016	0.06	
	Ciprofloxacin	5	132	0.016	0.03	
	Ofloxacin	4	102	0.06	0.125	
	Ceftazidime	1	37	0.125	0.25	
	Tobramycin	1	26	0.5	2	
<i>Haemophilus influenzae</i>	Sparfloxacin	3	785	<0.03	<0.03	
	Ciprofloxacin	3	783	<0.03	<0.03	
	Ofloxacin	2	77	0.03	0.06	
	Ampicillin	2	77	0.5	32	
	Erythromycin	2	67	8	32	

TABLE 11 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against selected gram-negative aerobes determined in 7 North American centers

Organism	Drug	No. of centers	No. of strains	MIC (μg/mL)		Range
				MIC ₅₀	MIC ₉₀	
<i>Haemophilus influenzae</i> (β lac +)	Sparfloxacin	1	223	<0.03	<0.03	--
	Ciprofloxacin	1	223	<0.03	<0.03	
<i>Haemophilus influenzae</i> (β lac -)	Sparfloxacin	1	485	<0.03	<0.03	
	Ciprofloxacin	1	483	<0.03	<0.03	
<i>Haemophilus parainfluenzae</i>	Sparfloxacin	1	50	<0.125	<0.125	
<i>Helicobacter pylori</i>	Sparfloxacin	1	25	0.5	0.5	
	Ciprofloxacin	1	25	0.25	0.25	
<i>Klebsiella oxytoca</i>	Sparfloxacin	2	12	0.03	0.06	
	Ciprofloxacin	2	12	0.015	0.03	
	Ofloxacin	2	12	0.125	0.125	
<i>Klebsiella pneumoniae</i>	Sparfloxacin	5	90	0.06	0.5	
	Ciprofloxacin	5	90	0.06	0.25	
	Ofloxacin	4	60	0.125	1	
<i>Moraxella catarrhalis</i>	Sparfloxacin	4	702	<0.03	<0.03	
	Ciprofloxacin	4	731	<0.03	0.06	
	Ofloxacin	2	276	0.06	0.125	
	Ceftazidime	2	34	<0.03	0.25	
<i>Moraxella catarrhalis</i> (β lac +)	Sparfloxacin	1	550	<0.03	<0.03	
	Ciprofloxacin	1	555	<0.03	0.06	
	Ofloxacin	1	145	0.06	0.125	
<i>Moraxella catarrhalis</i> (β lac -)	Sparfloxacin	1	57	<0.03	<0.03	
	Ciprofloxacin	1	57	0.06	0.06	
	Ofloxacin	1	57	0.125	0.125	
<i>Morganella morganii</i>	Sparfloxacin	3	24	0.125	0.25	
	Ciprofloxacin	3	24	0.008	0.016	
	Ofloxacin	3	24	0.06	0.25	
<i>Neisseria gonorrhoeae</i>	Sparfloxacin	1	12	<0.03	<0.03	
	Ciprofloxacin	1	12	0.004	0.015	
	Ofloxacin	1	12	0.008	0.03	
	Erythromycin	1	12	0.125	0.5	
<i>Neisseria meningitidis</i>	Sparfloxacin	2	110	<0.125	<0.125	
	Ciprofloxacin	1	10	<0.008	<0.008	

TABLE 11 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against selected gram-negative aerobes determined in 7 North American centers

Organism	Drug	No. of centers	No. of strains	MIC ($\mu\text{g/mL}$)		Range
				MIC ₅₀	MIC ₉₀	
<i>Pasteurella multocida</i>	Sparfloxacin	2	9	0.015	-	
	Ciprofloxacin	2	9	0.03	-	
<i>Proteus mirabilis</i>	Sparfloxacin	5	62	0.25	0.5	
	Ciprofloxacin	5	62	0.03	0.06	
	Ofloxacin	4	52	0.125	0.25	
	Ceftazidime	3	22	0.06	0.06	
	Tobramycin	2	12	0.5	1	
<i>Proteus vulgaris</i>	Sparfloxacin	4	32	0.5	0.5	
	Ciprofloxacin	4	32	0.03	0.125	
	Ofloxacin	3	22	0.125	0.25	
<i>Providencia rettgeri</i>	Sparfloxacin	3	21	0.25	1	
	Ciprofloxacin	3	21	0.06	1	
	Ofloxacin	3	21	0.5	4	
<i>Providencia stuartii</i>	Sparfloxacin	3	23	0.25	1	
	Ciprofloxacin	3	23	0.125	2	
	Ofloxacin	3	23	1	4	
<i>Pseudomonas aeruginosa</i>	Sparfloxacin	6	315	1	4	
	Ciprofloxacin	6	315	0.25	2	
	Ofloxacin	5	300	2	8	
	Ceftazidime	4	250	2	32	
	Tobramycin	4	158	2	32	
<i>Pseudomonas cepacia</i>	Sparfloxacin	6	46	1	8	
	Ciprofloxacin	6	47	2	8	
	Ofloxacin	5	36	8	32	
	Ceftazidime	4	29	4	32	
	Tobramycin	2	15	64	64	
<i>Pseudomonas fluorescens</i>	Sparfloxacin	3	21	0.5	2	
	Ciprofloxacin	3	21	0.125	0.5	
	Ofloxacin	3	21	1	4	
<i>Salmonella species</i>	Sparfloxacin	1	13	0.06	0.06	
	Ciprofloxacin	1	13	0.016	0.03	
	Ofloxacin	1	13	0.06	0.125	
	Ceftazidime	1	13	0.25	0.5	
	Tobramycin	1	13	1	32	

TABLE 11 (cont.)
 Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against
 selected gram-negative aerobes determined in 7 North American centers

Organism	Drug	No. of centers	No. of strains	MIC ($\mu\text{g/mL}$)		Range
				MIC ₅₀	MIC ₉₀	
<i>Serratia marcescens</i>	Sparfloxacin	5	92	0.5	8	
	Ciprofloxacin	5	92	0.125	4	--
	Ofloxacin	4	72	0.25	16	
	Ceftazidime	2	32	0.25	1	
	Tobramycin	1	12	0.5	2	
<i>Xanthomonas malitophilia</i>	Sparfloxacin	5	52	0.5	2	
	Ciprofloxacin	5	52	2	8	
	Ofloxacin	4	38	2	8	
	Ceftazidime	2	17	64	128	
<i>Yersinia enterocolitica</i>	Sparfloxacin	3	21	0.016	0.06	
	Ciprofloxacin	3	21	0.016	0.03	
	Ofloxacin	3	21	0.06	0.25	

Abbreviations:

- β lac += Beta-lactamase positive
 β lac - = Beta-lactamase negative.

TABLE 12
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against anaerobes determined in 14 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Bacteroides distasonis</i>	Sparfloxacin	24 (1) ^b			
	Ciprofloxacin	24			
	Clindamycin	24			
	Metronidazole	24			
<i>Bacteroides fragilis</i>	Sparfloxacin	313 (5)		143	
	Ciprofloxacin	313		143	
	Clindamycin	165		-	
	Metronidazole	165		30	
<i>Bacteroides ovatus</i>	Sparfloxacin	43 (2)			
	Ciprofloxacin	34			
	Clindamycin	34			
	Metronidazole	34			
<i>Bacteroides thetaiotaomicron</i>	Sparfloxacin	61 (2)		20	
	Ciprofloxacin	51		20	
	Clindamycin	51		-	
	Metronidazole	51		-	
<i>Bacteroides uniformis</i>	Sparfloxacin	13 (1)			
	Ciprofloxacin	13			
	Clindamycin	13			
	Metronidazole	13			
<i>Bacteroides vulgatus</i>	Sparfloxacin	37 (2)			
	Ciprofloxacin	28			
	Clindamycin	28			
	Metronidazole	28			
<i>Clostridium perfringens</i>	Sparfloxacin	21 (2)		26	
	Ciprofloxacin	21		26	
<i>Clostridium</i> species	Sparfloxacin	49 (5)		11	
	Ciprofloxacin	23		11	
	Clindamycin	12			
	Metronidazole	12			
<i>Eubacterium</i> species	Sparfloxacin	18 (1)			
	Ciprofloxacin	18			
	Clindamycin	18			
	Metronidazole	18			

TABLE 12 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against anaerobes determined in 14 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Fusobacterium</i> species	Sparfloxacin	33 (2)			
	Ciprofloxacin	33			
	Clindamycin	20			
	Metronidazole	20			
<i>Peptostreptococcus</i> species	Sparfloxacin	74 (5)		62	
	Ciprofloxacin	74		62	
	Clindamycin	25		-	
	Metronidazole	25		11	
<i>Porphyromonas asaccharolytica</i>	Sparfloxacin	10 (1)			
	Ciprofloxacin	10			
	Clindamycin	10			
	Metronidazole	10			
<i>Prevotella bivia</i>	Sparfloxacin	23 (1)			
	Ciprofloxacin	23			
	Clindamycin	23			
	Metronidazole	23			
<i>Prevotella disiens</i>	Sparfloxacin	10 (1)			
	Ciprofloxacin	10			
	Clindamycin	10			
	Metronidazole	10			
<i>Veillonella parvula</i>	Sparfloxacin	10 (1)			
	Ciprofloxacin	10			
	Clindamycin	10			
	Metronidazole	10			

Footnotes:

- a = Seven North American and 7 foreign study centers tested isolates; MIC₉₀ if only one center tested.
- b = Number of North American centers testing sparfloxacin are indicated in parentheses but number of centers testing comparator drugs may be less.

TABLE 13
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against intracellular pathogens determined in 16 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Chlamydia pneumoniae</i>	Sparfloxacin	18 (2) ^b		1	
	Ciprofloxacin	10		1	
	Ofloxacin	22		-	
<i>Legionella pneumophila</i>	Sparfloxacin	131 (2)		15	
	Ciprofloxacin	98		15	
	Ofloxacin	98		-	
	Erythromycin	98		-	
<i>Legionella</i> species	Sparfloxacin	21 (2)		-	
	Ciprofloxacin	21		-	
	Erythromycin	21		-	
<i>Mycobacterium avium-intracellulare</i>	Sparfloxacin	134 (5)		13	
	Ciprofloxacin	99		13	
<i>Mycobacterium tuberculosis</i>	Sparfloxacin	-		42	
	Ciprofloxacin	-		17	
	Ofloxacin	-		42	
<i>Mycoplasma pneumoniae</i>	Sparfloxacin	69 (2)		21	
	Ciprofloxacin	69		-	
	Ofloxacin	39		21	
	Tetracycline	69		-	
	Erythromycin	69		21	

Footnotes:

a= Ten North American and 6 foreign study centers tested isolates. MIC₉₀ if only one center tested.

b = Number of North American centers testing sparfloxacin are indicated in parenthesis but number of centers testing comparator drugs may be less.

TABLE 14
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against resistant organisms determined in 14 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
Gram-positive Aerobes					
<i>Enterococcus faecalis</i> (GMR)	Sparfloxacin	121 (2) ^b			
	Ciprofloxacin	20			
	Ofloxacin	20			
	Vancomycin	20			
	Penicillin	20			
<i>Staphylococcus aureus</i> (QR,MR)	Sparfloxacin	173 (5)		220	
	Ciprofloxacin	173		220	
	Ofloxacin	153		185	
	Vancomycin	71		-	
	Erythromycin	20		-	
<i>Staphylococcus epidermidis</i> (QR,MR)	Sparfloxacin	25 (1)		52	
	Ciprofloxacin	25		52	
	Ofloxacin	25		41	
	Vancomycin	25		-	
<i>Staphylococcus epidermidis</i> (QR,MS)	Sparfloxacin	317 (4)			
	Ciprofloxacin	317			
	Ofloxacin	57			
	Vancomycin	37			
<i>Staphylococcus haemolyticus</i> (QR,MR)	Sparfloxacin	15 (1)			
	Ciprofloxacin	15			
	Ofloxacin	15			
	Vancomycin	15			
<i>Staphylococcus</i> spp. (coagulase neg. QR)	Sparfloxacin	372 (2)		122	
	Ciprofloxacin	372		122	
	Ofloxacin	372		-	
<i>Streptococcus pneumoniae</i> (ERYS)	Sparfloxacin	31 (1)			
	Ciprofloxacin	31			
	Ofloxacin	31			
	Cefuroxime	31			
	Erythromycin	31			
<i>Streptococcus pneumoniae</i> (ERYR)	Sparfloxacin	50 (1)		43	
	Ciprofloxacin	50		-	
	Ofloxacin	50		-	

TABLE 14 (cont.)
Antimicrobial activity (MIC₉₀ range) of sparfloxacin and comparators against
resistant organisms determined in 14 worldwide centers

Organism	Drug	North American		Foreign	
		No. of strains	MIC ₉₀ (μg/mL) range ^a	No. of strains	MIC ₉₀ (μg/mL) range ^a
<i>Streptococcus pneumoniae</i> (PEN I)	Sparfloxacin	154 (3)			
	Ciprofloxacin	154			
<i>Streptococcus pneumoniae</i> (PENR)	Sparfloxacin	152 (4)			
	Ciprofloxacin	152			
	Ofloxacin	59			
<u>Gram-negative Aerobes</u>					
<i>Haemophilus influenzae</i> (β lac +)	Sparfloxacin	370 (5)		113	
	Ciprofloxacin	370		42	
	Ofloxacin	338		93	
	Ampicillin	132		-	
	Erythromycin	10		71	
<i>Enterobacteriaceae</i> (NAR)	Sparfloxacin	60 (2)			
	Ciprofloxacin	60			
<i>Pseudomonas aeruginosa</i> (QR)	Sparfloxacin	24 (1)			
	Ciprofloxacin	24			

Footnotes:

a = MIC₉₀ if only one center tested.

b = Number of North American centers that tested sparfloxacin are indicated in parentheses, but number of centers testing comparator drugs may be less.

c = MIC₉₀ frequency distribution of 5 N. A. centers testing sparfloxacin; 0.125 μg/mL (1 center), 4 μg/mL (2 centers), 8 μg/mL (1 center), and 16 μg/mL (1 center)

d = Mean MIC value reported.

Abbreviations:

β lac + = Beta-lactamase positive.

ERY S = Erythromycin-sensitive (≤ 0.5 μg/mL).

ERY R = Erythromycin-resistant (≥ 4 μg/mL).

GMR = High level gentamicin resistance (> 2,000 μg/mL)

MR = Methicillin (oxacillin)-resistant (≥ 4 μg/mL).

MS = Methicillin (oxacillin)-sensitive (≤ 2 μg/mL).

NAR = Nalidixic acid-resistant (≥ 32 μg/mL).

PEN R = Penicillin-resistant (≥ 2 μg/mL).

PEN I = Penicillin-intermediate (0.1-1 μg/mL).

QR = Quinolone-resistant (Ciprofloxacin MIC ≥ 4 μg/mL)

ACTIVITY AGAINST GRAM-POSITIVE AEROBES (TABLE 8 & 9)

Bacillus cereus—one study: 15 isolates: MIC₉₀ 0.25 µg/mL.

Bacillus species—one study: 10 isolates: MIC₉₀ 0.25 µg/mL.

In 2 selected N.A. centers: 12 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.25 µg/mL:

Range: µg/mL

According to the ASM Manual of Clinical Microbiology *Bacillus* species when present in respiratory tract infections are rarely if ever pathogens. These organisms will not be allowed in the label.

Corynebacterium jeikeium—4 studies: 49 isolates: MIC₉₀s 0.25-0.5 µg/mL.

In 2 selected N.A. centers: 20 isolates: MIC₅₀ 0.25 µg/mL: MIC₉₀ 0.25 µg/mL:

Range µg/mL.

According to the ASM Manual of Clinical Microbiology *Corynebacterium* species other than *Corynebacterium diphtheriae* when present in respiratory tract infections are rarely if ever pathogens. This organisms will not be allowed in the label.

Enterococcus avium—two studies: 34 isolates: MIC₉₀s 1-2 µg/mL.

In 1 selected N.A. centers: 10 isolates: MIC₅₀ 1 µg/mL: MIC₉₀ 2 µg/mL:

Range: µg/mL.

The MIC₉₀ is above the susceptible breakpoint in one of the two studies. Only 34 isolates were tested. *Enterococcus* species are rarely encountered in respiratory tract specimens and when they are present they are rarely pathogens. This species will not be in the label. The sponsor has not put this species in their label.

Enterococcus faecalis—11 N.A. studies: 586 isolates: MIC₉₀s 0.5-1 µg/mL.

10 Foreign studies: 445 isolates: MIC₉₀ 0.39->16 µg/mL.

In 5 selected N.A. centers: 148 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 1 µg/mL:

Range µg/mL.

The MIC₉₀ values are clustered at or near the susceptible breakpoint of 1 µg/mL. One foreign study which was performed according to NCCLS methods had a very high MIC₉₀ value. This study was performed in Spain and tested 32 isolates. Another Spanish study with 20 isolates had an MIC₉₀ of 2 µg/mL. Since the MIC₉₀ values are often at or above the susceptible breakpoint and *Enterococcus* species are not usual pathogens in respiratory tract infections this organism will not be in the label.

Enterococcus faecium—5 N.A. studies: 97 isolates: MIC₉₀s 1-4 µg/mL.
6 Foreign studies: 139 isolates: MIC₉₀ 0.39-50 µg/mL.
In 4 selected N.A. centers: 59 isolates: MIC₅₀ 1 µg/mL: MIC₉₀ 2 µg/mL.
Range: µg/mL.

The MIC₉₀ value in several studies is above 1 µg/mL. The foreign study with the MIC₉₀ value of 50 µg/mL and a range of 0.39-50 µg/mL was performed in Japan using Mueller-Hinton agar but an inoculum of 10³ CFU/spot instead of 10⁴ CFU/spot. A Swiss study using a broth dilution technique and an inoculum of 10⁴ CFU/mL had an MIC₉₀ of 8 µg/mL and a range of µg/mL. There appear to be some strains that are very resistant to sparfloxacin. These strains seem to be seen only in foreign studies. All N.A. studies had isolates at or below 4 µg/mL. Since the MIC₉₀s may be above the susceptible breakpoint and *Enterococcus* species are not usual pathogens in respiratory tract infections, *Enterococcus faecium* will not be allowed in the label. The sponsor has not placed this species in the label.

Listeria monocytogenes—5 N.A. studies: 70 isolates: MIC₉₀ 1-4 µg/mL.
5 Foreign studies: 71 isolates: MIC₉₀ 1-2 µg/mL.
In 4 selected N.A. center: 25 isolates: MIC₅₀ 1 µg/mL: MIC₉₀ 1 µg/mL.
Range: µg/mL.

Several studies had MIC₉₀s above the 1 µg/mL breakpoint. According to "A Clinician's Dictionary of Bacteria and Fungi" this species may be isolated from the nasopharynx and may cause upper respiratory tract infections. It will not be allowed in the label since the MIC₉₀ values may be high. The sponsor has not included this species in their proposed label.

Staphylococcus aureus—2 N.A. studies: 1019 isolates: MIC₉₀ 0.06-0.125 µg/mL.
3 Foreign studies: 346 isolates: MIC₉₀ 0.125-0.5 µg/mL.
In 6 selected N.A. centers: 420 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

The organisms in these studies did not have methicillin susceptibility specified. In the two N.A. centers 984 of the 1019 isolates were from one study.

Staphylococcus aureus (MR)—6 N.A. studies: 322 isolates: MIC₉₀ 0.125-0.25 µg/mL.
4 Foreign studies: 128 isolates: MIC₉₀ 0.06-2 µg/mL.
In 5 selected N.A. centers: 146 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

Staphylococcus aureus (MS)—6 N.A. studies: 545 isolates: MIC₉₀ 0.06-0.25 µg/mL.
4 Foreign studies: 409 isolates: MIC₉₀ 0.06-0.25 µg/mL.
In 4 selected N.A. centers: 127 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

Staphylococcus aureus (QR, MR)—5 N.A. centers: 173 isolates: MIC₉₀ 0.125-16 µg/mL.
4 Foreign studies: 220 isolates: MIC₉₀ 0.2-16 µg/mL.

According to the ASM Manual of Clinical Microbiology *Staphylococcus* species when present in respiratory tract infections are occasionally involved in disease production. Since many isolates were tested in a large number of centers and the MIC₉₀ values were below 1.0 µg/mL, except for the quinolone-resistant strains, *Staphylococcus aureus* (excluding quinolone-resistant) strains will be allowed in the label.

Staphylococcus epidermidis—2 N.A. centers: 60 isolates: MIC₉₀ 0.125 µg/mL.
3 Foreign studies: 134 isolates: MIC₉₀ 0.125-2 µg/mL.
In 5 selected N.A. centers: 219 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

The organisms in these studies did not have methicillin susceptibility specified.

Staphylococcus epidermidis (MR)—3 N.A. centers: 89 isolates: MIC₉₀ 0.125-0.25 µg/mL
5 Foreign studies: 235 isolates: MIC₉₀ 0.125-0.25
In 3 selected N.A. centers: 150 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

Staphylococcus epidermidis (MS)—3 N.A. centers: 95 isolates: MIC₉₀ 0.06-0.5 µg/mL.
5 Foreign studies: 359 isolates: MIC₉₀ 0.06-0.25
In 2 selected N.A. centers: 29 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

Staphylococcus epidermidis (QR, MR)—1 N.A. center: 25 isolates: MIC₉₀ 6.3 µg/mL.
2 Foreign studies: 52 isolates: MIC₉₀ 3.13-8

Staphylococcus epidermidis (QR, MS)—4 N.A. centers: 317 isolates: MIC₉₀ 0.1-8 µg/mL.
The last studies shown above indicate that quinolone-resistant mutants are resistant to sparfloxacin, but methicillin-resistance by itself does not make the isolate resistant to sparfloxacin.

Since many isolates have been tested in a number of centers and the MIC₉₀s are below 1.0 µg/mL, except for the quinolone resistant mutants, *Staphylococcus epidermidis* (excluding quinolone-resistant strains) will be allowed in the label.

Staphylococcus haemolyticus--1 N.A. center: 15 isolates: MIC₉₀ 0.125 µg/mL.
No Foreign studies.

In 4 selected N.A. centers: 38 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

Staphylococcus haemolyticus (MS)--1 N.A. center: 13 isolates: MIC₉₀ 0.08 µg/mL.
1 Foreign study: 16 isolates: MIC₉₀ 0.06 µg/mL.

Staphylococcus haemolyticus (MR)—1 N.A. center: 100 isolates: MIC₉₀ 0.125 µg/mL.
No Foreign studies.

Staphylococcus haemolyticus (QR, MR)—1 N.A. center: 15 isolates: MIC₉₀ 6.8 µg/mL.
Although there were fewer isolates tested than for *S. aureus* and *S. epidermidis*, if all studies are combined there are over 100 isolates tested and the highest MIC₉₀ values, excluding the quinolone resistant study, was 0.25 µg/mL. *Staphylococcus haemolyticus* will be allowed in the label.

Staphylococcus hominis--1 N.A. center: 11 isolates: MIC₉₀ 0.12 µg/mL.

No Foreign studies.

In 3 selected N.A. center: 25 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.

Range: µg/mL.

Staphylococcus hominis (MR)--1 N.A. center: 100 isolates: MIC₉₀ 0.12 µg/mL.

Although most of the isolates tested were from one study, there were 4 different centers that did do testing. Over 100 total isolates were tested and the highest MIC₉₀ value was 0.25 µg/mL. The highest MIC in the 3 selected studies was 0.5 µg/mL. All these MIC values are below 1.0 µg/mL. *Staphylococcus hominis* will be allowed in the label.

Staphylococcus saprophyticus--3 N.A. centers: 122 isolates: MIC₉₀ 0.25 µg/mL.

4 Foreign studies: 98 isolates: MIC₉₀ 0.125-0.5 µg/mL

In 3 selected N.A. centers: 25 isolates: MIC₅₀ 0.03 µg/mL: MIC₉₀ 0.125 µg/mL.

Range: µg/mL.

Staphylococcus saprophyticus (MS)--1 N.A. center: 22 isolates: MIC₉₀ 0.09 µg/mL.

Staphylococcus saprophyticus (MR)--1 N.A. center: 18 isolates: MIC₉₀ 0.14 µg/mL.

Although a large number of isolates were tested in a number of centers and all the MIC₉₀ values were 0.5 µg/mL or less, this species is usually found associated with urinary tract infections and not respiratory tract infections. *Staphylococcus saprophyticus* will not be allowed in the label.

Staphylococcus simulans--1 N.A. center: 14 isolates: MIC₉₀ 0.125 µg/mL.

1 Foreign study: 14 isolates: MIC₉₀ 0.125 µg/mL.

In 2 selected N.A. center: 8 isolates: MIC₅₀ 0.06 µg/mL.

Not enough strains were tested to allow this species into the label.

Streptococcus agalactiae--7 N.A. centers: 192 isolates: MIC₉₀ 0.5 µg/mL.

5 Foreign studies: 89 isolates: MIC₉₀ 0.5-2 µg/mL.

In 5 selected N.A. center: 94 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 0.5 µg/mL.

Range: µg/mL.

Only one foreign study has an MIC₉₀ value greater than 1.0 µg/mL. This was a study performed in the Netherlands with Iso Sensitest Agar. This study tested 20 isolates and the MIC₅₀ value was 0.5 µg/mL, which is a value equal to that in several other studies. Since only 20 isolates were tested the MIC₉₀ value would be 2.0 µg/mL if only 2 isolates had this MIC value. Since over 100 isolates were tested and all MIC₉₀ values were 1.0 µg/mL or less in all but one foreign study, *Streptococcus agalactiae* will be allowed into the label since the ASM Manual of Clinical Microbiology states that streptococci when present may be involved in respiratory tract infections.

**RHONE-POULENC RORER
SPARFLOXACIN TABLETS**

Streptococcus Group G--2 N.A. center: 41 isolates: MIC₉₀ 0.5-1 µg/mL.

No Foreign studies.

In 1 selected N.A. center: 6 isolates: MIC₅₀ 0.125 µg/mL: Range: µg/mL.

Since the MIC₉₀ value is close or equal to 1.0 µg/mL, which is the susceptibility breakpoint for sparfloxacin and only a few isolates were tested in only 3 centers, this organism group will not be allowed into the label.

Streptococcus pneumoniae--All N.A. studies separated the isolates by Penicillin susceptibility.

5 Foreign studies: 279 isolates: MIC₉₀ 0.25 µg/mL.

Streptococcus pneumoniae (PEN S)--4 N.A. centers: 626 isolates: MIC₅₀ 0.25 µg/mL

MIC₉₀ 0.5 µg/mL: Range: µg/mL-1 µg/mL.

Streptococcus pneumoniae (PEN I)--3 N.A. centers: 154 isolates: MIC₅₀ 0.25 µg/mL:

MIC₉₀ 0.5 µg/mL: Range: µg/mL.

Streptococcus pneumoniae (PEN R)--4 N.A. centers: 152 isolates: MIC₅₀ 0.25 µg/mL:

MIC₉₀ 0.5 µg/mL: Range: µg/mL.

Streptococcus pneumoniae (ERY S)--1 N.A. center: 31 isolates: MIC₅₀ 0.125 µg/mL:

MIC₉₀ 0.125 µg/mL: Range µg/mL.

Streptococcus pneumoniae (ERY R)--1 N.A. center: 50 isolates: MIC₅₀ 0.5 µg/mL

MIC₉₀ 1 µg/mL: Range µg/mL.

A large number of studies were performed in a number of centers. All MIC₉₀ values were below or equal to 1.0 µg/mL. Penicillin susceptibility had little if any effect on sparfloxacin susceptibility. Erythromycin resistance may have some effect on sparfloxacin susceptibility, but only one study was performed with only a few isolates. *Streptococcus pneumoniae* (including PEN I and PEN R strains) will be allowed in the *in vitro* list of organisms in the label.

Streptococcus pyogenes--8 N.A. centers: 334 isolates: MIC₉₀ 0.5-2 µg/mL.

7 Foreign studies: 228 isolates: MIC₉₀ 0.5-2 µg/mL.

In 6 selected N.A. centers: 753 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 1 µg/mL:

Range µg/mL.

Only 3 of 15 studies (2 foreign) had MIC₉₀ values of 2 µg/mL. Nine studies had MIC₉₀ of 0.5 µg/mL or less. One of the foreign studies used Iso Sensitest Agar instead of Mueller-Hinton agar and the other foreign study used an inoculum of 10³ instead of 10⁴ CFU/spot. Since only a few studies had MIC₉₀s above 1 µg/mL and many were below 1 µg/mL and most of these studies were foreign, *Streptococcus pyogenes* will be allowed into the label.

Streptococcus viridans Group--3 N.A. centers: 46 isolates: MIC₉₀ 0.5-1 µg/mL.

2 Foreign studies: 64 isolates: MIC₉₀ 0.5-1 µg/mL.

In 1 selected N.A. center: 30 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 1 µg/mL:

Range: µg/mL.

There were over 100 isolates tested in 5 studies. All MIC₉₀s were ≤ 1 µg/mL.

Streptococcus viridans group will be allowed into the label.

**ACTIVITY AGAINST GRAM-NEGATIVE AEROBES
(TABLES 10 & 11)**

Acinetobacter anitratus--5 N.A. centers: 99 isolates: MIC₉₀ 0.06-0.25 µg/mL.
5 Foreign studies: 127 isolates: MIC₉₀ 0.03-0.5 µg/mL.
In 2 selected N.A. centers: 20 strains: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.125 µg/mL.
Over 100 isolates were tested at a number of different centers. All the MIC₉₀s were below 1 µg/mL. According to the ASM Manual of Clinical Microbiology *Acinetobacter* species may cause respiratory tract infections. *Acinetobacter anitratus* will be allowed into the label.

Acinetobacter lwoffii--2 N.A. centers: 28 isolates: MIC₉₀ ≤ 0.03-0.06 µg/mL.
1 Foreign study: 23 isolates: MIC₉₀ 0.016 µg/mL.
There were only 3 studies performed and a total of 51 isolates tested, but the MIC₉₀ values were very low and the highest MIC value found in these studies was 0.12 µg/mL. Since over 50 isolates were tested at 3 different centers and the MICs were all far below the 1 µg/mL breakpoint, *Acinetobacter lwoffii* will be allowed in the label.

Aeromonas hydrophila--4 N.A. centers: 70 isolates: MIC₉₀ 0.06-0.25 µg/mL.
2 Foreign studies: 39 isolates: MIC₉₀ ≤ 0.06 µg/mL.
In 3 selected N.A. centers: 14 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.
This species is not often associated with respiratory tract infections and will not be allowed in the label.

CDC group EF-4--1 N.A. center: 13 isolates: MIC₉₀ ≤ 0.03 µg/mL.
This group is not a pathogen in respiratory tract infections. Only one center with 13 isolates were tested. This is not enough isolates or centers to allow this group into the label even if it was a pathogen.

Citrobacter amalonaticus--2 N.A. centers: 21 isolates: MIC₉₀ 0.06-0.25 µg/mL.
Not enough testing was performed to allow this species into the label. It is also not a pathogen in respiratory tract infections.

Citrobacter diversus--4 N.A. centers: 122 isolates: MIC₉₀ 0.06-0.5 µg/mL.
3 Foreign studies: 32 isolates: MIC₉₀ 0.06-0.25 µg/mL.
In 3 selected N.A. centers: 25 isolates: MIC₅₀ ≤ 0.015 µg/mL: MIC₉₀ ≤ 0.03 µg/mL.
Range: µg/mL.
Over 100 isolates were tested in a number of different centers. All MIC₉₀s were below 1 µg/mL. This species may cause pneumonia according to "A Clinician's Dictionary of Bacteria and Fungi". *Citrobacter diversus* will be allowed into the label.

Citrobacter freundii—5 N.A. centers: 164 isolates: MIC₉₀ 0.5-2 µg/mL.
6 Foreign studies: 236 isolates: MIC₉₀ 0.125-4 µg/mL.
In 4 selected N.A. centers: 65 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 1 µg/mL.
Range: µg/mL.

One United States and two Foreign studies had MIC₉₀s of 2 µg/mL. One foreign study had an MIC₉₀ of 4 µg/mL. The study with the MIC₉₀ of 4 µg/mL used NCCLS criteria for testing. The two foreign studies with MIC₉₀ of 2 µg/mL used Iso Sensitest Agar and Sensitivity Disk Agar-N. These differences may have contributed to the slightly higher values. Many studies had MIC₉₀ values at or close to 1 µg/mL and several studies had MIC₉₀s above the 1 µg/mL breakpoint. Since this organism often has MIC values above the susceptibility breakpoint it will not be allowed into the label.

Eikenella corrodens—2 N.A. centers: 22 isolates: MIC₉₀ 0.06 µg/mL.
Not enough testing was performed to allow this organism into the label.

Enterobacter aerogenes—4 N.A. centers: 173 isolates: MIC₉₀ 0.06-0.25 µg/mL.
5 Foreign studies: 73 isolates: MIC₉₀ 0.125-4 µg/mL.
In 4 selected N.A. studies: 53 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.125 µg/mL.
Range: µg/mL.

All MIC₉₀s were well below 1 µg/mL, except for one foreign study with an MIC₉₀ of 4 µg/mL. This was a German study, but NCCLS criteria were used. This study tested 29 isolates. All other MIC₉₀s were ≤ 0.5 µg/mL (one study with 0.5 µg/mL, rest 0.25 µg/mL or less). This species may cause pneumonia. Since only one study had a high MIC₉₀ value and all other studies had MIC₉₀s well below 1 µg/mL, this species will be allowed in the label.

Enterobacter agglomerans—4 N.A. centers: 74 isolates: MIC₉₀ 0.03-0.125 µg/mL.
1 Foreign study: 12 isolates: MIC₉₀ 0.06 µg/mL.
In 3 selected N.A. centers: 24 isolates: MIC₅₀ 0.03 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

This species is not an usual pathogen in respiratory tract infections. It will not be in the label.

Enterobacter cloacae—5 N.A. centers: 322 isolates: MIC₉₀ 0.125-0.5 µg/mL.
8 Foreign studies: 365 isolates: MIC₉₀ 0.03-12.5 µg/mL.
In 4 selected N.A. studies: 65 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.125 µg/mL.
Range: µg/mL.

The MIC₉₀ values were all 0.5 µg/mL or less except for one Japanese study which had an MIC₉₀ of 12.5 µg/mL. This study used Mueller-Hinton agar, but an inoculum of 10³ instead of 10⁴ CFU/spot. According to "A Clinician's Dictionary of Bacteria and Fungi" this species may cause pneumonia. *Enterobacter cloacae* may be placed in the label.

Enterobacter sakazakii—1 N.A. study: 19 isolates: MIC₉₀ 0.06 µg/mL.
1 Foreign study: 18 isolates: MIC₉₀ 0.03 µg/mL.
Not enough testing has been performed to allow this species into the label.

Escherichia coli—8 N.A. centers: 1457 isolates: MIC₉₀ 0.016-0.06 µg/mL.
9 Foreign studies: 884 isolates: MIC₉₀ 0.016-0.125 µg/mL.
In 5 selected N.A. centers: 132 isolates: MIC₅₀ 0.016 µg/mL: MIC₉₀ 0.06 µg/mL.
Range: µg/mL.

A very large number of isolates were tested at a number of centers. All the MIC₉₀s were well below 1 µg/mL. According to "A Clinician's Dictionary of Bacteria and Fungi" this organism may cause pneumonia. *Escherichia coli* will be allowed into the label.

Haemophilus influenzae—3 N.A. centers: 64 isolates: MIC₉₀ ≤0.008-≤0.03 µg/mL.
5 Foreign studies: 348 isolates: MIC₉₀ ≤0.004-0.016 µg/mL
3 selected N.A. centers: 785 isolates: MIC₅₀ <0.03 µg/mL: MIC₉₀ <0.03 µg/mL.
Range: µg/mL.

Haemophilus influenzae(β-lac +)—5 N.A. centers: 370 isolates: MIC₉₀ ≤0.008-≤0.06
5 Foreign studies: 113 isolates: MIC₉₀ ≤0.008-≤0.06
In 1 selected N.A. center: 223 isolates: MIC₅₀ <0.03 µg/mL: MIC₉₀ <0.03 µg/mL.
Range: µg/mL.

Haemophilus influenzae (β-lac -)—4 N.A. centers: 630 isolates: MIC₉₀ ≤0.004-≤0.03
4 Foreign studies: 86 isolates: MIC₉₀ 0.016-≤0.06
In 1 selected N.A. center: 485 isolates: MIC₅₀ <0.03 µg/mL: MIC₉₀ <0.03 µg/mL.
Range: µg/mL.

A large number of isolates were tested. The MIC₉₀s were approximately equal for both the β-lactamase positive and β-lactamase negative strains. All MIC₉₀s were well below 1 µg/mL. *Haemophilus influenzae* will be allowed in the label.

Haemophilus parainfluenzae—2 N.A. centers: 60 isolates: MIC₉₀ 0.06-≤0.125 µg/mL
No Foreign studies.
In 1 selected N.A. center: 50 isolates: MIC₅₀ ≤0.125 µg/mL: MIC₉₀ ≤0.125 µg/mL.
Range: µg/mL.

Although only 60 isolates were tested in two studies, the MIC₉₀s are very low. *Haemophilus parainfluenzae* will be allowed in the package insert.

Hafnia alvei—2 N.A. centers: 32 isolates: MIC₉₀ 0.25 µg/mL.
1 Foreign study: 21 isolates: MIC₉₀ 0.06 µg/mL.
Only a few isolates were tested in 3 studies. This organism is not a usual pathogen in respiratory tract infections. It will not be allowed into the label.

Helicobacter pylori—1 N.A. center: 25 isolates: MIC₉₀ 0.5 µg/mL.
1 Foreign study: 25 isolates: MIC₉₀ 0.5 µg/mL.
In 1 selected N.A. study: 25 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 0.5 µg/mL.
Range: µg/mL.

This organism is not a pathogen in respiratory tract infections. It will not be allowed into the label.

Klebsiella oxytoca—4 N.A. centers: 169 isolates: MIC₉₀ ≤0.03-0.125 μg/mL.
8 Foreign studies: 371 isolates: MIC₉₀ 0.06-0.25 μg/mL.
In 2 selected N.A. centers: 12 isolates: MIC₅₀ 0.03 μg/mL: MIC₉₀ 0.06 μg/mL.
Range: μg/mL.

Over 100 isolates were tested at a number of studies. The MIC₉₀s were all below 1 μg/mL. According to "A Clinician's Dictionary of Bacteria and Fungi" this species causes disease similar to that due to *K. pneumoniae*. The ASM Manual of Clinical Microbiology states that *Enterobacteriaceae* species may be involved in disease production in respiratory tract specimens. *Klebsiella oxytoca* will be allowed into the label.

Klebsiella pneumoniae—6 N.A. centers: 424 isolates: MIC₉₀ 0.125-0.5 μg/mL.
10 Foreign studies: 514 isolates: MIC₉₀ 0.1-1 μg/mL.
In 5 selected N.A. centers: 90 isolates: MIC₅₀ 0.06 μg/mL: MIC₉₀ 0.5 μg/mL.
Range: μg/mL.

Over 100 isolates were tested at many different sites. All MIC₉₀s were 1 μg/mL or less. Although a few isolates had high MIC values these are rare and the MIC₉₀s are still low. *Klebsiella pneumoniae* will be allowed into the label.

Legionella pneumophila—2 N.A. centers: 131 isolates: MIC₉₀ 0.19-1 μg/mL.
1 Foreign study: 15 isolates: MIC₉₀ ≤0.06 μg/mL.
Over 100 isolates were tested in a total of three studies. All MIC₉₀s were ≤1 μg/mL. This species will be allowed in the label.

Moraxella catarrhalis—3 N.A. centers: 99 isolates: MIC₉₀ 0.016-≤0.03 μg/mL.
10 Foreign studies: 486 isolates: MIC₉₀ ≤0.008-0.06 μg/mL.
In 4 selected N.A. centers: 702 isolates: MIC₅₀ <0.03 μg/mL: MIC₉₀ <0.03 μg/mL.
Range: μg/mL.

Moraxella catarrhalis (β-lac +)—2 N.A. centers: 698 isolates: MIC₉₀ ≤0.03-0.125 μg/mL.
In 1 selected N.A. center: 550 isolates: MIC₅₀ <0.03 μg/mL: MIC₉₀ <0.03 μg/mL.
Range: μg/mL.

Moraxella catarrhalis (β-lac -)—2 N.A. centers: 98 isolates: MIC₉₀ ≤0.03-0.125 μg/mL.
In 1 selected N.A. center: 57 isolates: MIC₅₀ <0.03 μg/mL: MIC₉₀ <0.03 μg/mL.
Range: μg/mL.

Well over 100 isolates were tested at many different centers. Beta-lactamase production had only a slight if any effect on activity. All MIC₉₀s were well below the 1 μg/mL breakpoint. *Moraxella catarrhalis* will be allowed into the label.

Morganella morganii—4 N.A. centers: 183 isolates: MIC₉₀ 0.25-1 µg/mL
9 Foreign studies: 385 isolates: MIC₉₀ 0.25-1.56 µg/mL.
In 3 selected N.A. centers: 24 isolates: MIC₅₀ 0.125 µg/mL: MIC₉₀ 0.25 µg/mL.
Range: µg/mL.

Well over 100 isolates were tested at a number of sites. Only one Japanese study that used Mueller-Hinton agar but an inoculum of 10³ instead of the usual 10⁴ CFU/spot had an MIC₉₀ value greater than 1 µg/mL. Most studies had MIC₉₀s of µg/mL. Two studies had MIC₉₀s of 1.0 µg/mL. Since this species is a member of the *Enterobacteriaceae* which may cause disease in respiratory tract infections and the MIC₉₀ value in almost all studies was ≤ 1 µg/mL, *Morganella morganii* will be allowed in the label.

Neisseria gonorrhoeae—2 N.A. centers: 43 isolates: MIC₉₀ 0.016-≤0.03 µg/mL.
5 Foreign studies: 151 isolates: MIC₉₀ 0.004-0.1 µg/mL.
In 1 selected N.A. center: 12 isolates: MIC₅₀ ≤0.03 µg/mL: MIC₉₀ ≤0.03 µg/mL.
Range: µg/mL.

Neisseria gonorrhoeae (β-lac +)—2 N.A. centers: 97 isolates: MIC₉₀ 0.004-≤0.03 µg/mL
2 Foreign studies: 33 isolates: MIC₉₀ 0.008-≤0.06 µg/mL.

Neisseria gonorrhoeae (β-lac -)—1 N.A. center: 257 isolates: MIC₉₀ ≤0.03 µg/mL.
2 Foreign studies: 51 isolates: MIC₉₀ 0.008-≤0.06 µg/mL

There were well over 100 isolates tested at many different sites. All MIC₉₀s were very low. Beta-lactamase production did not effect activity of sparfloxacin. According to the ASM Manual of Clinical Microbiology this species is rarely encountered in clinical respiratory tract infections. *Neisseria gonorrhoeae* will not allowed in the label.

Neisseria meningitidis—2 N.A. centers: 110 isolates: MIC₉₀ 0.03-≤0.125 µg/mL.
4 Foreign studies: 47 isolates: MIC₉₀ ≤0.004-≤0.06 µg/mL.
In 2 selected N.A. centers: 110 isolates: MIC₅₀ ≤0.125 µg/mL: MIC₉₀ ≤0.125 µg/mL.
Range: µg/mL.

Over 100 isolates were tested. Most (100 isolates) in the N.A. studies were tested in only one study. The MIC₉₀s are all well below the 1 µg/mL breakpoint. Since this product is not being approved for meningitis this organism will not be allowed in the label.

Pasteurella multocida—2 N.A. centers: 24 isolates: MIC₉₀ ≤0.03 µg/mL.
No Foreign studies.

In 1 selected N.A. center: 9 isolates: MIC₅₀ 0.015 µg/mL: Range µg/mL.
No enough testing was performed to allow this species into the label.

Proteus mirabilis—6 N.A. centers: 282 isolates: MIC₉₀ 0.25-1 µg/mL.
10 Foreign studies: 473 isolates: MIC₉₀ 0.25-0.5 µg/mL.
In 5 selected N.A. centers: 62 isolates: MIC₅₀ 0.25 µg/mL: MIC₉₀ 0.5 µg/mL.
Range: µg/mL.

Many more than 100 isolates were tested at a number of centers. All MIC₉₀s were ≤1 µg/mL. A few isolates had high MIC values but not enough to raise the MIC₉₀ value above the susceptible breakpoint. This organism is isolated from sputum and may cause disease when present. It will be allowed in the label.

Proteus vulgaris—4 N.A. centers: 121 isolates: MIC₉₀ 0.5-1 µg/mL.
9 Foreign studies: 241 isolates: MIC₉₀ 0.39-1 µg/mL.
In 4 selected N.A. centers: 32 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 0.5 µg/mL.
Range: µg/mL.

A large number of isolates were tested at a number of sites. All MIC₉₀s were ≤1 µg/mL. This species will be allowed in the label, since it may cause disease and is sometimes isolated from respiratory tract specimens.

Providencia rettgeri—3 N.A. centers: 76 isolates: MIC₉₀ 0.5->4 µg/mL.
6 Foreign studies: 120 isolates: MIC₉₀ 0.25->100 µg/mL.
In 3 selected N.A. centers: 21 isolates: MIC₅₀ 0.25 µg/mL: MIC₉₀ 1 µg/mL.
Range: µg/mL.

One United States study performed using NCCLS criteria had an MIC₉₀ value of >4 µg/mL. This study tested 40 isolates and the MIC₅₀ value was 0.5 µg/mL. One Japanese study using Mueller-Hinton agar and an inoculum of 10⁵ CFU/spot had a very high MIC₉₀ value of >100 µg/mL. This study tested 25 isolates and the MIC₅₀ value was 6.25 µg/mL. Some isolates of *Providencia rettgeri* appear to be resistant to sparfloxacin. There are enough of these isolates that they often appear and cause a high MIC₉₀ value. This species will not be in the label. The sponsor has not included this species in their proposed label.

Providencia stuartii—2 N.A. centers: 69 isolates: MIC₉₀ 1->4 µg/mL.
5 Foreign studies: 148 isolates: MIC₉₀ 0.2-6.25 µg/mL.
In 3 selected N.A. centers: 23 isolates: MIC₅₀ 0.25 µg/mL: MIC₉₀ 1 µg/mL.
Range: µg/mL.

Once again there appear to be a number of resistant strains. Enough of these strains are present in nature and can cause the MIC₉₀ value in many studies to be high. This species will not be in the label. The sponsor has not included this species in their proposed label.

Pseudomonas aeruginosa—12 N.A. centers: 755 isolates: MIC₉₀ 1-8 µg/mL.
8 Foreign studies: 710 isolates: MIC₉₀ 1-128 µg/mL.
In 6 selected N.A. centers: 315 isolates: MIC₅₀ 1 µg/mL: MIC₉₀ 4 µg/mL.
Range: µg/mL.

Pseudomonas aeruginosa (QR)—1 N.A. center: 24 isolates: MIC₉₀ >8 µg/mL.
Many studies had MIC₅₀s greater than 1 µg/mL. No study had an MIC₉₀ below
1 µg/mL. *Pseudomonas aeruginosa* will not be in the label. The sponsor has not
included this species in the label.

Pseudomonas cepacia—2 N.A. centers: 20 isolates: MIC₉₀ 1-16 µg/mL.
5 Foreign studies: 100 isolates: MIC₉₀ 2->16 µg/mL.
In 6 selected N.A. centers: 46 isolates: MIC₅₀ 1 µg/mL: MIC₉₀ 8 µg/mL.
Range: µg/mL.

Many isolates had high MIC values. Many studies had MIC₉₀s >1 µg/mL.
This species will not be in the label. The sponsor has not placed this species
in the proposed label.

Pseudomonas fluorescens—2 N.A. centers: 32 isolates: MIC₉₀ 2 µg/mL.
1 Foreign study: 20 isolates: MIC₉₀ 2 µg/mL.
In 3 selected N.A. centers: 21 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 2 µg/mL.
Range: µg/mL.

Only a limited number of isolates were tested in 5 centers. The MIC₉₀ value
was 2 µg/mL in all studies. This species is not in the sponsor's proposed
label and it will not be allowed in the label.

Pseudomonas putida—1 N.A. center: 20 isolates: MIC₉₀ 1 µg/mL.
1 Foreign study: 18 isolates: MIC₉₀ 2 µg/mL.

Only a very few isolates were tested in 2 studies. The MIC₉₀ values were at
or greater than 1 µg/mL. This species will not be allowed in the label. The
sponsor has included this species in the proposed label, but not enough
testing was performed and the MIC₉₀s are at or over the proposed breakpoint
for sparfloxacin.

Salmonella species—4 N.A. centers: 274 isolates: MIC₉₀ 0.06-1 µg/mL.
7 Foreign studies: 339 isolates: MIC₉₀ 0.03-0.125 µg/mL.
In 1 selected N.A. center: 13 isolates: MIC₅₀ 0.06 µg/mL: MIC₉₀ 0.06 µg/mL.
Range: µg/mL.

Well over 100 isolates were tested in a large number of studies. Only 1 study
had an MIC₉₀ of 1 µg/mL. All other studies had MIC₉₀s ≤0.12 µg/mL. This
genus is not a respiratory tract pathogen and will, therefore, not be allowed in
the label.

Serratia liquefaciens--2 N.A. centers: 20 isolates: MIC₉₀ 0.125-4 µg/mL.
4 Foreign studies: 50 isolates: MIC₉₀ 0.125-2 µg/mL.
Only a few strains were tested and the MIC₉₀s were often greater than 1 µg/mL. This species will not be in the label. It is not in the sponsor's proposed label.

Serratia marcescens--8 N.A. centers: 233 isolates: MIC₉₀ 0.5-4 µg/mL.
7 Foreign studies: 318 isolates: MIC₉₀ 0.5-25 µg/mL.
In 5 selected N.A. centers: 92 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 8 µg/mL.
Range: µg/mL.

A large number of isolates were tested in a large number of studies. Many studies had MIC₉₀s greater than 1 µg/mL. This species is not in the proposed label and will not be allowed in the label.

Shigella species--2 N.A. centers: 27 isolates: MIC₉₀ 0.016-0.06 µg/mL.
6 Foreign studies: 340 isolates: MIC₉₀ 0.016-0.125 µg/mL.
A large number of isolates were tested in a number of studies. All MIC₉₀s were below 1 µg/mL. This genus is not a respiratory tract pathogen and will, therefore, not be allowed in the label.

Xanthomonas maltophilia--9 N.A. centers: 301 isolates: MIC₉₀ 0.5-4 µg/mL.
8 Foreign studies: 214 isolates: MIC₉₀ 0.5-4 µg/mL.
In 5 selected N.A. centers: 52 isolates: MIC₅₀ 0.5 µg/mL: MIC₉₀ 2 µg/mL.
Range: µg/mL.
Many studies had MIC₉₀s greater than 1 µg/mL. This species is not in the proposed label and will not be allowed into the label.

Yersinia enterocolitica--2 N.A. centers: 51 isolates: MIC₉₀ 0.06 µg/mL.
4 Foreign studies: 74 isolates: MIC₉₀ 0.03-0.25 µg/mL.
In 3 selected N.A. centers: 21 isolates: MIC₅₀ 0.016 µg/mL: MIC₉₀ 0.06 µg/mL.
Range: µg/mL.
Over 100 isolates were tested in 6 centers. All MIC₉₀s were below 1 µg/mL. This organism is not, however, a pathogen in respiratory tract infections and will, therefore, not be in the label.

ACTIVITY AGAINST ANEROBES (TABLE 12)

Bacteroides distasonis--1 N.A. center: 24 isolates: MIC₉₀ 2 µg/mL.
No Foreign studies.

Only 24 isolates were tested in one study. The MIC₉₀ was greater than 1 µg/mL. This species is not in the proposed label and will not be in the final label.

Bacteroides fragilis--5 N.A. centers: 313 isolates: MIC₉₀ 1-4 µg/mL.
6 Foreign studies: 143 isolates: MIC₉₀ 1-16 µg/mL

Well over 100 isolates were tested. Many MIC₉₀s were greater than 1 µg/mL. This species will not be in the label. The sponsor has not included this species in their label.

Bacteroides ovatus--2 N.A. center: 43 isolates: MIC₉₀ 2-4 µg/mL.
No foreign studies.

Only two studies with 43 isolates. MIC₉₀s greater than 1 µg/mL. Species will not be in the label.

Bacteroides thetaiotaomicron--2 N.A. center: 61 isolates: MIC₉₀ 4 µg/mL.
1 Foreign study: 20 isolates: MIC₉₀ 16 µg/mL.
MIC₉₀s are greater than 1 µg/mL. Species is not in sponsor's label and will not be in the label.

Bacteroides uniformis--1 N.A. center: 13 isolates: MIC₉₀ 8 µg/mL.
No Foreign studies.

Only 13 isolates in one study. MIC₉₀ above 1 µg/mL. Not in sponsor's label. Will not be in label.

Bacteroides vulgatus--2 N.A. centers: 37 isolates: MIC₉₀ 4-16 µg/mL.
No Foreign studies.

Only 37 isolates in two studies. MIC₉₀ above 1 µg/mL. Not in sponsor's label. Will not be in label.

Clostridium species--5 N.A. centers: 49 isolates: MIC₉₀ 2-4 µg/mL.
1 Foreign study: 11 isolates: MIC₉₀ 4 µg/mL.

Only a few isolates tested. All MIC₉₀s greater than 1 µg/mL. Not in label.

Clostridium perfringens--2 N.A. centers: 21 isolates: MIC₉₀ 0.5-2 µg/mL.
2 Foreign studies: 26 isolates: MIC₉₀ 0.78-2 µg/mL

Only a total of 47 isolates were tested in a total of 4 studies. Two of the four studies had MIC₉₀s of 2 µg/mL. The sponsor has included this species in their proposed label. Since many MIC₉₀s are greater than the 1 µg/mL breakpoint this species will not be in the label. According to the ASM Manual of Clinical Microbiology *Clostridium* species may cause disease when present in respiratory tract infections.

Eubacterium species--1 N.A. center: 18 isolates: MIC₉₀ 0.5 µg/mL.
No Foreign studies.

Only 18 isolates have been tested in one study. These are not enough data to allow this genus into the label.

Fusobacterium species--2 N.A. centers: 33 isolates: MIC₉₀ 2->32 µg/mL.
No Foreign studies.

Only 33 isolates tested in 2 studies. MIC₉₀s are greater than 1 µg/mL. Genus will not be in the label.

Pepto.streptococcus species--5 N.A. centers: 74 isolates: MIC₉₀ 0.5-2µg/mL.
4 Foreign studies: 62 isolates: MIC₉₀ 0.78-4 µg/mL

Three of the nine studies had MIC₉₀s greater than 1 µg/mL. Three other studies had MIC₉₀s of 1 µg/mL. Since many studies had MIC₉₀s at or above the breakpoint for sparfloxacin susceptibility, this genus will not be allowed in label.

Porphyromonas asaccharolytica--1 N.A. center: 10 isolates: MIC₉₀ 2 µg/mL.
No Foreign studies.

Not enough data collected. MIC₉₀ greater than 1 µg/mL. Not in label.

Prevotella bivia--1 N.A. center: 23 isolates: MIC₉₀ 16 µg/mL.
No Foreign studies.

Not enough data collected. MIC₉₀ greater than 1 µg/mL. Not in label.

Prevotella disiens--1 N.A. center: 10 isolates: MIC₉₀ 2 µg/mL.
No Foreign studies.

Not enough data collected. MIC₉₀ greater than 1 µg/mL. Not in label.

Veillonella parvula--1 N.A. center: 10 isolates: MIC₉₀ 0.25 µg/mL.
No Foreign studies.

Not enough data collected to allow this species into the label. The sponsor has included this organism in their proposed label, but not enough data has been collected to include it. According to the ASM Manual of Clinical Microbiology this species is also rarely involved in disease production in respiratory tract infections.

**ACTIVITY AGAINST INTRACELLULAR PATHOGENS
TABLE 13**

Chlamydia pneumoniae--2 N.A. centers: 18 isolates: MIC₉₀ 0.25 µg/mL.
1 Foreign study: 1 isolate: MIC 0.5 µg/mL.

Although it is difficult to perform susceptibility testing on this organism, there is still not enough testing and different studies to allow this organism into the label on *in vitro* only data. Twelve of the 18 isolates in the 2 North American studies are from one study. This species may be allowed into the label if the Medical Officer indicates that it was cured clinically. Serology was used to determine clinical response.

Mycobacterium avium-intracellulare--5 N.A. centers: 134 isolates: MIC₉₀ 0.5-4 µg/mL
1 Foreign study: 13 isolates: MIC₉₀ 4 µg/mL

Over 100 isolates were studied in a total of 6 studies. MIC₉₀s were often greater than 1 µg/mL. This species will not be allowed in the label. The sponsor has not included this species in their proposed label.

Mycoplasma pneumoniae--2 N.A. centers: 69 isolates: MIC₉₀ 0.125-0.5 µg/mL
1 Foreign study: 21 isolates: MIC₉₀ 0.1 µg/mL

Ninety isolates were tested in a total of 3 studies. All MIC₉₀ were below 1 µg/mL. This species will be allowed in the label.

Mycobacterium tuberculosis--No N.A. centers.

2 Foreign studies: 42 isolates: MIC₉₀ 0.2-0.5 µg/mL

No data from United States isolates are given. Only 2 studies with a total of 42 isolates are presented. The MIC₉₀ in one study is 0.5 µg/mL, which is only one dilution from the breakpoint. This organism will not be allowed in the label.

SUMMARY OF IN VITRO ACTIVITY

The following organisms which the sponsor has placed in the label must be deleted:

Gram-positive aerobes:

Bacillus cereus--not enough testing was performed. Species is also not a respiratory pathogen.

Bacillus species--not enough testing was performed. Genus is not a respiratory pathogen.

Corynebacterium jeikeium--Not a respiratory tract pathogen.

Staphylococcus saprophyticus--Not a respiratory tract pathogen. Species is associated with urinary tract infections.

Staphylococcus simulans--Not enough testing was performed.

Streptococcus group G--Not enough testing performed. MIC₉₀ often at 1 µg/mL.

Gram-negative aerobes:

- Aeromonas hydrophilia*--Not a respiratory tract pathogen.
CDC group EF-4--Not enough testing performed. Not a respiratory tract pathogen.
Citrobacter amalonaticus--Not enough testing performed. Not a respiratory tract pathogen. Usually associated with urinary tract infections.
Citrobacter freundii--Several studies had MIC₉₀s > 1 µg/mL.
Eikenella corrodens--Not enough testing performed.
Enterobacter agglomerans--Not a respiratory tract pathogen.
Enterobacter sakazakii--Not enough testing performed.
Hafnia alvei--Not enough testing performed. Not an usual respiratory pathogen.
Helicobacter pylori--Not a respiratory pathogen. Drug not approved for ulcers.
Neisseria gonorrhoeae--Not an usual respiratory pathogen.
Neisseria meningitidis--Drug not approved for meningitis.
Pasteurella multocida--Not enough testing performed.
Pseudomonas putida--Not enough testing performed. High MICs.
Salmonella species--Not a respiratory pathogen.
Shigella species--Not a respiratory pathogen.
Yersinia enterocolitica--Not a respiratory pathogen.

Anaerobic microorganisms:

- Clostridium perfringens*--High MIC₉₀s
Eubacterium species--Not enough testing performed.
Peptostreptococcus species--Many MIC₉₀s 2 µg/ml. or above.
Veillonella parvula--Not enough testing performed. Not a respiratory pathogen.

Other microorganisms:

- Chlamydia pneumoniae*--Not enough testing performed. May be allowed into the label if clinically cured.
Mycobacterium tuberculosis--No North American studies. Only 2 studies with 42 isolates.

The list of organisms should, therefore, read as follows:

Organisms with both clinical efficacy (if this is shown) and *in vitro* activity:

Gram-positive microorganisms:

Staphylococcus aureus

Streptococcus pneumoniae (statement about strains with decreased susceptibility or resistance to penicillin may only be placed in this section if these strains were eradicated in the clinical trials submitted, otherwise this statement may be placed in the *in vitro* activity only list)

Streptococcus pyogenes

Gram-negative microorganisms:

Enterobacter cloacae

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Moraxella catarrhalis

Other microorganism:

Chlamydia pneumoniae (if clinically cured)

Mycoplasma pneumoniae

In vitro activity list with MIC₉₀ values of $\leq 1 \mu\text{g/mL}$:

Aerobic gram-positive microorganisms:

Staphylococcus epidermidis

Staphylococcus haemolyticus

Staphylococcus hominis

Streptococcus agalactiae

Viridans group streptococci

Aerobic gram-negative microorganisms:

Acinetobacter anitratus

Acinetobacter lwoffii

Citrobacter diversus

Enterobacter aerogenes

Escherichia coli

Klebsiella oxytoca

Legionella pneumophila

Morganella morganii

Proteus mirabilis

Proteus vulgaris

EFFECT OF MISCELLANEOUS FACTORS ON ACTIVITY

Effect of Medium

The effect of medium of MICs of sparfloxacin for gram-positive and gram-negative bacteria was studied. MICs and MBCs for two isolates each of *S. pneumoniae*, *S. aureus*, *Escherichia coli*, *Enterobacter cloacae* and *P. aeruginosa* determined in cation-supplemented Mueller-Hinton broth, Iso-Sensitest broth, brain heart infusion broth and Todd-Hewitt broth (all at pH 7.2 to 7.4) were identical or only 2-fold different (9). MICs of sparfloxacin determined by broth microdilution and agar dilution for 30 isolates each of staphylococci and gram-negative bacilli (in Mueller-Hinton agar and broth) and 53 isolates of anaerobic bacteria (in Wilkens-Chalgren agar and broth) were identical or only 2-fold different (10).

Effect of Inoculum

The effect of inoculum size on MICs and MBCs of sparfloxacin was evaluated. MICs of sparfloxacin and ciprofloxacin for two isolates each of methicillin-susceptible and -resistant *S. aureus* were unchanged (≤ 2 -fold) as inoculum was increased from 5×10^3 to 5×10^5 CFU/mL. MICs of sparfloxacin and ciprofloxacin for one isolate of each phenotype increased from $\mu\text{g/mL}$ and $\mu\text{g/mL}$, respectively, as inoculum was increased from 5×10^5 to 5×10^7 CFU/mL (11). Mean MICs of sparfloxacin for five isolates each of *S. aureus* and *E. faecalis* were unchanged as inoculum was increased from 10^3 to 10^5 CFU/mL and increased from $\mu\text{g/mL}$ and $\mu\text{g/mL}$, respectively, as inoculum was increased from 10^5 to 10^7 CFU/mL (12) (see TABLE 15).

Mean MICs and MBCs of sparfloxacin for five isolates each of *E. coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae were generally increased 2-fold or less as inoculum was increased from CFU/mL and from CFU/mL , while MICs and MBCs for *P. aeruginosa* were increased 4-fold as inoculum was increased from CFU/mL (12) (see TABLE 15). MICs and MBCs of sparfloxacin for one isolate each of *Moraxella catarrhalis* and *Bacteroides fragilis* were unchanged (≤ 2 -fold) while MICs for one isolate each of *Haemophilus influenzae*, *E. cloacae* and *K. pneumoniae* were increased 2-fold to 4-fold as inoculum was increased from CFU/mL (13). MICs of sparfloxacin for 26 isolates of gram-negative bacteria were generally (≤ 2 -fold) unchanged as inoculum was increased from CFU and were unchanged or increased 2-fold to 4-fold as inoculum was increased from CFU (14,15).

TABLE 15
 Effect of inoculum size on MICs and MBCs of sparfloxacin --

Geometric mean MIC/MBC ($\mu\text{g/mL}$) in Mueller-Hinton broth with the following inocula

(CFU/mL)

Organism	10^7	10^5	10^3
<i>S. aureus</i>	0.1/0.57	0.04/0.06	0.03/0.04
<i>E. faecalis</i>	1.5/1.7	0.21/0.43	0.18/0.25
<i>E. coli</i>	0.015/0.02	0.007/0.009	0.004/0.007
<i>Enterobacter</i> spp.	0.09/0.14	0.07/0.12	0.015/0.02
<i>Klebsiella</i> spp.	0.14/0.18	0.08/0.12	0.019/0.26
<i>M. morgani</i>	0.43/1.5	0.21/0.33	0.14/0.24
<i>P. vulgaris</i>	0.56/2	0.76/1.3	0.5/0.66
<i>P. mirabilis</i>	0.16/0.37	0.18/0.28	0.12/0.16
<i>Salmonella</i> spp.	0.03/0.08	0.009/0.014	0.004/0.007
<i>Shigella</i> spp.	0.01/0.02	0.003/0.004	0.0007/0.001
<i>P. aeruginosa</i>	1.3/2.3	0.32/1.15	0.24/0.87

Effect of pH

The effect of pH on MICs and MBCs of sparfloxacin was evaluated. MICs and MBCs of sparfloxacin for 2 isolates of *S. pneumoniae* (MIC, 0.5 $\mu\text{g/mL}$; MBC, 1 $\mu\text{g/mL}$) in Mueller-Hinton broth were generally unchanged at pH 6.0 and 8.0 compared to pH 7.0 and were increased 2-fold at pH 5.0 (9). However, other organisms showed a marked effect at pH 5.

Mean MICs and MBCs of sparfloxacin for 2 isolates each of *S. aureus* and *E. faecalis* in Mueller-Hinton broth were unchanged at pH 6.0 and 8.0 compared to pH 7.0 but were 4-fold to 8-fold higher at pH 5.0 (12) (see TABLE 16). In another study with 5 isolates each of *E. coli*, *E. cloacae*, *Providencia stuartii*, *S. marcescens*, *P. aeruginosa*, and *Xanthomonas maltophilia*, MICs of sparfloxacin in Mueller-Hinton agar were increased 2-fold to 4-fold as the pH was decreased from _____ and increased 2-fold to 8-fold as the pH was decreased to _____

TABLE 16
 Effect of pH on MICs and MBCs of sparfloxacin
 Geometric mean MIC/MBC ($\mu\text{g/mL}$) in
 Mueller-Hinton broth at pH

Organism	5	6	7	8
<i>S. aureus</i>	0.29/0.33	0.04/0.06	0.04/0.04	0.05/0.06
<i>E. faecalis</i>	1.3/2	0.33/0.5	0.33/0.43	0.37/0.43
<i>E. coli</i>	0.14/0.21	0.019/0.02	0.007/0.009	0.005/0.009
<i>Enterobacter</i> spp.	0.58/1.15	0.12/0.33	0.12/0.21	0.06/0.1
<i>Klebsiella</i> spp.	0.24/0.57	0.10/0.16	0.08/0.08	0.02/0.02
<i>M. morgani</i>	0.57/3.5	0.37/1	0.21/0.25	0.21/0.28
<i>P. vulgaris</i>	No growth	0.1/3.03	0.75/1.32	0.87/1.74
<i>P. mirabilis</i>	0.24/1.5	0.19/0.87	0.14/0.21	0.1/0.12
<i>Salmonella</i> spp.	0.07/0.08	0.03/0.04	0.008/0.01	0.006/0.009
<i>Shigella</i> spp.	0.023/0.04	0.007/0.017	0.002/0.006	0.012/0.03
<i>P. aeruginosa</i>	1.32/3.42	1/2	0.32/1	0.5/0.87

Effect of Divalent Cations

Mean MICs and MBCs of sparfloxacin for five isolates each of *S. aureus* and *E. faecalis* in unsupplemented Mueller-Hinton broth (0.3 mM Mg^{2+}) were generally unchanged at 1.1 mM (the concentration in normal human serum) but were usually increased 4-fold to 8-fold at 8.4 mM (12) (see TABLE 17). In Mueller-Hinton agar, MICs of sparfloxacin for two isolates of *S. aureus* and one isolate of *E. faecalis* were unchanged as the final concentration of Mg^{2+} was increased 10-fold compared to the usual concentration in this agar (15). Mean MICs of sparfloxacin for Enterobacteriaceae and *P. aeruginosa* in Mueller-Hinton agar were also increased approximately 2-fold to 4-fold by the addition of 4 mM Ca^{2+} (14).

TABLE 17
 Effect of Mg^{2+} on MICs and MBCs of sparfloxacin

Geometric mean MIC/MBC ($\mu\text{g/mL}$) in
 Mueller-Hinton broth with Mg^{2+} (mM)

Organism	0.3	1.1	4.4	8.4
<i>S. aureus</i>	0.04/0.06	0.06/0.08	0.21/0.24	0.18/0.21
<i>E. faecalis</i>	0.21/0.43	0.29/0.43	0.58/1	1.3/1.7
<i>E. coli</i>	0.007/0.009	0.02/0.03	0.05/0.08	0.04/0.06
<i>Enterobacter</i> spp.	0.07/0.12	0.03/0.04	0.05/0.06	0.09/0.09
<i>Klebsiella</i> spp.	0.08/0.12	0.06/0.09	0.07/0.08	0.16/0.18
<i>M. morgani</i>	0.21/0.33	0.03/0.04	0.25/0.5	0.33/0.65
<i>P. vulgaris</i>	0.76/1.3	0.87/1.7	1.0/1.7	1.15/2
<i>P. mirabilis</i>	0.18/0.18	0.09/0.24	0.16/0.5	0.3/0.5
<i>Salmonella</i> spp.	0.009/0.014	0.02/0.03	0.04/0.06	0.04/0.08
<i>Shigella</i> spp.	0.003/0.004	0.006/0.009	0.015/0.016	0.02/0.04
<i>P. aeruginosa</i>	0.32/1.15	0.75/1.14	2.0/3.5	4.6/7

Effect of Serum

Median MICs of sparfloxacin for two isolates of *S. aureus* in Mueller-Hinton broth containing human serum (50% final concentration) were unchanged while MICs of ciprofloxacin were increased 4-fold (16). Although human serum alone was not bactericidal, median MICs of sparfloxacin and ciprofloxacin for two isolates of *S. epidermidis* determined in Mueller-Hinton broth containing 50% serum were decreased to $\mu\text{g/mL}$ from $\mu\text{g/mL}$. Similarly, MICs of sparfloxacin for six isolates of *P. aeruginosa* in serum-supplemented broth were decreased to $\mu\text{g/mL}$ from $\mu\text{g/mL}$ while MICs of ciprofloxacin were decreased to $\mu\text{g/mL}$. In other studies, MICs of sparfloxacin for *S. epidermidis*, *E. faecalis*, *E. coli*, and *P. aeruginosa* in Mueller-Hinton broth containing 25% to 50% human serum were unchanged or increased 2-fold compared to MICs determined in serum-free broth (11,13).

Effect of Urine

In two of three studies, MICs of sparfloxacin were decreased in urine. Consistent with studies on the effect of pH, MICs of sparfloxacin in 100% pooled human urine at pH 6 for one isolate each of *S. aureus*, *E. faecalis*, *E. coli* and *P. aeruginosa* were increased 16-fold to 64-fold (13). Specifically, MICs of sparfloxacin for *S. aureus* and *E. faecalis* in urine increased from $\mu\text{g/mL}$, respectively, to $\mu\text{g/mL}$. Likewise, MICs of sparfloxacin for *E. coli* and *P. aeruginosa* increased from $\mu\text{g/mL}$ and $\mu\text{g/mL}$, respectively, to $\mu\text{g/mL}$ and $\mu\text{g/mL}$.

In a contrasting study, MICs of sparfloxacin for two isolates each of *S. aureus* and *S. epidermidis* and six isolates of *P. aeruginosa* in 100% human urine were unchanged or 2-fold lower than MICs determined in Mueller-Hinton broth (16).

In urine at pH 6, the MBC of sparfloxacin for one isolate of *E. coli* was increased from $\mu\text{g/mL}$ to $\mu\text{g/mL}$, while the MBC of sparfloxacin for one isolate of *P. aeruginosa* was increased from $\mu\text{g/mL}$ to $\mu\text{g/mL}$ (14).

This reviewer can not explain the contrasting study in which urine did not effect the MIC of sparfloxacin. This study used the same species and methods as the other studies and does not fit in with the rest of the data or the data from the effect of pH studies which showed that lower pH lowered the activity of sparfloxacin. This drug is not being approved for urinary tract infections, so the fact that urine and pH effect activity will not be bothersome.

Summary of Effects of Miscellaneous Factors on Activity

One study was used as a primary focus since it used the same set of bacteria to observe different effects (12). This study showed that in general, the influence of the tests factors on MICs was minimal except at pH 5 or with Mg^{2+} at 8.4 mM (which is about 8 times the amount in normal human serum). A small 4-fold inoculum effect on MICs was seen when the inoculum was increased from _____ CFU but not from _____ CFU. There was no effect of pH on MICs for *Streptococcus pneumoniae* and *Staphylococcus epidermidis*, however, there was a 4-fold to 16-fold increase in MICs and MBCs at pH 5 for *S. aureus*, *E. faecalis*, and gram-negative bacilli. MICs for *S. aureus*, *E. faecalis*, and gram-negative bacilli were not affected by Mg^{2+} at 1.1 mM but were increased up to 8-fold when the Mg^{2+} level was increased to 8.4 mM. A similar but lesser effect was seen with Ca^{2+} for gram-negative bacilli.

In most studies there was no effect of up to 50% serum supplementation on MICs of sparfloxacin for *S. aureus*, *S. epidermidis*, *E. faecalis* and gram-negative bacilli. In one study serum enhanced rather than decreased the activity of sparfloxacin against *S. aureus* and *P. aeruginosa*. Consistent with the effect of pH, MICs of sparfloxacin determined in 100% urine at pH 6 were increased 16-fold to 64-fold compared to MICs in broth.

ACTIVITY OF METABOLITE

Sparfloxacin glucuronide is a metabolite recovered in human urine and bile. MICs of sparfloxacin and sparfloxacin glucuronide for *S. aureus*, *E. coli*, and *Klebsiella* species have been determined (17) (see TABLE 18). The parent compound was 25 to 40 times more active than the metabolite against most strains tested. These data, however, are likely an over-estimate of the metabolite's activity because the glucuronide is prone to hydrolysis to free sparfloxacin under *in vitro* susceptibility test conditions.

TABLE 18
 MICs of sparfloxacin and sparfloxacin glucuronide

<u>Organism (# isolates)</u>	<u>Geometric mean MIC/MBC (μg/mL)</u>	
	<u>Sparfloxacin</u>	<u>Glucuronide</u>
<i>S. aureus</i> (5)	0.044	1.18
<i>E. coli</i> (9)	0.039	1.45
<i>Klebsiella</i> spp. (5)	0.02	0.78

BACTERICIDAL ACTIVITY

The bactericidal activity of sparfloxacin against a variety of bacteria was assessed by kill curve experiments designed to detect a 99.9% ($3 \log_{10}$) reduction in viability of a starting inoculum following exposure to various concentrations of drug. In order to assess the kinetics of bactericidal activity, bacterial viability in cultures exposed to sparfloxacin following incubation times ranging from 1 to 24 hours was determined by time-kill studies.

In a standard broth dilution assay for determining the minimal bactericidal concentration (MBC), bacterial viability in cultures exposed to varying concentrations of sparfloxacin following overnight incubation (18-24 hours) was determined. In these studies tubes from the MIC studies with no growth were subcultured into broth with no drug. After further incubation a sample was taken and the number of surviving cells determined. In these assays, the MBC was defined as the lowest concentration of drug which killed at least 99.9% of the starting inoculum.

Using time-kill studies, sparfloxacin was bactericidal against five isolates of penicillin-susceptible and penicillin-resistant isolates of *S. pneumoniae* within six hours at the MIC (MIC range, $\mu\text{g/mL}$) and bactericidal against five other isolates within 12 or 24 hours at concentrations which were equal to or exceeded the MIC (18). Concentrations of ciprofloxacin required for bactericidal activity within 6 to 24 hours were equal to or exceeded the MIC (MIC range $\mu\text{g/mL}$). Isolates for which sparfloxacin was bactericidal at the MIC did not regrow within 24 hours, whereas, although ciprofloxacin was initially bactericidal at the MIC for some isolates, regrowth within 24 hours following exposure to ciprofloxacin at the MIC was seen. Sparfloxacin was also bactericidal against three isolates (one penicillin-resistant) at $0.5 \mu\text{g/mL}$ (MIC range, $\mu\text{g/mL}$) within 24 hours and at $2 \mu\text{g/mL}$ within 6 hours in another study (19) (see TABLE 19).

Sparfloxacin at $0.1 \mu\text{g/mL}$ (2x MIC) and ciprofloxacin at $0.8 \mu\text{g/mL}$ (2x MIC) were bactericidal within 24 hours against one isolate of methicillin-susceptible *S. aureus* (20). Sparfloxacin was also bactericidal against two isolates of methicillin-resistant *S. aureus* within 4 to 6 hours after exposure to $0.5 \mu\text{g/mL}$ (2x MIC) in another study (21). Although ciprofloxacin was also bactericidal against one of these isolates within 4 to 6 hours at $1 \mu\text{g/mL}$ (2x MIC), only sparfloxacin exhibited bactericidal activity which was sustained after 24 hours incubation. Sparfloxacin was bactericidal against *S. aureus* within three hours at approximately $0.1 \mu\text{g/mL}$ and within 1 hour at $3 \mu\text{g/mL}$ (the optimal bactericidal concentration; 50x MIC); the concentrations of ciprofloxacin needed to achieve similar results ranged from $\mu\text{g/mL}$ (22,23) (see TABLE 19).

Sparfloxacin was bactericidal against two isolates each of *S. sanguis* and *S. mitis* within 12 to 24 hours at $4 \mu\text{g/mL}$ (MIC range, $\mu\text{g/mL}$) (24) (see TABLE 19).

Against *E. coli*, sparfloxacin and ciprofloxacin produced similar results. Sparfloxacin and ciprofloxacin at 0.03 to 0.06 $\mu\text{g/mL}$ (2x MIC) reduced bacterial counts of three isolates by 2 to 4 $\log_{10}$ within 3 to 6 hours (20, 25, 26) (see TABLE 19). Sparfloxacin and ciprofloxacin at approximately 0.1 $\mu\text{g/mL}$ (MIC not stated) were bactericidal against *E. coli* within 3 hours (22). The concentrations of sparfloxacin and ciprofloxacin required to reduce viability of *E. coli* by 99.9% within one hour ranged from $\mu\text{g/mL}$ and $\mu\text{g/mL}$, respectively, for the two drugs (26). Concentrations of sparfloxacin needed to achieve results similar to those of ciprofloxacin against other *Enterobacteriaceae* were 3 to 33 times those of ciprofloxacin.

These data show that sparfloxacin is bactericidal within 24 hours (often within 3 to 6 hours) against *S. pneumoniae*, *S. aureus*, and *E. coli* at concentrations 1 to 2 times the MIC in most studies. This concentration is usually 0.1 to 0.5 $\mu\text{g/mL}$, which is below serum concentrations achieved with normal dosing. Against the gram positive bacteria, sparfloxacin appears to give better results than ciprofloxacin. Ciprofloxacin often had regrowth by the 24 hour test point. Against *E. coli*, ciprofloxacin produced better results. Ciprofloxacin has lower MICs against this organism than does sparfloxacin. Against enterococci and streptococci (other than *S. pneumoniae*) sparfloxacin is only bactericidal at concentrations many times the MIC and these concentrations are usually not achievable with normal dosing. No testing was performed against *S. pyogenes*. When streptococcal species are encountered, sparfloxacin may not be bactericidal against them if this *in vitro* data equilibrates with clinical results.

TABLE 19
 Concentrations of sparfloxacin and exposure times required
 for 99.9% reduction in bacterial variability

Organism (#)	Test	MIC	Exposure	Reference
	Conc. ($\mu\text{g/mL}$)	Multiple	Time (h)	
<i>S. pneumoniae</i> (5)		1x	6	18
<i>S. pneumoniae</i> (5)		$\geq 1x$	24	18
<i>S. pneumoniae</i> (3)		2x, 4x	24	19
<i>S. pneumoniae</i> (3)		8x, 16x	6	19
<i>S. sanguis</i> (2)		8x to 16x	12 to 24	24
<i>S. mitis</i> (2)		8x to 16x	12 to 24	24
MRSA (1)		2x	24	20
MRSA (2)		2x	6	21
<i>S. aureus</i> (1)		Not stated	3	22
<i>S. aureus</i> (1)		50x	1	23
<i>E. coli</i> (1)		1x	3	20
<i>E. coli</i> (1)		2x	6	26

MRSA = methicillin-resistant *S. aureus*
S. pneumoniae included penicillin-susceptible and penicillin-resistant strains

Against *Streptococcus pneumoniae* MBCs of sparfloxacin were equal to or 2 to 4 times the MIC (28, 29, 30); data for ciprofloxacin were comparable. MBCs of sparfloxacin were, however, 2 to 8 times lower than those of ciprofloxacin (see TABLE 20)

TABLE 20
 MBCs of sparfloxacin for *Streptococcus pneumoniae*

Organism (#)	Sparfloxacin			Ciprofloxacin			Reference
	MIC ^a	MBC	MBC:MIC	MIC	MBC	MBC:MIC	
<i>S. pneumoniae</i> (7) ^b	0.2-0.5	0.2-0.5	1	0.01-1	0.01-2	1-2	28
<i>S. pneumoniae</i> (7) ^c	0.1-0.2	0.2-0.5	2	0.2-0.5	0.5-1	2	28
<i>S. pneumoniae</i> (5)	0.25-1	0.25-1	1	0.5-4	1-8	2	29
<i>S. pneumoniae</i> (2)	0.5	1	2	Not tested			30

^a data are ranges of MICs and MBCs

^b penicillin-susceptible

^c penicillin-resistant or -intermediate

These data show that sparfloxacin is bactericidal at concentrations that are achievable with normal dosing. Ciprofloxacin's MBC are higher and may not be achievable.

MICs of sparfloxacin for *S. aureus*, *S. epidermidis*, *S. pyogenes*, *S. viridans*, and *Enterococcus* species were 2 to 4 times the respective MICs (20,25,28,31,32); data for ciprofloxacin were comparable. MBCs of sparfloxacin were, however, generally 2 to 8 times lower than those of ciprofloxacin (see TABLE 21)

TABLE 21
 MBCs of sparfloxacin for aerobic gram-positive cocci

Organism (#)	Sparfloxacin			Ciprofloxacin			Reference
	MIC ^a	MBC	MBC:MIC	MIC	MBC	MBC:MIC	
MRSA (50)	≤0.06 ^a	0.12 ^a	≥2	0.5 ^a	1 ^a	2	31
MRSE (50)	0.12 ^a	0.25 ^a	2	0.25 ^a	0.5 ^a	2	31
<i>S. aureus</i> (20)	0.1 ^a	0.1	2	3.13 ^a	3.13 ^a	1	20
<i>S. aureus</i> (5)	0.06 ^b	0.25 ^b	4	0.25 ^b	1 ^b	4	25
<i>S. epidermidis</i> (5)	0.12 ^b	0.25 ^b	2	0.12 ^b	0.5 ^b	4	32
Enterococci (19)	1 ^a	2 ^a	2	4 ^a	8 ^a	2	28

^a data are MIC₉₀ and MBC₉₀

^b data are median MIC and MBC

MRSA = methicillin-resistant *S. aureus*

MRSE = methicillin-resistant *S. epidermidis*

These data show that sparfloxacin's MBCs are achievable with normal dosing. Once again enterococci present the greatest chance that MBC concentrations will not be met. Ciprofloxacin's MBCs are higher than sparfloxacin's.

MBCs of sparfloxacin for *E. coli* and other Enterobacteriaceae were equal to or 2 times the MIC (20,33); data for ciprofloxacin were comparable. MBCs of sparfloxacin were, however, generally 2 times greater than those of ciprofloxacin for these organisms (see TABLE 22).

TABLE 22
 MBCs of sparfloxacin for Enterobacteriaceae

Organism (#)	Sparfloxacin			Ciprofloxacin			Reference
	MIC ^a	MBC	MBC:MIC	MIC	MBC	MBC:MIC	
<i>E. coli</i> (20)	0.39 ^a	0.39 ^a	1	0.2 ^a	0.2 ^a	1	20
<i>E. coli</i> (5)	0.007 ^b	0.009 ^b	1	NT			33
<i>K. pneumoniae</i> (20)	0.78 ^a	0.78 ^a	1	0.78 ^a	0.78 ^a	1	20
<i>S. marcescens</i> (20)	6.25 ^a	12.5 ^a	2	6.25 ^a	6.25 ^a	1	20

^a data are MIC₉₀ and MBC₉₀

^b data are geometric mean MICs and MBCs

NT = not tested

These data show that sparfloxacin is bactericidal for these organisms (excluding *S. marcescens* which has a high MIC value) at concentrations that are achievable. Ciprofloxacin MICs and MBCs are usually one dilution lower.

The MBC₉₀ of sparfloxacin and ciprofloxacin for 108 isolates of *H. influenzae* was 0.03 µg/mL which was three times the MIC₉₀ (34). The MBC₉₀ of sparfloxacin for 20 isolates of *P. aeruginosa* was 3.13 µg/mL which was equal to the MIC₉₀ (20). The MBC₉₀ for ciprofloxacin was 1.56 µg/mL which was twice the MIC₉₀. The MBC of sparfloxacin for one isolates of *Moraxella catarrhalis* was 0.06 µg/mL which was twice the MIC (35). The geometric mean MIC and MBC of sparfloxacin for *Chlamydia pneumoniae* were 0.09 µg/mL which was approximately 30 times less than those of ciprofloxacin (36) (see TABLE 23).

TABLE 23
 MBCs of sparfloxacin for gram-negative and miscellaneous organism

Organism (#)	Sparfloxacin			Ciprofloxacin			Reference
	MIC ^a	MBC	MBC:MIC	MIC	MBC	MBC:MIC	
<i>H. influenzae</i> (108)	0.01 ^a	0.03 ^a	3	0.01 ^a	0.03 ^a	3	34
<i>M. catarrhalis</i> (1)	0.03	0.06	2	NT			35
<i>P. aeruginosa</i> (20)	3.13 ^a	3.13 ^a	1	0.78 ^a	1.56 ^a	2	20
<i>C. pneumoniae</i> (6)	0.09 ^b	0.09 ^b	1	2.13 ^b	3.0 ^b	1.4	36

^a data are MIC₉₀ and MBC₉₀

^b data are geometric mean MIC and MBC

These data show that sparfloxacin is bactericidal (except for perhaps *P. aeruginosa*) against these organisms at achievable concentrations.

POSTANTIBIOTIC EFFECT

The suppressive effect on bacterial growth which is seen following exposure to an antimicrobial agent and subsequent rapid removal of that agent is described as the postantibiotic effect (PAE).

$$PAE = T - C$$

where T is the time required for a drug-exposed bacterial culture to increase $1 \log_{10}$ (10-fold) above the count observed immediately after drug removal and C is the time required for a drug-free control culture to increase $1 \log_{10}$ above the count observed immediately after completion of the same procedure used to remove drug from the test culture. In most of these studies rapid removal of the test drug is accomplished by drug inactivation, dilution of drug, filtration to remove drug but retain bacteria, or repeated washings of concentrated bacteria. Bacteria are normally quantitated by using a direct plate count.

The PAE of sparfloxacin for *S. pneumoniae*, *S. aureus*, and *Enterococcus faecalis* were shown to be time and concentration dependent.

The PAE of sparfloxacin for one isolate of *S. pneumoniae* following exposure to the MIC (0.25 $\mu\text{g}/\text{mL}$) for 1 to 5 hours increased from approximately 7 to 12 hours (37). Following exposure to 1x to 4x the MIC for 5 hours increased the PAE from approximately 12 to 16 hours (see TABLE 24). In another study with a one hour exposure time, the PAE of sparfloxacin (MIC, 0.32 $\mu\text{g}/\text{mL}$) and ciprofloxacin (MIC, 1.28 $\mu\text{g}/\text{mL}$) for two isolates of *S. pneumoniae* following exposure to 1x to 10x the MIC ranged from approximately 1 to 2 hours (38). Although the PAE of ciprofloxacin for *S. pneumoniae* was also shown to be time and concentration dependent, greater concentrations of ciprofloxacin or longer incubation times were usually needed to achieve a PAE similar to that seen for sparfloxacin. For example, 1 $\mu\text{g}/\text{mL}$ of ciprofloxacin was needed to achieve the same PAE seen with 0.25 $\mu\text{g}/\text{mL}$ of sparfloxacin.

The PAE of sparfloxacin for one isolate of *S. aureus* following exposure to the MIC (0.1 $\mu\text{g}/\text{mL}$) for one to five hours increased from approximately 4 to 7 hours (37). The PAE of sparfloxacin following exposure to 2x to 16x the MIC for 5 hours increased from approximately 6 to 9 hours. Greater concentrations of ciprofloxacin (MIC, 0.25 $\mu\text{g}/\text{mL}$) or longer incubations in the presence of ciprofloxacin were needed to achieve a PAE similar to that seen with sparfloxacin against *S. aureus*. For example, 1 $\mu\text{g}/\text{mL}$ of ciprofloxacin was needed to achieve the same PAE seen with 0.1 $\mu\text{g}/\text{mL}$ of sparfloxacin. In other studies the PAE of sparfloxacin for two other isolates of *S. aureus* (including one MRSA) following exposure to 2 $\mu\text{g}/\text{mL}$ (17x or 33x MIC) for 0.5, 1 and 2 hours was approximately 3 hours (39,40) (see TABLE 24).

The PAE of sparfloxacin (MIC, 0.5 µg/mL) and ciprofloxacin (MIC, 0.5 µg/mL) for one isolate of *E. faecalis* following exposure to 1 to 4 times the MIC for 1 to 5 hours increased from approximately 3 to 7 hours (37). The PAE of sparfloxacin (MIC, 0.64 µg/mL) and ciprofloxacin (MIC, 1.28 µg/mL) for two isolates of *S. pyogenes* following a 1 hour exposure increased from approximately 1 to 3 hours as the concentration of sparfloxacin was increased from 1x to 10x the MIC, respectively (38). Twofold greater concentrations of ciprofloxacin (MIC, 1.28 µg/mL) were needed to achieve the same PAE seen with sparfloxacin against *S. pyogenes* (see TABLE 24).

TABLE 24
 Postantibiotic Effect of Sparfloxacin against gram-positive aerobes

Organism (#)	MIC µg/mL	Sparfloxacin			MIC µg/mL	Ciprofloxacin			Ref
		Test Conc	Exposure Time (hr)	PAE (hr)		Test Conc	Exposure Time (hr)	PAE (hr)	
<i>Streptococcus pneumoniae</i> (1)	0.25	1xMIC	2	9±1.57	0.5	1xMIC	2	not done	37
		2xMIC	2	11±1.06		2xMIC	2	6.5±0.88	
		4xMIC	2	10.8±1.05		4xMIC	2	10.3±1.57	
<i>S. aureus</i> (1)	0.1	1xMIC	2	4.9±0.18	0.25	1xMIC	2	2.3±0.71	37
		2xMIC	2	5.6±0.18		2xMIC	2	3.8±0.35	
		4xMIC	2	6±0.35		4xMIC	2	5.6±0.18	
<i>S. aureus</i> (1)	0.06	33xMIC	0.5	2.75	0.12	17xMIC	0.5	0.8	39
			1	3.6			1	>3.75	
MRSA (1)	0.12	17xMIC	2	3	not done				
<i>Streptococcus pyogenes</i> (2)	0.64	1xMIC	1	0.6-1.0	1.28	1xMIC	1	0.9-1.2	38
		2xMIC	1	1.4-2.0		2xMIC	1	1.3-1.8	
		10xMIC	1	1.6-3.4		10xMIC	1	1.4-3.1	
<i>E. faecalis</i> (1)	0.5	1xMIC	2	4±0.53	0.5	1xMIC	2	3±0	37
		2xMIC	2	5±0.53		2xMIC	2	4.1±0.18	
		4xMIC	2	5.4±0.53		4xMIC	2	5.9±0.18	

MRSA = methicillin-resistant *S. aureus*

The PAE of sparfloxacin for one isolate of *E. coli* was also shown to be time and concentration dependent. The PAE of sparfloxacin following exposure to the MIC (0.01 µg/mL) for 1 to 5 hours increased from approximately 2.5 to 7 hours (37). The PAE of sparfloxacin for this isolate following exposure to 1x to 8x the MIC for 5 hours increased from approximately 7 to 13 hours. At concentrations ranging from the MIC to 8x the MIC of sparfloxacin or ciprofloxacin (MIC, 0.01 µg/mL) for this isolate, the PAE of ciprofloxacin was approximately 1 to 4 hours greater than that observed for sparfloxacin. At 1 µg/mL (100x MIC) exposure to sparfloxacin resulted in no regrowth of cultures while exposure to ciprofloxacin resulted in regrowth after 11 to 15 hours (see TABLE 25). A concentration of 1 µg/mL is achievable with normal dosing of sparfloxacin.

The PAE of sparfloxacin for 4 isolates of *H. influenzae* and 2 isolates of *M. catarrhalis* following exposure to the MIC, 4x, and 10x the MIC (MIC range, µg/mL) for 1 hour was approximately 1 to 3 hours (38); identical results were seen for ciprofloxacin (MIC range, µg/mL) against these isolates. Following a 2 hour exposure to 4x the MIC of sparfloxacin (MIC 0.5 µg/mL), the PAE for one isolate each of *Serratia marcescens* and *Pseudomonas aeruginosa* was 1.5 hours and 0 hours, respectively (40) (see TABLE 25).

TABLE 25
 Postantibiotic Effect of Sparfloxacin against gram-negative aerobes

Organism (#)	Sparfloxacin				Ciprofloxacin				Ref
	MIC µg/mL	Test Conc	Exposure Time (hr)	PAE (hr)	MIC µg/mL	Test Conc	Exposure Time (hr)	PAE (hr)	
<i>E. coli</i> (1)	0.01	1xMIC	2	6.1±0.53	0.01	1xMIC	2	7.8±1.41	37
		2xMIC	2	6.8±0.35		2xMIC	2	8.6±0.18	
		4xMIC	2	8.3±0		4xMIC	2	11.6±1.23	
		8xMIC	2	12.3±0		8xMIC	2	12.9±3.35	
		100xMIC	2	No regrowth		100xMIC	2	12.6±0.18	
<i>Haemophilus influenzae</i> (4)	0.005- 0.02	1xMIC	1	0.7-1.8	0.005- 0.01	1xMIC	1	0.7-1.8	38
		4xMIC	1	2.3-2.7		4xMIC	1	1.4-3.0	
		10xMIC	1	3.4-4.3		10xMIC	1	2.8-4.2	
<i>Moraxella catarrhalis</i> (2)	0.02- 0.04	1xMIC	1	0.8-1.2	0.04	1xMIC	1	0.7-1.8	38
		4xMIC	1	1.8-2.9		4xMIC	1	1.4-3.0	
		10xMIC	1	3.0-3.3		10xMIC	1	2.8-4.2	
<i>Serratia marcescens</i> (1)	0.5	4xMIC	2	1.5	Not Done			40	
<i>Pseudomonas aeruginosa</i> (1)	0.5	4xMIC	2	0	Not Done			40	

These data show that the PAE of sparfloxacin for gram-positive and gram-negative bacteria is time and concentration dependent. Under the same set of conditions (drug concentration and exposure time) the PAE is generally greater for gram-positive aerobes (except *S. pyogenes* and *E. faecalis*) than for gram-negative bacteria. The PAE for *Serratia marcescens* and *Pseudomonas aeruginosa* is short or does not exist. Since sparfloxacin is rapidly bactericidal against most bacteria, exposure time of greater than one hour may be inducing bactericidal activity.

The clinical significance of PAE is not known, but a prolonged PAE may indicate that longer dosing intervals may still give satisfactory efficacy. Since the clinical significance is not known and dosing has been set, there is no need for a statement about PAE to be in the label.

ANTIBACTERIAL INTERACTION WITH OTHER ANTIBIOTICS

To investigate the effect of combining sparfloxacin with other drugs, combination studies using time-kill curves were performed.

The bactericidal activity of sparfloxacin alone at supra-MIC concentrations and in combination with vancomycin, teicoplanin, cefotaxime, penicillin or rifampin at sub-MIC concentrations against 3 isolates of *S. pneumoniae* (1 penicillin-resistant) was determined by time-kill methodology (41). In general, the combination of sparfloxacin at 2 times the MIC and vancomycin, cefotaxime, penicillin or rifampin at sub-MIC concentrations after 2 to 6 hour exposures did not produce an additional reduction in viability or reduced viable counts by approximately an additional 1 log₁₀ compared to reductions in viability seen with sparfloxacin alone. Following 24 hour exposure, the combination of sparfloxacin with these agents reduced viable counts by an additional 2 log₁₀ compared to reductions in viability seen following exposure to sparfloxacin alone. Antagonism was not seen in these combination studies (see TABLE 26).

TABLE 26
 Approximate log₁₀ reduction in CFU of *S. pneumoniae* following exposure to sparfloxacin alone or in combination with other drugs

Drug combination (MIC multiple tested)	Log ₁₀ Reduction ^a in CFU/mL for each agent alone or in combination after exposure for			
	2h	4h	6h	24h
Sparfloxacin (2xMIC; MIC=0.25 µg/mL)	1	1	1.5	3
+ vancomycin (0.5 MIC; MIC=0.25µg/mL)	2	2	2	5
+ teicoplanin (0.8 MIC; MIC=0.12µg/mL)	1	1	2	5
+ cefotaxime (MIC; MIC=0.005 µg/mL)	2	2	2	5
+ penicillin (0.33 MIC; MIC=0.03 µg/mL)	2	2	2	5
+ rifampin (0.33 MIC; MIC=0.03 µg/mL)	1.5	2	2	5

The bactericidal activity of sparfloxacin or ciprofloxacin alone and in combination with several drugs was determined by time-kill methodology after 24 hours exposure against 4 isolates of *S. aureus* (1 isolate each of quinolone-susceptible and quinolone-resistant MRSA, 1 isolates of MRSA moderately susceptible to quinolones and 1 isolate of quinolone-susceptible MSSA) (42). In this study, sparfloxacin when tested at 0.5 and 2.0 $\mu\text{g/mL}$, was tested at 5 to 80 times the MIC (MIC range, $\mu\text{g/mL}$) against quinolone-susceptible and moderately susceptible isolates and at times the MIC (MIC 6.25 $\mu\text{g/mL}$) against a quinolone-resistant isolate, while ciprofloxacin was tested at times the MIC (MIC, $\mu\text{g/mL}$) against quinolone-susceptible and moderately susceptible isolates and at times the MIC (MIC 12.5 $\mu\text{g/mL}$) against a quinolone-resistant isolate. In general, these combinations generally at supra-MIC levels had an effect on killing which was indifferent (the combined effect was neither greater than nor less than the effect observed for the most active drug alone). Antagonisms was frequently seen for the combination of sparfloxacin or ciprofloxacin with fusidic acid or rifampin against a methicillin and quinolone-susceptible isolate and a methicillin-resistant, moderately susceptible quinolone isolate (see TABLE 27). Similar results were seen against four isolates of *S. epidermidis* with the same phenotypes as above.

TABLE 27
 Effect of combining sparfloxacin or ciprofloxacin at
 0.5 or 2 $\mu\text{g/mL}$ with other drugs for 24 hours
 against 4 isolates of *Staphylococcus aureus*

Combination Drug ^b	Sparfloxacin		Ciprofloxacin	
	Syn or Indiff	Antag	Syn or Indiff	Antag
Oxacillin (10 $\mu\text{g/mL}$)	4/4	0/4	4/4	0/4
Fusidic Acid (2 $\mu\text{g/mL}$)	1/4	3/4	3/4	1/4
Rifampin (1 $\mu\text{g/mL}$)	2/4	2/4	2/4	2/4
Vancomycin (10 $\mu\text{g/mL}$)	4/4	0/4	3/4	1/4
Amikacin (2 or 8 $\mu\text{g/mL}$)	4/4	0/4	4/4	0/4
Phosphonomycin (0.5 $\mu\text{g/mL}$)	4/4	0/4	4/4	0/4

^a Syn = synergy, Indiff = indifference; Anag = antagonism; synergy and indifference were not individually specified in the study. Indiff is the usual outcome, the combination had the same activity as the most potent drug. Antag was a 2 log decrease in activity with the combination over the most active drug.

^b Fusidic acid, vancomycin and phosphonomycin were tested at concentrations exceeding the MIC for all isolates. Rifampin was tested at concentrations exceeding the MIC for 3 isolates while amikacin was tested at concentrations below the MIC for 3 isolates. Oxacillin was tested at concentrations exceeding the MIC for 1 isolate.

This study showed that sparfloxacin was often antagonistic with fusidic acid and rifampicin. The other combinations were usually indifferent. Fusidic acid is not an approved drug, but rifampicin is and this antagonism may be important clinically if both drugs were used together.

The bactericidal activity of sparfloxacin alone or in combination with ceftazidime, imipenem or tobramycin for one isolate each of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* was determined by time-kill methodology (43). In these experiments, drugs were combined at concentrations equal to one-half the MIC, the MIC, and 2 times the MIC. Compared to viable counts following exposure to sparfloxacin alone for 24 hours, bacterial viability was reduced an additional 2 to 3 log₁₀ following exposure to combinations of each drug at the MIC or 2 times the MIC. Although exposure to each drug alone at one-half its MIC generally did not result in killing, viable counts following exposure to combinations of 1/2X MIC were reduced by approximately 0.5 to 1 log₁₀ after 4 to 6 hours exposure; at 24 hours, however, viable counts of cultures exposed to these combinations had increased by 2-3 log₁₀ CFU/mL (see TABLE 28).

TABLE 28
 Approximate log₁₀ reduction in CFU following exposure
 to sparfloxacin alone (at 2xMIC) or in combination
 with other drugs at (2xMIC) after 24 hours incubation

Organism/Drugs	MIC μg/mL	Log ₁₀ reduction ^a in CFU/mL for each agent alone or in combination	
		Alone	Combined
<i>E. coli</i> V9033			
sparfloxacin	0.016	1	---
+ ceftazidime	0.13	0.5	4
+ imipenem	0.25	0	4
+ tobramycin	1.0	0.5	4
<i>P. aeruginosa</i> E9910			
sparfloxacin	1.0	1	---
+ ceftazidime	32.0	0.5	4
+ imipenem	2.0	1	3
+ tobramycin	0.25	1	3
<i>A. baumannii</i> E3194			
sparfloxacin	0.03	1	---
+ ceftazidime	8.0	1	3
+ imipenem	0.5	1	3
+ tobramycin	1.0	1	4

^a rounded to nearest log₁₀

In another study, synergism was not reported for combinations of sparfloxacin plus mezlocillin or sparfloxacin plus cefotaxime against 32 isolates of multi-resistant Enterobacteriaceae (44). The combination of sparfloxacin plus cefotaxime, however, was synergistic for 6 of 30 isolates of *Pseudomonas aeruginosa*. Antagonism was not observed in these studies.

These data show that in most studies and for most organisms sparfloxacin in combination with other drugs was indifferent. There appears to be antagonism with some drugs such as fusidic acid or rifampin for some gram-positive bacteria. Against gram-negative bacteria the evidence seems to be contradictory between the two studies presented. One study showed that against *E. coli*, *P. aeruginosa*, and *A. baumannii* that combinations of sparfloxacin and other drugs caused a greater reduction in viable count after 24 hours than sparfloxacin alone, while another study with different drugs, but still members of the beta-lactam class which one of the drugs in the previous study also belonged to, showed synergistic effects only for a few isolates of one species. It appears that most combinations are indifferent, but sparfloxacin probably should not be combined with rifampin or fusidic acid.

MECHANISMS OF RESISTANCE STUDIES

The *in vitro* development of resistance to sparfloxacin was assessed by experiments designed to detect single-step and multi-step chromosomal mutations resulting in an altered drug target, particularly *gyrA* gene mutations. The development of single-step resistance was assessed by exposure of bacteria to concentrations of drug which exceeded the MIC by multiples of 2, 4, 8, or 16. The development of multi-step resistance was assessed by serial transfer of bacteria in increasing subinhibitory concentrations of drug. In these studies, resistance was defined as a 4 to 8-fold increase in the MIC to sparfloxacin.

Single-step resistance to sparfloxacin in eight isolates of *Streptococcus pneumoniae* after single exposures to sparfloxacin was not detected (45,46,47). In these studies 10^8 to 10^{10} bacteria were exposed to concentrations of drug at various multiples of the MIC of the organism. Colonies that were capable of growth were counted and divided by the total number of cells on the plate to obtain a mutation frequency. For two additional isolates, only 1 of 3 experimental attempts resulted in the selection of sparfloxacin resistant mutants with a frequency of approximately 10^{-8} to 10^{-7} (47). Similar results were seen with ciprofloxacin. MICs of sparfloxacin and ciprofloxacin for these mutants were $\leq 1.25 \mu\text{g/mL}$ and $\geq 4 \mu\text{g/mL}$, respectively. The results of these experiments are shown in TABLE 29.

TABLE 29
 Frequency of single-step resistance to sparfloxacin
 in quinolone-susceptible *Streptococcus pneumoniae*

Organism(#)	Frequency of Mutation			
	Selection at	Sparfloxacin	Ciprofloxacin	Reference
<i>S. pneumoniae</i> (5)	3,5,10X MIC	<10 ⁻⁸ to 10 ⁻⁷	<10 ⁻⁸ to 10 ⁻⁷	47
<i>S. pneumoniae</i> (4)	Not stated	<10 ⁻¹⁰	Not stated	45
<i>S. pneumoniae</i> (1)	1,2,3,4X MIC	<10 ⁻⁹ to <10 ⁻⁸	10 ⁻⁶	46

This table shows that the single-step mutation frequency of sparfloxacin for *S. pneumoniae* are equal to or less than those for ciprofloxacin. These data show that a large inoculum is needed before any resistant cells are seen.

The development of multi-step resistance in three isolates of *Streptococcus pneumoniae* following serial transfer in increasing concentrations of sparfloxacin was determined in a study by Carsenti and Dellamonica (48). With inocula adjusted to approximately 10⁶ cells/mL and 15 or 19 serial transfers in a macrobroth dilution assay, MICs of sparfloxacin for a penicillin-susceptible, penicillin-intermediate, and penicillin-resistant isolate had increased 8 to >16 times respectively. MICs of ciprofloxacin for these same isolates, increased 8 to 16 times (TABLE 30).

TABLE 30
 Multi-step selection for resistance in quinolone-susceptible
Streptococcus pneumoniae following serial transfer

Organism (#)	Initial MIC/Ending MIC		No. of Serial Transfers	
	Sparfloxacin	Ciprofloxacin	Sparfloxacin	Ciprofloxacin
PEN (S) (1)	0.125/1	0.5/8	19	19
PEN (I) (1)	0.125/8	0.25/4	15	15
PEN (R) (1)	0.25/64	0.5/4	15	15

These data show that *S. pneumoniae* isolates will develop resistance to both drugs when transferred in sub-inhibitory concentrations. It appears that a greater increase in MIC occurs for the more penicillin resistant strains when sparfloxacin is used. This does not seem to be the case with ciprofloxacin. Only one study was conducted so this fact has not been verified.

The inhibitory effects of sparfloxacin on DNA supercoiling activity of purified DNA gyrase from sparfloxacin-susceptible and -resistant strains of *Streptococcus pneumoniae* were not determined.

Single-step resistance to sparfloxacin in 16 isolates of quinolone-susceptible *Staphylococcus aureus* following single exposures to 2, 4, 8 or 16 times the MIC was not selected (49,50,51,52,53,54)(no colonies were seen growing) while ciprofloxacin resistant mutants were sometimes seen with frequencies ranging from _____ (the limit was the amount of cells in the inoculum which ranged from _____ CFU). In two other studies the frequency of resistance for three additional isolates ranged from _____ for both drugs (55,56). The frequency of resistance to sparfloxacin in methicillin-resistant *S. aureus* was not greater than that seen for methicillin-susceptible *S. aureus*. For an isolate of ciprofloxacin-resistant *S. aureus*, the frequency of single-step resistance to sparfloxacin ranged from MIC to _____. This isolate had about the same frequency for sparfloxacin as the other isolates in the study. At 4 x MIC for ciprofloxacin the frequency of resistance for this strain was 2.5×10^{-6} which was about 1600 times the frequency for most other isolates (54). The frequency of resistance to sparfloxacin in five isolates of *Enterococcus faecalis* ranged from _____ which was similar to that seen for ciprofloxacin (45,50,51,57) (see TABLE 31).

TABLE 31
 Frequency of single-step resistance to sparfloxacin in gram-positive cocci
 Frequency of Mutations to

Organism (#)	Selection at	Sparfloxacin	Ciprofloxacin	Ref
<i>S. aureus</i> (1)	4,8,16X MIC	$10^{-11.3}$	$10^{-10.4}$ to $<10^{-11.4}$	51
MRSA (5)	4,8,16X MIC	$<6 \times 10^{-9}$ to $<4 \times 10^{-9}$	2×10^{-6} to $<6 \times 10^{-9}$	54
MSSA (5)	4,8,16X MIC	$<1.5 \times 10^{-9}$	10^{-7} to $<1.5 \times 10^{-9}$	54
<i>S. aureus</i> (1)	4X MIC	$<5.6 \times 10^{-9}$	$<5.6 \times 10^{-9}$	53
<i>S. aureus</i> (2)	4,8X MIC	5×10^{-7} to $<10^{-9}$	7×10^{-7} to $<10^{-9}$	55
<i>S. aureus</i> (1)	4 X MIC	$<10^{-9}$	3×10^{-8}	52
<i>E. faecalis</i> (1)	4,8,16X MIC	$<10^{-10.6}$	$<10^{-11.2}$	51
<i>E. faecalis</i> (1)	2,4,8X MIC	7×10^{-9} to $<10^{-10}$	Not tested	57

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*

These data show that spontaneous single-step mutations to sparfloxacin in *S. aureus* and *E. faecalis* are rare. Mutation frequencies are often at the limit of the number of cells used in the inoculation of plates. Mutation frequencies are similar to those seen with ciprofloxacin, although in some cases they may be lower, especially in quinolone-resistant mutants.

The development of multistep resistance in *S. aureus* and *S. epidermidis* following serial transfer in increasing concentration of drug was also studied. With inocula adjusted to approximately 2 to 5×10^5 bacteria/mL, MICs of sparfloxacin for one isolate of methicillin-resistant *S. aureus* and two isolates of methicillin-susceptible *S. aureus* increased ≤ 8 times after 10 to 15 serial transfers in broth dilution assays (50,58,59) (see TABLE 32). In an agar dilution assay, growth from overnight agar plates was used as inocula for serial transfer

experiments with five isolates each of methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermidis* (60). In these experiments, MICs of sparfloxacin increased 2 to 4 times while those of ciprofloxacin increased 16 to 32 times. In a microbroth dilution assay with 0.1 mL of overnight growth as inocula and approximately 10 serial transfers, MICs of sparfloxacin and ciprofloxacin for *S. aureus* increased from $\mu\text{g/mL}$ and $\mu\text{g/mL}$, respectively (51); similar results were seen for *E. faecalis* (51) (see TABLE 32). These data suggest that although single-step mutations selected *in vitro* are rare, multiple exposure of organisms to subinhibitory concentrations of sparfloxacin can select for resistance.

TABLE 32
 Multistep selection for resistance in aerobic gram-positive cocci following serial transfer in subinhibitory drug concentrations

Organism (#)	Initial MIC ($\mu\text{g/mL}$) / Ending MIC		No. of Serial Transfers		Ref
	Sparfloxacin	Ciprofloxacin	Sparfloxacin	Ciprofloxacin	
<i>S. aureus</i> (1)	0.06 / 16	0.125 / 32	12	13	51
MSSA (2)	<8 fold increase	<8 fold increase	10	10	58
MRSA (5)	$\leq 0.06 / 0.25$	0.25 / 8	Not stated	Not stated	60
MRSA (1)	0.06 / 0.5	Not tested	15	Not tested	50
MRSE (5)	$\leq 0.06 / 0.12$	0.25 / 4	Not stated	Not tested	60
<i>E. faecalis</i> (1)	0.25 / 128	1 / 256	9	11	51

MSSA = methicillin susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*
 MRSE = methicillin-resistant *S. epidermidis*.

The inhibitory effects of sparfloxacin on DNA synthesis and DNA supercoiling activity of purified DNA gyrase from fluoroquinolone susceptible and resistant *S. aureus* have been determined. The concentration of sparfloxacin which inhibited DNA synthesis and DNA supercoiling by 50% (IC_{50}) correlated with MICs (61). The IC_{50} of DNA supercoiling and the MIC of sparfloxacin for a susceptible (parent) isolate were $10.5 \mu\text{g/mL}$ and $0.05 \mu\text{g/mL}$, respectively, while the IC_{50} and MIC of sparfloxacin for a resistant mutant isolate were $>800 \mu\text{g/mL}$ and $12.5 \mu\text{g/mL}$, respectively (61).

The frequency of single-step resistance to sparfloxacin in *Escherichia coli* and other Enterobacteriaceae following single exposures to sparfloxacin was decreased as the concentration was increased from $\mu\text{g/mL}$ times the MIC (49, 50, 51, 53, 56, 57). The frequency of selecting sparfloxacin resistance after exposure to 4, 8 and 16 times the MIC ranged from $\mu\text{g/mL}$ and increased to $\mu\text{g/mL}$ after exposure to 2 times the MIC. Results with ciprofloxacin were similar, but often a lower frequency was seen (see TABLE 33).

TABLE 33
 Frequency of single-step resistance to sparfloxacin in Enterobacteriaceae

Organism (#)	Selection at	Frequency of Mutations to		Ref
		Sparfloxacin	Ciprofloxacin	
<i>E. coli</i> (1)	4,8,16X MIC	10 ⁻⁹ to 10 ⁻¹⁰	10 ⁻⁹ to <10 ⁻¹¹	51
<i>E. coli</i> (1)	4,8 X MIC	<10 ⁻⁹	<10 ⁻⁹	53
<i>E. coli</i> (1)	2,4,8 X MIC	10 ⁻⁷ to 10 ⁻¹⁰	Not tested	57
<i>K. pneumoniae</i> (1)	4,8,16 X MIC	10 ⁻⁸ to 10 ⁻¹⁰	10 ⁻⁹ to <10 ⁻¹¹	51
<i>E. cloacae</i> (1)	2,4,8X MIC	10 ⁻⁷ to <10 ⁻¹⁰	Not tested	57
<i>S. marcescens</i> (1)	4,8,16x MIC	10 ⁻⁸ to 10 ⁻⁹	10 ⁻¹⁰ to <10 ⁻¹⁰	51
<i>P. stuartii</i> (2)	4,8X MIC	<10 ⁻⁹	Not tested	50

The development of multi-step resistance in the Enterobacteriaceae following serial transfer in increasing concentrations of drug has been studied. With inocula adjusted to approximately 5 x 10⁵ bacteria/mL, the MICs of sparfloxacin for *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens* and *Providencia stuartii* increased 8 to 512 times following 10 to 15 serial transfers in microbroth dilution assays (50, 59). In macrobroth dilution assays with 0.1 mL of overnight growth of *E. coli*, *K. pneumoniae* or *S. marcescens* as inocula and 11 to 14 serial transfers, MICs of sparfloxacin and ciprofloxacin increased _____ times and _____ times, respectively (51) (see TABLE 34).

TABLE 34
 Multistep selection for resistance in Enterobacteriaceae following serial transfer in subinhibitory drug concentrations

Organism (#)	Initial MIC (µg/mL)/ Ending MIC		No. of Serial Transfers		Ref
	Sparfloxacin	Ciprofloxacin	Sparfloxacin	Ciprofloxacin	
<i>E. coli</i> (1)	0.06 / 0.5	0.03 / 2	14	11	51
<i>K. pneumoniae</i> (1)	0.06 / 8	0.125 / 16	14	11	51
<i>E. cloacae</i> (1)	0.06 / 4	Not tested	15	Not tested	50
<i>S. marcescens</i> (1)	0.06 / 16	0.03 / 16	14	12	51
<i>P. stuartii</i> (1)	0.12 / 64	Not tested	15	Not tested	50

These data suggest that although single-step mutations selected *in vitro* are rare, multiple exposure of organisms to subinhibitory concentrations of sparfloxacin can select for resistance.

The inhibitory effects of sparfloxacin on DNA synthesis and DNA supercoiling activity of purified DNA gyrase from fluoroquinolone-susceptible and -resistant *E. coli* have been determined. In these studies, the concentrations of sparfloxacin which inhibited DNA synthesis and DNA supercoiling correlated with MICs (56,62). The minimum concentration of sparfloxacin which inhibited DNA supercoiling and the MIC of sparfloxacin for a susceptible isolate were _____ µg/mL and _____ µg/mL, respectively, and _____ µg/mL, respectively, for a resistant mutant isolate (62).

Single-step resistance to sparfloxacin in five isolates of *Haemophilus influenzae* following single exposure to 2 µg/mL and 3, 5, and 10 times the MIC was not selected (47) (see TABLE 35).

The frequency of single-step resistance to sparfloxacin in 16 isolates of *Pseudomonas aeruginosa* following single exposure to sparfloxacin was generally decreased from _____ as the concentration of sparfloxacin was increased from 4 to 16 times the MIC (50,51,53,57,58). Results with ciprofloxacin were usually comparable to those with sparfloxacin. For two isolates the frequency of resistance selection after exposure to 8 times the MIC of sparfloxacin or ciprofloxacin was _____ (58) (see TABLE 35). As with other fluoroquinolones, it appears that *Pseudomonas aeruginosa* may be more prone to mutations that render the isolate resistant.

The frequency of single-step resistance to sparfloxacin in two isolates of *Acinetobacter anitratus* after exposure to 4 and 8 times the MIC was _____ (50). This was the limit of detection in the study (see TABLE 35).

The frequency of single-step resistance to sparfloxacin in four isolates of *Xanthomonas maltophilia* after exposure to 4, 8, and 16 times the MIC ranged from 1.5×10^{-7} to 5×10^{-7} while that of ciprofloxacin ranged from _____ (63) (see TABLE 35). Like *Pseudomonas aeruginosa* this species is more prone to resistance than most other species.

The frequency of single-step resistance to sparfloxacin in two isolates of *Mycoplasma hominis* after single exposure to 0.32 µg/mL (although the MICs were not given the MIC₉₀ for this species is usually _____ µg/mL, so this is about 10 x MIC) was approximately 10^{-6} while resistant mutants were not selected after exposure to 1 µg/mL (64) (see TABLE 35).

TABLE 35
 Frequency of single-step resistance to sparfloxacin in gram-negative bacilli and miscellaneous microorganisms

Organism (#)	Selection at	Frequency of Mutations to		Ref
		Sparfloxacin	Ciprofloxacin	
<i>H. influenzae</i> (5)	3,5,10X MIC	None detected	None detected	47
<i>P. aeruginosa</i> (1)	4,8,16X MIC	10^{-9} to $<10^{-11}$	10^{-8} to 10^{-11}	51
<i>P. aeruginosa</i> (11)	4,8X MIC	$>10^{-6}$ to $<10^{-9}$	$>10^{-6}$ to $<10^{-9}$	58
<i>X. maltophilia</i> (4)	4,8,16X MIC	$<10^{-7}$	10^{-6} to $<10^{-7}$	63
<i>A. anitratus</i> (2)	4,8X MIC	$<10^{-9}$	Not Tested	50
<i>M. hominis</i> (2)	0.32, 1 µg/mL	$\sim 10^{-6}$	Not Tested	64

In microbroth dilution assays with inocula adjusted to approximately 2×10^5 bacteria/mL, MICs of sparfloxacin for 4 isolates of *Pseudomonas aeruginosa* increased eightfold or greater following 10 serial transfers while MICs of ciprofloxacin increased less than eightfold (58). In a similar study with inocula of approximately 5×10^7 bacteria/mL, MICs of sparfloxacin for one isolate each of *Pseudomonas aeruginosa* and *Xanthomonas maltophilia* increased from _____ µg/mL following 15 serial transfers (50). In a microbroth dilution assay with 0.1 mL of overnight growth as inocula and

approximately 10 serial transfers, MICs of sparfloxacin for one isolates of *Pseudomonas aeruginosa* increased from $\mu\text{g/mL}$ while MICs of ciprofloxacin increased from $\mu\text{g/mL}$ (51) (see TABLE 36).

TABLE 36
 Multistep selection for resistance in gram-negative bacilli
 following serial transfer in subinhibitory drug concentrations

Organism (#)	Initial MIC ($\mu\text{g/mL}$) / Ending MIC		No. of Serial Transfers		Ref
	Sparfloxacin	Ciprofloxacin	Sparfloxacin	Ciprofloxacin	
<i>P. aeruginosa</i> (1)	0.5 / 4	0.125 / 2	9	13	51
<i>P. aeruginosa</i> (4)	≥ 8 fold increase	< 8 fold increase	10	10	58
<i>X. maltophilia</i> (1)	0.12 / 16	Not tested	15	Not tested	50

These data show that serial transfers in subinhibitory concentrations of drug can lead to large increases in MICs.

The minimum concentrations of sparfloxacin which inhibited DNA supercoiling and the MIC of sparfloxacin for a susceptible isolate of *Pseudomonas aeruginosa* were $0.5 \mu\text{g/mL}$ and $1 \mu\text{g/mL}$, respectively, and $10 \mu\text{g/mL}$ and $32 \mu\text{g/mL}$, respectively, for a resistant isolate (62). This shows that inhibition of DNA supercoiling and MICs are correlated.

RESISTANCE DEVELOPMENT DURING THERAPY

There was a very low incidence of resistance development in isolates from patients receiving therapy with sparfloxacin, only 0.3% of 1100 cases. Among 668 patients with infections in non-urinary sites there were only 3 cases in which sparfloxacin resistance emerged. Resistance development occurred in trial #356(ABECB) [one *S. aureus* and 2 *P. aeruginosa* strains became resistant]. Among 162 patients treated in trail #353 one provided a *E. faecalis* isolate with markedly decreased sparfloxacin susceptibility in the intermediate category.

Among patients receiving therapy with comparator agents, the incidence of resistance development was 0.3% of 787 cases. Among 38 erythromycin treated patients in trail #301 (CAP), 1 patient had a *S. pneumoniae* which emerged resistant during treatment. In trial #353 one ciprofloxacin resistant isolate of *S. epidermidis* was recovered from 154 patients and one isolate of *S. aureus* went from susceptible to intermediate. Among 100 patients being treated with cefaclor in trail # 352 (CAP), two provided *H. parainfluenzae* isolates with markedly decreased cefaclor susceptibility in the intermediate category. Among 251 patients treated with ofloxacin in trail # 356 (ABECB), there were no instances in which bacteria became ofloxacin resistant (see TABLE 37).

TABLE 37

Summary of emerging resistance to therapy with sparfloxacin or comparator antibiotics (bacteriologically evaluable patients)

Infection	Treatment Drug (No. Patients)	Organism	MIC ($\mu\text{g/mL}$) of Drug	
			Pre-RX	Post-RX
Community Acquired Pneumonia Trail #301	Erythromycin (38)	<i>S. pneumoniae</i>	0.06	8
	Sparfloxacin (49)	None	—	—
Community Acquired Pneumonia Trial #352	Cefaclor (100)	<i>H. influenzae</i>	0.5	4
		<i>H. influenzae</i>	1	4
Complicated Skin and Skin Structure Trail #353	Sparfloxacin (109)	None	—	—
	Ciprofloxacin (154)	<i>S. aureus</i>	0.25	1
Acute Exacer- bations of Chronic Bronchitis Trial #356		<i>S. epidermidis</i>	0.12	4
	Sparfloxacin (162)	<i>E. faecalis</i>	0.25	2
Sinusitis Trail #359	Ofloxacin (251)	None	—	—
	Sparfloxacin (253)	<i>S. aureus</i>	0.06	8
		<i>P. aeruginosa</i>	1	8
		<i>P. aeruginosa</i>	0.5	4
	Sparfloxacin (95)	None	—	—

EPIDEMIOLOGICAL STUDIES

Sparfloxacin has been approved in a number of countries. In most of these countries it was approved in June to September 1994, so it has been used for about a year and one-half. It was approved in Japan in July 1993, so it has been used there for about 2½ years.

The drug is marketed in Japan by _____ and in France by _____. In Europe it has been approved but not yet marketed in England, Belgium, Switzerland, Denmark and Finland. It was not approved in Sweden based on a lack of medical need. After a sharp rise in the number of reports of photosensitivity, France removed the indication of bronchitis and altered the indications for community acquired pneumonia and sinusitis by restricting its use to cases that have failed conventional therapy, either caused by pneumococci highly resistant to penicillin and other antimicrobials or occurring in an epidemiological environment indicating that the risk of such multiresistant strain is high. It has been marketed in Japan since August

1993, without the above restrictions. In most countries the drug has the same indications as the proposed United States indications; some countries have urethritis as an added indication. In Japan the drug is approved for almost everything from skin and skin structure infections (including acne), surgical infections, respiratory infections, biliary tract infections, enteritis, gynecological infections, ophthalmological infections, otitis media, sinusitis, and dental infections.

There are no studies from countries where the drug has been used that show how resistance rates have been altered. Studies from Japan would probably be the most interesting since the drug is used more than in most other countries. The drug has been used for only about 2 years so there probably is not much data compiled on increases in resistance as of yet. It is known that other quinolones often cause rapid increases in resistance after their introduction into the market place, especially against *Pseudomonas* species. The *in vitro* data submitted suggest that sparfloxacin is probably similar to ciprofloxacin and that resistant strains will be selected over time.

PRECLINICAL EFFICACY (*IN VIVO*)

PHARMACOKINETICS/BIOAVAILABILITY

The information in this section is taken from the NDA studies submitted by the sponsor and have not been reviewed by a Biopharmaceutical Reviewer.

After oral administration (400 mg loading dose, then 200 mg daily), sparfloxacin achieves maximum plasma concentrations of around 1.3 $\mu\text{g}/\text{mL}$ in about 4 hours. The plasma concentration is $\geq 0.5 \mu\text{g}/\text{mL}$ over the entire 24 hour dosing period. Area under the curve (AUC) values increase in a dose-proportional manner up to 2000 mg doses. After a 400 mg single dose the AUC value was 34 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (average of 3 studies with 61 subjects). The absolute oral bioavailability is approximately 90% and steady state concentrations are achieved by the second or third dose. The volume of distribution at steady state is 3.6 L/kg. Binding to serum proteins is 42-46%, primarily to albumin. The plasma elimination half-life is approximately 18 to 20 hours. It is eliminated primarily by conjugation with only 9% and 2% of the administered dose unchanged in urine and bile, respectively. Mean concentrations in urine exceeded 12 $\mu\text{g}/\text{mL}$ in the first 4 hours postdose and measurable levels ($\geq 0.2 \mu\text{g}/\text{mL}$) of active drug was seen in urine six days following a single 400 mg oral dose.

Studies of the tissue distribution of sparfloxacin have shown generally a greater concentration of drug in tissues and fluids compared to plasma (65,66,67,68). The C_{max} of sparfloxacin in respiratory tissues (lung parenchyma, bronchus wall, bronchial mucosa and epithelial lining fluid) following standard dosing is approximately 3 to 15 times greater than the C_{max} in plasma. The drug also concentrates in alveolar macrophages compared to plasma. Concentrations in skin and muscle are 4 to 7 times greater than in plasma. Concentrations in tonsils and lymph node are 2 to 4 times greater. Concentrations in blister fluid are about equal to plasma levels (see TABLE 38).

TABLE 38
 Summary of sparfloxacin pharmacokinetics in man

Ref	Tissue ^a (No. Samples) ^b	Collection times postdosing	C _{max} ($\mu\text{g/mL}$) ^c	$\frac{C_{\text{max}} \text{ Tissue/}}{C_{\text{max}} \text{ Plasma}}$ Ratios ^d
67 (single 400 mg dose; 8 subjects)	Plasma (≥ 8)	2-6h postdose	1.86 $\pm$ 0.33	—
	LP(8)	2-6h postdose	10.03 $\pm$ 1.37	5.92 $\pm$ 0.91
	Bronchus wall (8)	2-6h postdose	4.87 $\pm$ 0.87	2.76 $\pm$ 0.44
67 (single 400 mg dose; 7 subjects)	Plasma (≥ 7)	12-24h postdose	1.02 $\pm$ 0.27	—
	LP (7)	12-24h postdose	10.32 $\pm$ 1.60	15.77 $\pm$ 5.05
	Bronchus wall (7)	12-24h postdose	3.79 $\pm$ 0.50	5.74 $\pm$ 1.45
68 (single 400 mg dose; 6 subjects)	Plasma (~66)	0.5-52h postdose	1.6 $\pm$ 0.3	—
	Blister fluid (~66)	0.5-52h postdose	1.3 $\pm$ 0.3	~1.23
66 (Day 1, 400 mg od D2-3, 200 mg od; 10 subjects)	Plasma (10)	2.9-4.9h post last	1.2 $\pm$ 0.41	—
	AM (10)	2.9-4.9h post last	53.70 $\pm$ 38.41	~44.75
	BM (10)	2.9-4.9h post last	4.40 $\pm$ 3.00	~3.67
	ELF (10)	2.9-4.9h post last	15.00 $\pm$ 8.34	~12.5
65 (single 400 mg dose; 35 subjects)	Plasma (44)	2-6h postdose	0.74 $\pm$ 0.31	—
	Sinus mucosa (8)	2-6h postdose	5.81	~7.85
	Tonsils (5)	2-6h postdose	3.09	~4.18
	Lymph nodes (9)	2-6h postdose	1.49	~2.01
	Skin (11)	2-6h postdose	5.54	~7.49
	Muscle (17)	2-6h postdose	3.06	~4.14

^a LP = lung parenchyma; AM = alveolar macrophages; BM = bronchial mucosa; ELF = epithelial lining fluid

^b Number of samples per study

^c Mean maximum concentration ($\mu\text{g/mL}$ in fluids; $\mu\text{g/g}$ in tissues) + SEM (standard error of the mean)

^d Ratio of mean maximum concentration in tissue to mean maximum concentration in plasma

Using 1.3 $\mu\text{g/mL}$ as a representative mean C_{max} in plasma following recommended dosing the following TABLE 39 shows that the C_{max} value is at least almost 3 times the MIC₉₀ value for the targeted pathogens. Since the respiratory tissue levels are all at least 3 times (for bronchial mucosa) to 10 times (for lung parenchyma) the plasma concentration the amount of drug is almost at least 9 times the MIC₉₀ value for all pathogens.

TABLE 39
 MICs of sparfloxacin for N.A. clinical trial isolates
 versus C_{max} in man ($C_{max} = 1.3 \mu\text{g/mL}$)

	MIC ₅₀	C_{max}/MIC_{50}	MIC ₉₀	C_{max}/MIC_{90}
<i>S. pneumoniae</i> (192)	0.25	5.2	0.25	5.2
<i>S. aureus</i> (367)	0.06	21.6	0.125	10.4
<i>S. pyogenes</i> (53)	0.25	5.2	0.5	2.6
<i>M. catarrhalis</i> (112)	0.015	86.6	0.03	43.3
<i>H. influenzae</i> (292)	0.015	86.6	0.03	43.3
<i>E. coli</i> (696)	0.03	43.3	0.06	21.6
<i>K. pneumoniae</i> (109)	0.06	21.6	0.06	21.6
<i>A. anitratus</i> (32)	0.03	43.3	0.06	21.6

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

The *in vitro* activity of sparfloxacin and ciprofloxacin were evaluated in systemic infections in mice following intravenous or intraperitoneal inoculation of bacteria at 4 to 180 times the LD₅₀ (lethal dose for 50% of untreated animals) (69) (see TABLE 40). In these studies, drugs were orally administered immediately after inoculation and 6 hours later. Mice intraperitoneally inoculated with *Streptococcus pneumoniae* at 100 LD₅₀ were also dosed at 24 and 30 hours post-inoculation. Therapeutic outcome, in terms of percentage of surviving mice, was determined at 1 or 2 weeks post-inoculation.

The ED₅₀s (effective dose for 50% of treated animals) for infections with one strain each of *Staphylococcus aureus*, penicillin-susceptible *Streptococcus pneumoniae* and *Streptococcus pyogenes* were 0.8, 6.3 and 3.4 $\mu\text{g/mL}$, respectively, which was one fifth to one tenth of those for ciprofloxacin. The ED₅₀s of sparfloxacin for one strain each of *Escherichia coli* and *Pseudomonas aeruginosa* were 0.5 and 1.6 $\mu\text{g/mL}$, respectively, which ranged from equal to one half of those for ciprofloxacin (see TABLE 40).

TABLE 40
 Comparative activities of sparfloxacin and ciprofloxacin against systemic infection in mice

Organism CFU/mouse	Drug	MIC ($\mu\text{g/mL}$)	ED ₅₀ (mg/kg)	Ref
<i>S. aureus</i> (5×10^6)	Sparfloxacin	0.05	0.8	69
	Ciprofloxacin	0.2	8.2	
<i>S. pyogenes</i> (3×10^7)	Sparfloxacin	0.39	3.4	69
	Ciprofloxacin	0.2	20.3	
<i>S. pneumoniae</i> (3×10^3)	Sparfloxacin	0.39	6.3	69
	Ciprofloxacin	0.78	31.3	
<i>E. coli</i> (9×10^6)	Sparfloxacin	0.01	0.5	69
	Ciprofloxacin	0.006	0.5	
<i>P. aeruginosa</i> (4×10^3)	Sparfloxacin	0.39	1.6	69
	Ciprofloxacin	0.1	2.8	

In a similar experiment (70) using three different strains of *S. pneumoniae*, an inoculum of 10^2 to 10^3 CFU/mouse, and dosing twice a day; the ED₅₀s ranged from mg/kg. These values were much lower than the range of 42 $\mu\text{g/mL}$ for ofloxacin (see TABLE 41).

TABLE 41
 Comparative activities of sparfloxacin and ofloxacin against three isolates of *S. pneumoniae*

Organism CFU/mouse	Drug	MIC ($\mu\text{g/mL}$)	ED ₅₀ (mg/kg)	Ref
<i>S. pneumoniae</i> 6254/01 (10^2 - 10^3)	Sparfloxacin	0.25	50	70
	Ofloxacin	2	218	
<i>S. pneumoniae</i> 4314/03 (10^2 - 10^3)	Sparfloxacin	0.50	44	70
	Ofloxacin	2	180	
<i>S. pneumoniae</i> 6460/06 (10^2 - 10^3)	Sparfloxacin	0.25	4.6	70
	Ofloxacin	2	42	

**RHONE-POULENC RORER
SPARFLOXACIN TABLETS**

The above experiments show that sparfloxacin is usually superior to the other fluoroquinolones in mice systemic infections. The data also show that factors other than just the MIC of the organism are important in determining how effective the drug may be in an systemic infection. Ciprofloxacin may also be slightly more effective than sparfloxacin in certain gram-negative infections. In these experiments drug was given immediately after inoculation of organisms. In human respiratory infections the patient has the infection established before treatment begins. All the sparfloxacin ED₅₀s were well below 50mg/kg which has been shown to be the dose in mice that produces the same AUC as human dosing proposed in the NDA.

In another experiment (71), normal mice were intraperitoneally inoculated with 10⁹ CFU of *Streptococcus pneumoniae*. Treatment by subcutaneous injection of drug was delayed for 6 hours post-infection and continued every 12 hours for 6 days. Therapeutic success was measured as survival rates at 6 days post-infection, by which time untreated mice have died. Survival rates following sparfloxacin treatment increased from 0% to 90% to 100% as the dosage was increased from 5 to 15 to 50 mg/kg/12/hr, respectively. Mutants resistant to sparfloxacin were not selected following sparfloxacin treatment even at 5 mg/kg/12h. The MIC of sparfloxacin for pre-treatment and post-treatment isolates was 0.5 µg/mL. In contrast, 100% of the mice died following treatment with ciprofloxacin even at 50 mg/kg/12h. The MIC of ciprofloxacin increased from 2 µg/mL (pre-treatment) to 16 µg/mL (post-treatment).

The AUC in mice in this study was shown to be 31 µg-hr/mL with the 50 mg/kg dosing. This is comparable to the AUC in humans after normal dosing (400 mg followed by daily 200 mg doses). Since the mouse and human dose produce equivalent AUCs this may mean that the 50 mg/kg dose which allowed 100% survival in mice is equivalent to the normal human dose and may lead to success in humans. This experiment also delayed the time after inoculation that the drug was given, which more closely represents what happens in normal infections.

The activity of sparfloxacin, amoxicillin, and ciprofloxacin were evaluated against a penicillin-susceptible and a macrolide-resistant strain of *S. pneumoniae* in models of acute pneumonia in immunocompetent Swiss mice (72). Following tracheal inoculation of 10⁵ CFU of bacteria, infected mice received at total of 6 subcutaneous injections of 50 mg/kg sparfloxacin, 5 mg/kg amoxicillin, or 100 mg/kg ciprofloxacin starting at 6 or 18 hours post-infection (doses of 250 mg/kg of ciprofloxacin were also used in the 18 hour study). Untreated mice died within two to five days. In a subacute (in C57BL/6 mice) pneumonia model the penicillin-susceptible strain was used. Infected mice received two subcutaneous doses of 50 mg/kg of sparfloxacin or 100 mg/kg of ciprofloxacin starting 24 hours post-infection or sparfloxacin in 4 injections starting 48 hours post-infection or 6 injections starting 72 hours post-infection. In the subacute model untreated mice died within 7 to 10 days. Therapeutical outcome, in terms of percentage of surviving mice, was determined at 14 days postinfection.

When treatment was initiated at 6 hours post-infection with the penicillin-susceptible strain in acute pneumonia, sparfloxacin at 50 mg/kg/dose and amoxicillin at 5 mg/kg/dose were fully protective (100% survival) while ciprofloxacin at 100 mg/kg/dose prevented death in only 50% of the infected mice (72). When treatment was started at 18 hours post-infection with the penicillin-susceptible strain, sparfloxacin at 50 mg/kg/dose was more effective (80% survival) than ciprofloxacin at 100 mg/kg/dose (23% survival) and 250 mg/kg/dose (50% survival) (see TABLE 42).

Results with the macrolide-resistant strain were as follows: When treatment was started at 6 hours post-infection, sparfloxacin and ciprofloxacin both protected 100% of the mice. When treatment was delayed for 18 hours, sparfloxacin at 50 mg/kg, six administrations, protected 80% of the mice, while ciprofloxacin at 100 mg/kg protected only 40% (see TABLE 42).

In the subacute model penicillin-susceptible strain survival rates following subcutaneous injection of sparfloxacin at 50 mg/kg/dose were the same (94%) when treatment was started at 24 hour (two doses) or 48 hours (four doses) and was 75% when started at 72 hours. Ciprofloxacin started at 24 hours protected only 40% of the animals (see TABLE 42).

TABLE 42
 Comparative activities of sparfloxacin, ciprofloxacin and amoxicillin against *Streptococcus pneumoniae* in mouse models of pneumonia

Model	Strain	Drug	Start	Dose in mg/kg (# doses)	% survival
Acute pneumonia	PENS	Spar	6h	50 (6)	100
		Cipro	6h	100 (6)	50
		Amox	6h	5 (6)	100
		Spar	18h	50 (6)	80
		Cipro	18h	100 (6)	23
		Cipro	18h	250 (6)	50
Acute pneumonia	macrolide resistant	Spar	6h	50 (6)	100
		Cipro	6h	100 (6)	100
		Spar	18h	50 (6)	80
		Cipro	18h	100 (6)	40
Subacute	PENS	Spar	24h	50 (2)	94
			48h	50 (4)	94
			72h	50 (6)	75
		Cipro	24	100 (2)	40

These data show that sparfloxacin was better than ciprofloxacin in a pneumonia model in mice. They also show that the later treatment starts the worse the result will be. Sparfloxacin, however, at the equivalent of normal dosing still has some protective power even if treatment is delayed for 72 hours. There was not much difference between a macrolide-resistant strain and a penicillin-susceptible strain. No penicillin-resistant strain could be found that was virulent in normal mice in this model.

The *in vivo* activities of orally administered sparfloxacin and ciprofloxacin were studied in pulmonary, urinary and skin infections in mice following inoculation with 3 to 100 times the LD₅₀ of gram-negative bacteria and *S. aureus* (69) (see TABLE 43).

In a pulmonary infection model, mice intranasally infected with 3 to 20 times the LD₅₀ of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were orally treated twice, immediately after challenge and 6 hours later; or three times, immediately after challenge and 1 and 3 hours later (69). Therapeutic success was measured by survival rates at 1 or 2 weeks post-infection. The ED₅₀s of sparfloxacin for pulmonary infections with *K. pneumoniae* and *P. aeruginosa* were 1.6 and 2.9 mg/kg, respectively, which were one half to one third those for ciprofloxacin (see TABLE 43).

In a urinary tract infection model, mice infected with 10 to 100 times the LD₅₀ of infecting organisms by direct injection into the bladder were treated orally at 3, 8, 24, 30, 48, and 50 hours post-challenge (69). Therapeutic success was measured by the absence of organisms in both kidneys following culture at 5 days post-infection. In urinary tract infections with *S. aureus*, *E. coli*, *P. aeruginosa* and *S. marcescens*, the ED₅₀s of sparfloxacin were 17.8, 0.8, 1.1, and 5.8 µg/mL, respectively, which ranged from equal to one fifth of those for ciprofloxacin (see TABLE 43). These data indicate that sparfloxacin may be useful in urinary tract infections and is similar or perhaps slightly better than ciprofloxacin. In this study many doses were given and treatment was started shortly after infection. Sparfloxacin is not being proposed for urinary tract infections in this NDA.

In a dermal infection model, mice infected with 16 times the LD₅₀ of *P. aeruginosa* by subcutaneous inoculation were treated orally, immediately after challenge and 3, 6, 24, 27, and 30 hours post-infection (69). Therapeutic success was measured by the absence of skin abscesses at 4 days post-infection. The ED₅₀ of sparfloxacin for skin infections with *P. aeruginosa* was 1.1 µg/mL, which was one fifth that for ciprofloxacin (see TABLE 43). Once again treatment in this study was started immediately and many doses were given. The experiment may also have been more useful if *S. aureus* or streptococci were used since most skin infections are caused by them. The sponsor is not seeking a claim for skin infections.

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TABLE 43
 Comparative activities of sparfloxacin and ciprofloxacin against
 pulmonary, urinary tract and skin infections in mice

Type or infection and organism CFU/mouse	Drug	MIC ($\mu\text{g/mL}$)	ED ₅₀ (mg/kg)	Ref
Pulmonary				
<i>K. pneumoniae</i> (2×10^5)	Sparfloxacin	0.02	1.6	69
	Ciprofloxacin	0.02	4.0	
<i>P. aeruginosa</i> (2×10^7)	Sparfloxacin	0.39	2.9	69
	Ciprofloxacin	0.1	5.4	
Urinary Tract				
<i>S. aureus</i> (2×10^5)	Sparfloxacin	0.05	17.8	69
	Ciprofloxacin	0.2	54.4	
<i>E. coli</i> (2×10^7)	Sparfloxacin	0.01	0.8	69
	Ciprofloxacin	0.006	0.9	
<i>P. aeruginosa</i> (2×10^4)	Sparfloxacin	0.39	1.1	69
	Ciprofloxacin	0.1	5.9	
<i>S. marcescens</i> (3×10^7)	Sparfloxacin	0.2	5.8	69
	Ciprofloxacin	0.05	11.7	
Skin				
<i>P. aeruginosa</i> (9×10^6)	Sparfloxacin	0.39	1.1	69
	Ciprofloxacin	0.1	5.3	

A rabbit model of endophthalmitis was used to study the *in vivo* activities of sparfloxacin and pefloxacin. In this study, rabbits infected by intravitreal inoculation of 10^6 CFU of *Streptococcus* Group G received a single intravitreal injection of 800 μg of sparfloxacin at 20 hours post-infection. Compared to bacterial counts in the vitreous humor of untreated controls at 24 hours post-treatment, bacterial counts in sparfloxacin treated animals were reduced by approximately 2 $\log_{10}$ while bacterial counts in pefloxacin treated animals were not reduced. While this experiment shows that sparfloxacin has *in vivo* activity and pefloxacin does not in this infection model, it is impossible to equilibrate the dose given with a normal human dose, and this NDA is not seeking an indication for eye infections.

The *in vivo* activity of sparfloxacin was also studied in immunodeficient mice (72). An acute pneumonia model in leukopenic mice was used. Mice were infected by tracheal inoculation of 10^6 CFU of either a penicillin-resistant, penicillin-intermediate and macrolide-resistant, or a penicillin-resistant and macrolide-resistant strain of *Streptococcus pneumoniae*. Mice received a total of six subcutaneous injections of drugs starting at 6 hours post-infection and continuing at 12 hour intervals. Therapeutic outcome, in terms of the percentage of surviving mice, was determined at 14 days post-infection.

Against the penicillin-resistant strain, sparfloxacin (50 mg/kg) protected 100% of the mice, amoxicillin (50 mg/kg) protected 70% of the mice. Against the multiresistant strains (penicillin-intermediate or resistant and macrolide-resistant), sparfloxacin at 50 mg/kg protected 100%, while ciprofloxacin at 50 mg/kg protected only 7%. Ciprofloxacin at 100 mg/kg protected 92%, and amoxicillin at 50 mg/kg protected 90%. These data show that sparfloxacin at a dose equivalent to the normal human dose protects mice against pneumonia caused by resistant *S. pneumoniae* even in immunodeficient hosts. In this experiment dosing was started 6 hours post-infection. It might have been more interesting to see what happens when dosing is delayed.

The prophylactic and therapeutic *in vivo* activities of sparfloxacin, ciprofloxacin, and vancomycin were studied in experimental models of infections caused by methicillin-resistant and quinolone-susceptible *S. aureus* (74). In a guinea pig model of prophylaxis, a single 50 mg/kg dose of sparfloxacin administered intraperitoneally 3 hours before inoculation of 10^4 bacteria into subcutaneously implanted tissue cages was more effective than ciprofloxacin (50 mg/kg dose) and vancomycin (30 mg/kg dose) in preventing infection. One hundred percent (100%) of tissue fluids obtained from the sparfloxacin group were culture-negative 7 days post-inoculation compared to <13% and 38% for ciprofloxacin and vancomycin, respectively. This study shows that sparfloxacin is better than ciprofloxacin and vancomycin in this model, but it does not represent a respiratory tract infection.

In a rat model of chronic subcutaneously implanted tissue infection, therapy with sparfloxacin, ciprofloxacin or vancomycin was initiated 3 weeks following implantation of 2×10^5 to 2×10^6 CFU of methicillin-resistant *S. aureus*. Sparfloxacin administered intraperitoneally (50 mg/kg twice a day for 7 days) considerably reduced bacterial counts in infected fluids by $1.2 \pm 0.26 \log_{10}$ CFU/mL compared to untreated control animals (74). In addition with the same dosing regimens, sparfloxacin was more effective than ciprofloxacin which reduced the counts only $0.25 \pm 0.22 \log_{10}$ CFU/mL and about the same as vancomycin which reduced the count by $1.7 \pm 0.20 \log_{10}$ (see TABLE 44). This study shows the *in vivo* effect of sparfloxacin is better than ciprofloxacin in this model of infection, but once again it does not tell us anything about respiratory tract infections which are the proposed indications in this NDA.

**RHONE-POULENC RORER
SPARFLOXACIN TABLETS**

The *in vivo* activities of sparfloxacin, penicillin and ceftriaxone against penicillin-resistant *S. pneumoniae* were evaluated in a rabbit model of meningitis (75). In this study, rabbits were treated with sparfloxacin (5 mg/kg/h), penicillin (100 mg/kg/h) or ceftriaxone (25 and 100 mg/kg/h) starting 16 hours after receiving an intracisternal inoculation of 10^5 CFU of *S. pneumoniae*. Treatments were given intravenously over 7 hours as a constant infusion after a bolus of 15% of the total dose.

Sparfloxacin and high-dose ceftriaxone (100 mg/kg/h) killed penicillin-resistant pneumococci in cerebrospinal fluid of infected animals at a rate of $0.5 \log_{10}$ CFU/mL/h, while low-dose ceftriaxone (25 mg/kg/h) killed at a rate of $0.1 \log_{10}$ CFU/mL/h and penicillin did not reduce the bacterial counts (see TABLE 44). Sparfloxacin is not being proposed for meningitis, but this experiment shows that it may have some activity in this type of infection. Trying to equilibrate the dose used in this model with a human dose is hard to do.

The *in vivo* activities of sparfloxacin and ceftriaxone were evaluated in experimental endocarditis in rats caused by penicillin-susceptible *Streptococcus sanguis* and penicillin-resistant *Streptococcus mitis* (76). In this study rats had a catheter induced into the aortic valve and were intravenously inoculated with 10^7 bacteria. Treatment with intravenous sparfloxacin (40 mg/kg four times a day—equivalent to 400 mg human single injection) or ceftriaxone (1.06 gm as a single daily dose, which is equivalent to the human dose of 2 gm) started 48 hours post-infection and last for 3 days. Animals were killed 24 hours after the last dose, when no residual drug could be detected in the blood. After 3 days treatment against penicillin-susceptible streptococci, sparfloxacin reduced the median log of bacterial densities in valvular vegetations by 2 to 4 $\log_{10}$ compared to untreated controls, but was less effective than ceftriaxone which reduced the median log of bacterial densities by 5 to 6 $\log_{10}$ (see TABLE 44). Against the penicillin-resistant strain, however, sparfloxacin was more effective than ceftriaxone. Sparfloxacin reduced the median log count of bacteria by at least 7 $\log_{10}$ compared to a reduction of $<1 \log_{10}$ for ceftriaxone. It seems strange that in this experiment sparfloxacin worked well against the penicillin-resistant strain, but only had limited success against the penicillin-susceptible strain. The results with ceftriaxone are reasonable since the penicillin-resistant strain would normally be resistant to other beta-lactams as well. Since doses that were equivalent to human doses were used this experimental design provides us with information that may be useful in setting up clinical trails in humans. The sponsor is not requesting an indication for endocarditis, however.

TABLE 44
 In vivo activity of sparfloxacin and comparator in deep seated infections

Infection Model (species)	Organism (Inoculum)	Drug/Route ^a /Dosage	Log ₁₀ CFU Reduction ^b	Ref
Chronic Foreign Body (rat)	MRSA (10 ⁵ -10 ⁶ CFU)	Sparfloxacin, IP, 100 mg/kg/day x 7 days	1.2	74
		Ciprofloxacin, IP, 100 mg/kg/day x 7 days	0.25	
		Vancomycin, IP, 100 mg/kg/day x 7 days	1.8	
Meningitis (rabbit)	<i>S. pneumoniae</i> penicillin-resistant (10 ⁵ CFU)	Sparfloxacin, IV, 5 mg/kg/h x 7 hours	0.5	75
		Penicillin, IV, 100 mg/kg/h x 7 hours	0	
		Ceftriaxone, IV, 25 mg/kg/h x 7 hours	0.1	
		Ceftriaxone, IV, 100 mg/kg/h x 7 hours	0.5	
Endocarditis (rat)	<i>S. mitis</i> penicillin-resistant (10 ⁷ CFU)	Sparfloxacin, IV, 40 mg/kg x 4 x 3 days	7	76
		Ceftriaxone, IV, 1.06 gm x 3 days	<1	
	<i>S. sanguis</i> penicillin-susceptible (10 ⁷ CFU)	Sparfloxacin, IV, 40 mg/kg x 4 x 3 days	2 to 4	76
		Ceftriaxone, IV, 1.06 mg/kg x 3 days	5 to 6	

^a IP; intraperitoneal; IV, intravenous

^b reduction of bacterial counts per mL of tissue fluid (foreign body model); reduction of bacterial counts per mL of hour in cerebrospinal fluid (meningitis model); reduction of bacterial counts in cardiac valvular tissue (endocarditis model);

The *in vivo* activities of sparfloxacin and erythromycin against *Legionella pneumophila* were evaluated in a guinea pig pneumonia model (77). In this study, guinea pigs were treated by intraperitoneal injections with sparfloxacin (10 mg/kg/day for 5 days) or erythromycin (60 mg/kg/day for 5 days) starting 1 day following intratracheal inoculation with about 3 x 10⁶ CFU *L. pneumophila*. Therapeutic success was measured by survival rates at 15 days post-infection. Sparfloxacin produced a 100% survival rate compared to a 93% rate with erythromycin (see TABLE 45). All eight lungs obtained from the sparfloxacin-treated group were culture negative, while five of the seven erythromycin treated lungs were culture positive. Serum and lung levels of sparfloxacin were also studied in this experiment. The C_{max} in the serum after a 10 mg/kg dose was 2.5-2.7 µg/mL and the C_{max} in lung was 1.5-1.6 µg/mL. The level in serum is about twice the human level and the level in lungs in this study may be 10 times lower than that in humans after normal dosing. This study does, however, show that sparfloxacin may be better than erythromycin which is normally used for atypical pneumonia and that it works in guinea pigs even at a dose that produces drug levels in the lungs that are lower than those in humans after normal dosing.

The *in vivo* activities of sparfloxacin, minocycline, clarithromycin, and ofloxacin were evaluated against *Chlamydia pneumoniae* in a leukopenic mouse pneumonia model (78). Mice were infected with 10^5 CFU/mouse (LD₁₀₀ by day 5). Mice were orally administered sparfloxacin (3.13 to 0.39 mg/kg), ofloxacin (50 to 6.25 mg/kg), clarithromycin (12.5 to 1.56 mg/kg) and minocycline (6.25 to 0.78 mg/kg) six times at 3, 8, 24, 30, 48 and 54 hours after infection. An untreated control group was also included. The number of surviving mice was recorded daily for 21 days. The ED₅₀ at day 21 was calculated. In this study orally administered sparfloxacin prevented death in infected mice in a dose-dependent manner. Sparfloxacin at 3.1 mg/kg/dose for six days prevented death in 100% of the animals at 21 days post-infection and was as effective as minocycline at 6.3 mg/kg/dose, clarithromycin at 12.5 mg/kg/dose and ofloxacin at 50 mg/kg/dose (see TABLE 45). The ED₅₀ of sparfloxacin in this study was 1.0 mg/kg which was lower than that for ofloxacin (16.6 mg/kg) and about equal to those for minocycline and clarithromycin. This study did not evaluate the pharmacokinetics of these drugs, so it is impossible to relate the dosing used to that of a normal human dose. It does appear, however, that in this model sparfloxacin is better than ofloxacin and about the same as minocycline and clarithromycin.

TABLE 45
 In vivo activity of sparfloxacin and comparators against treatment
 of intracellular infections

Infection Model (species)	Organism (inoculum)	Drug ^a /Route ^b /Dosage	Percent Survival	ED ₅₀ (µg/mL)	Ref
Pneumonia (guinea pig)	<i>L. pneumophila</i> (~3x10 ⁶ CFU)	Spar, IP, 10mg/kg/day x 5 days	100	N.D ^c	77
		Ery, IP, 60mg/kg/day x 5 days	93	N.D	
Pneumonia (mouse)	<i>C. pneumoniae</i> (10 ⁵ CFU)	Spar, p.o., 3.1mg/kg x 6 doses	100	1.0	78
		Oflox, p.o., 50 mg/kg x 6 doses	100	16.6	
		Clari, p.o., 12.5 mg/kg x 6 doses	100	4.7	
		Mino, p.o., 6.3 mg/kg x 6 doses	100	2.2	

^a Spar, sparfloxacin; Ery, erythromycin, Oflox, ofloxacin, Clari, clarithromycin, Mino, minocycline.

^b IP, intraperitoneal; p.o., oral.

^c N.D., not done.

The *in vivo* activities of sparfloxacin, isoniazid, and ofloxacin were evaluated against *Mycobacterium tuberculosis* infection in mice (79). Mice were infected intravenously with 2×10^6 CFU/mouse. Treatments were started on the day following infection. Animals were treated 6 times a week until 28 days post-infection. In the first experiment mice were treated with sparfloxacin and ofloxacin at 100 mg/kg daily; in the second experiment mice were treated respectively with sparfloxacin 12.5, 25, 50, 75 and 100 mg/kg daily and ofloxacin 100, 200, and 300 mg/kg daily. The survival rates were recorded weekly and all

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surviving mice were killed at 28 days and examined for lung lesions. In both experiments a group was treated with isoniazid at 25 mg/kg daily. In the first experiment, ofloxacin at 100 mg/kg daily displayed very limited activity. The survival rate and severity of lung lesions were virtually the same as in the untreated control group. The isoniazid group and the sparfloxacin treated group had 100% survival rates and no gross lung lesions. In the second experiment the survival rate at 28 days after infection was 13.3% for untreated controls, 100% in the isoniazid group, 53.3% in the 100 mg/kg ofloxacin group, and 100% in the other groups. This experiment shows that sparfloxacin is better than ofloxacin in this model and may be equivalent to isoniazid. No pharmacokinetic data was available in this study so it is difficult to extrapolate the effective dosages in mice to humans.

All the animal model data show that sparfloxacin may be effective for certain infections in certain animal models. Some of these experiments started treatment well after infection, which more closely represents what would normally happen in a clinical infections. Many studies included pharmacokinetic studies which equilibrated the doses used with the normal human dose. Some of these experiments showed that sparfloxacin dosed in mice equilibrated to a normal human clinical dose, with treatment started well after infection, cured respiratory tract infections.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)
ISOLATES/RELEVANCE TO APPROVED INDICATIONS

The sponsor has presented the following studies for the listed indications. A satisfactory response indicates that the pathogen was eradicated or presumed eradicated (nonculturable).

Community-Acquired Pneumonia (CAP)

Study RP 64206X-301--Double-blind randomized, comparative, multicenter study of sparfloxacin versus erythromycin

Study RP 64206X-352--Double-blind randomized, comparative, multicenter study of sparfloxacin versus cefaclor

Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB)

Study RP 64206X-356--Double-blind randomized, comparative, multicenter study of sparfloxacin versus ofloxacin

Pathogens isolated:

Study 301--CAP

Haemophilus parainfluenzae--67/72 satisfactory responses

Streptococcus pneumoniae --38/42 satisfactory responses

 Penicillin (S)--30/34 satisfactory responses

 Penicillin (I)--4/4 satisfactory responses

 Penicillin (R)--0

 (6 strains not tested for penicillin susceptibility)

Haemophilus influenzae--34/37 satisfactory responses

Mycoplasma pneumoniae--28/29 satisfactory responses (serology results)

Chlamydia pneumoniae--21/23 satisfactory responses (serology results)

Staphylococcus aureus--8/9 satisfactory responses

Moraxella catarrhalis--4/5 satisfactory responses

Enterobacter aerogenes--2/2 satisfactory responses

Enterobacter cloacae--1/2 satisfactory responses

Klebsiella pneumoniae--2/2 satisfactory responses

Streptococcus agalactiae--2/2 satisfactory responses

Neisseria meningitis--2/2 satisfactory responses
Klebsiella oxytoca--1/1 satisfactory response
Streptococcus equisimilis--1/1 satisfactory response
Streptococcus mitis--1/1 satisfactory response
Streptococcus pyogenes--1/1 satisfactory response

Study 352--CAP

Haemophilus parainfluenzae--56/62 satisfactory responses
Streptococcus pneumoniae--27/29 satisfactory responses
 Penicillin (S)--20/21 satisfactory responses
 Penicillin (I)--3/3 satisfactory responses
 Penicillin (R)--0
 (5 isolates not tested for penicillin susceptibility)
Haemophilus influenzae--24/28 satisfactory responses
Mycoplasma pneumoniae--21/23 satisfactory responses (serology results)
Chlamydia pneumoniae--10/13 satisfactory responses (serology results)
Staphylococcus aureus--6/7 satisfactory responses
Streptococcus agalactiae--5/5 satisfactory responses
Moraxella catarrhalis--4/4 satisfactory responses
Neisseria meningitis--4/4 satisfactory responses
Klebsiella pneumoniae--2/4 satisfactory responses
Pseudomonas aeruginosa--2/4 satisfactory responses
Klebsiella oxytoca--3/3 satisfactory responses
Serratia marcescens--3/3 satisfactory responses
Enterobacter cloacae--3/3 satisfactory responses
Streptococcus pyogenes--3/3 satisfactory responses
Acinetobacter anitratus--2/2 satisfactory responses
Streptococcus equisimilis--1/1 satisfactory response
Enterobacter aerogenes--1/1 satisfactory response

Study 356--ABECB

Haemophilus parainfluenzae--134/140 satisfactory responses
Haemophilus influenzae--69/77 satisfactory responses
Chlamydia pneumoniae--37/45 satisfactory responses (serology results)
Moraxella catarrhalis--41/43 satisfactory responses
Streptococcus pneumoniae--37/41 satisfactory responses
 Penicillin (S)--25/29 satisfactory responses
 Penicillin (I)--5/5 satisfactory responses
 Penicillin (R)--0
 (7 isolates not tested for penicillin susceptibility)
Staphylococcus aureus--24/28 satisfactory responses
Klebsiella pneumoniae--18/19 satisfactory responses
Pseudomonas aeruginosa--10/17 satisfactory responses
Enterobacter cloacae--12/13 satisfactory responses
Acinetobacter anitratus--7/7 satisfactory responses
Klebsiella oxytoca--5/6 satisfactory responses

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Acinetobacter lwoffii—3/4 satisfactory responses
Enterobacter aerogenes—4/4 satisfactory responses
Neisseria meningitidis—2/4 satisfactory responses
Serratia marcescens—1/3 satisfactory responses
Streptococcus agalactiae—1/2 satisfactory responses
Streptococcus pyogenes—1/1 satisfactory response
Streptococcus Group G —1/1 satisfactory response
Comamonas acidovorans—1/1 satisfactory response

Study 359—AMS

Streptococcus pneumoniae—18/22 satisfactory responses
 Penicillin (S)—11/12 satisfactory response
 Penicillin (I)—3/3 satisfactory response
 Penicillin (R)—3/4 satisfactory response
 (3 isolates not tested for penicillin susceptibility)
Haemophilus influenzae—17/17 satisfactory responses
Streptococcus sanguis—14/15 satisfactory responses
Staphylococcus aureus—14/14 satisfactory responses
Moraxella catarrhalis—11/11 satisfactory responses
Streptococcus mitis—12/12 satisfactory responses
Neisseria subflava—11/11 satisfactory responses
Streptococcus pyogenes—8/8 satisfactory responses
Streptococcus intermedius—3/5 satisfactory responses
Pseudomonas aeruginosa—4/5 satisfactory responses
Enterobacter aerogenes—4/4 satisfactory responses
Streptococcus salivarius—4/4 satisfactory responses
Micrococcus species—1/3 satisfactory responses
Klebsiella pneumoniae—3/3 satisfactory responses
Streptococcus constellatus—2/3 satisfactory responses
Streptococcus viridans—2/2 satisfactory responses
Neisseria lactamica—1/1 satisfactory response
Neisseria mucosa—1/1 satisfactory response
Neisseria sicca—1/1 satisfactory response
Streptococcus microaerophilic—1/1 satisfactory response
Streptococcus bovis—1/1 satisfactory response
Streptococcus milleri—1/1 satisfactory response
Streptococcus anginosus—1/1 satisfactory response
Acinetobacter anitratus—1/1 satisfactory response

DISK CONTENT STUDIES

Susceptibility test disks containing 2.5, and 10 µg of sparfloxacin were correlated with sparfloxacin MICs obtained using NCCLS broth microdilution methods against 547 bacterial isolates (80). Suggested zone diameter breakpoints were calculated from the regression analysis of scattergrams relating inhibition zone diameters to MICs. Error rates were based on a MIC breakpoint of $\leq 1 \mu\text{g/mL}$. The results of this analysis are shown in TABLE 46. The data show that disks containing 5-µg of sparfloxacin are best. They produced the lowest very major error rate and no major errors. The error rates were low, however, with all three disk masses. The authors state that the 2-µg disks produced zones of inhibition that were too small, and that the 10-µg disk produced large zones with resistant strains. The 5-µg disk produced zones of acceptable size.

TABLE 46
 Comparison of sparfloxacin disk mass for agar diffusion tests

Disk Potency	Zone Diameter (mm) Breakpoints			Interpretive Error (%)		
	Resist.	Intermed.	Suscept.	Minor	Major	Very Major
2-µg	≤ 11	12-14	≥ 15	3.5	0.3	0.3
5-µg	≤ 14	15-17	≥ 18	4.2	0	0.2
10-µg	≤ 16	17-19	≥ 20	4.2	0	0.5

The formulae for the regression lines for each of these disk masses are as follow:

2-µg: $y=13.5104 + -.3177 x$ $R=-.8319$
 5-µg: $y=14.3402 + -.3177 x$ $R=-.7994$
 10-µg: $y=14.6148 + -.3039 x$ $R=-.7562$

One lot of disks containing 5-µg of sparfloxacin that were prepared by Difco were evaluated for real time and accelerated stability (81). On real time stability, the disks were stored under a controlled storage temperature of 2-8°C. On accelerated stability, the disks were stored at an increased temperature of 25 °C to 35°C with humidity greater than 75%. The initial potency of the disks was 129% of label claim. After 40 weeks, the potency was 133% after storage at 2-8°C, 137% after storage at 25°C, and 136% after storage at 35°C. These data show that sparfloxacin disks are stable under all three storage conditions for at least 40 weeks.

Five lots of disks containing 5-µg of sparfloxacin prepared by _____ were tested for stability at 2-8°C (82). The results are shown in TABLE 47.

TABLE 47
 5- μ g sparfloxacin disks at 2-8°C

Stability of <u>Lot No.</u>	<u>Age in Months</u>	Assay	
		<u>(μg per disk)</u>	<u>% of label</u>
910542	0	6.3	126
	38	5.5	110
004527	0	5.2	104
	32	5.4	108
111555	0	6.0	120
	13	5.9	118
310642	0	5.7	114
	22	5.8	116
408502	0	6.3	126
	12	6.0	120

These data show that there is no significant decrease in potency when stored at 2-8°C for periods of up to about 3 years.

MIC BROTH/AGAR DILUTION COMPARISONS

Jones (83) showed that MIC values in Mueller Hinton agar and broth usually were similar or varied by only one dilution (see TABLE 48). In most cases, however, the MICs in agar were one doubling dilution higher than in broth.

TABLE 48
 Sparfloxacin MIC in Mueller-Hinton Agar and Broth

<u>Organism</u>	MIC (μ g/mL)	
	<u>Mueller-Hinton Agar</u>	<u>Mueller-Hinton Broth</u>
<i>E. coli</i> ATCC 25922	≤ 0.015	0.008
<i>E. coli</i> ATCC 35218	0.03	0.015
<i>E. faecalis</i> ATCC 29212	0.5	0.25
<i>P. aeruginosa</i> ATCC 27853	4	0.5
<i>S. aureus</i> ATCC 29213	0.03	0.06

Barry (80) compared MIC values obtained using the standard reference method (Wilkins-Chalgren agar) to those obtained with a broth microdilution method. In this study there was a tendency for broth microdilution MICs to be the same or one doubling dilution lower than in agar. This trend is the same as that observed in Jones study with aerobic reference strains (see TABLE 49).

TABLE 49
 Comparison of methods for determining susceptibility of anaerobic bacteria

MIC Methods Compared Antimicrobial Agent	Ratios of MICs by two methods ^a						Geometric Mean Ratio
	0.12	0.25	0.5	1.0	2.0	4.0	
Microdilution MIC							
Reference MIC	0	3	18	20	12	0	0.85

^a Total number of tests at each MIC ratio.

As indicated above there is a slight tendency for the microdilution test to be lower. As indicated by the geometric mean ratio, however, this tendency is slight and in most cases the results are within one dilution of each other. Since a one dilution difference is usually considered as being equal both agar dilution and broth dilution may be considered as equivalent test methods.

MIC/DISK DIFFUSION CORRELATION STUDIES

Two studies were performed in the United States to determine tentative disk diffusion susceptibility breakpoints for 5- μ g sparfloxacin disks against non-fastidious bacteria (84,85).

Fuchs, Barry, and Pfaller performed agar dilution and disk diffusion tests with 350 bacterial isolates from 27 non-fastidious bacterial species. The isolates were selected to include about 10% (9.7%) that were resistant to sparfloxacin (84). Ofloxacin susceptibility tests were done at the same time to provide internal control data. The data were analyzed to select the inhibition zone diameters that were most consistent with the tentative MIC breakpoints of $\leq 1 \mu\text{g/mL}$ for susceptible, $2 \mu\text{g/mL}$ for intermediate, and $\geq 4 \mu\text{g/mL}$ for resistant. By regression analysis, the zone diameter breakpoint for susceptibility was calculated to be $\geq 19 \text{ mm}$ and the breakpoint for resistance was $\leq 15 \text{ mm}$. With these zone size breakpoints, the error rates were as follows: very major, 0.3%; major, 0; minor, 5.7%; total 6.0%. These error rates are within the limits of $\leq 1.5\%$ for very major errors and $\leq 3\%$ for major errors. The regression line gave the following formula: $y=49.0-3.02x$ with a correlation coefficient of 0.73. The authors were concerned that with these proposed breakpoints, 16 of 20 minor errors were ones in which the disk test indicated greater susceptibility than the MIC category, i.e., an intermediate MIC but susceptible by disk test or a resistant MIC but intermediate by the disk test. The authors found that 12 of these 16 minor errors occurred with members of the genera *Pseudomonas* and *Xanthomonas*. They advised caution in interpreting the result of a disk test which indicates that a pseudomonad is fully susceptible to sparfloxacin. Since this drug is not being proposed for infections caused by pseudomonads, these errors should not be a problem. If the 55

pseudomonads were removed from the scattergram the total error rate for the remaining isolates would be 2.7% (all minor errors). Control tests with ofloxacin provided the 94.6% agreement between the methods.

Unlike the above study, Sutton and Jones (85) chose to include a very high proportion of sparfloxacin resistant isolates (58.3%) among the 300 strains that they selected for determining proposed tentative disk diffusion breakpoints. They also used a microdilution method to determine the MICs. Internal quality control was provided by ofloxacin tests. Quality control organisms were also run and were all within limits. In this study the regression equation was $y=15.8 - 0.36x$ with a correlation coefficient of 0.95. The authors proposed breakpoints were: ≥ 20 mm for susceptible, 17-19 for intermediate, and ≤ 16 for resistant. The error rates with these breakpoints were: very major, 0; major, 0.3%; and minor 5.7%.

In a German study (86), Kayser and Wurst studied 400 clinical isolates using NCCLS methods, 34.5% of these isolates were resistant to sparfloxacin. Using a susceptible breakpoint of $\leq 1 \mu\text{g/mL}$, the authors suggested zone diameter breakpoints of susceptible, ≥ 18 mm; intermediate, 14-17 mm; and resistant, ≤ 13 mm. The regression line had the equation; $y=20.134 - 7.081x$. The correlation coefficient was 0.937. There were 1.25% very major errors, 0.5% major errors, and 6.75% minor errors. These error rates are slightly higher than those seen in the United States studies. These authors also suggested an intermediate range of 4 mm, while most United States studies suggest a 3 mm range. Quality control strains were also tested in this study and were within limits.

A summary of all three studies may be seen in TABLE 50 below.

TABLE 50
 Sparfloxacin tentative disk diffusion criteria for non-fastidious aerobes

Reference	Proposed zone diameter criteria (mm)			% Interpretive Error		
	Susceptible	Intermediate	Resistant	Very Major	Major	Minor
84	≥ 19	16-18	≤ 15	0.3	0.0	5.7
85	≥ 20	17-19	≤ 16	0.0	0.3	5.7
86	≥ 20	16-19	≤ 15	1.25	0.5	6.75

All three studies suggested zone diameter breakpoints that were very similar. The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in the section of this review titled "Correlation of Test Results with Outcome Statistics".

QUALITY CONTROL STUDIES (MIC AND DISK DIFFUSION)

MIC QUALITY CONTROL STUDIES

Sparfloxacin quality control limits for MIC tests with non-fastidious bacteria were determined by NCCLS methods by Barry (87) in 1990. A collaborative study was conducted in five laboratories. Antibiotic powders of known potency were provided to each facility for preparation of microdilution trays, using cation-adjusted Mueller-Hinton broth currently being used at that institution. In addition to the individual laboratory test lots, a common sixth lot of broth was distributed as were standard ATCC control strains. Each laboratory performed five independent tests with their lot of trays and one with the common lot on each of five days against the four quality control strains. Each participant generated 20 MICs with their test lot and 5 with the common lot for each bacterial strain.

Results obtained with *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Escherichia coli* ATCC 25922 are displayed in TABLE 51.

TABLE 51
 Sparfloxacin MIC quality control data

MIC ($\mu\text{g/mL}$)	Number (%) of Times at MIC ^a			
	<i>E. faecalis</i> ATCC 29212	<i>P. aeruginosa</i> ATCC 27853	<i>S. aureus</i> ATCC 29213	<i>E. coli</i> ATCC 25922
≤ 0.002				34 (27)
0.004				<u>31 (25)</u>
0.008				<u>56 (45)</u>
0.016				<u>3 (2)</u>
0.03			<u>28 (22)</u>	1 (1)
0.06			<u>89 (71)</u>	
0.12	<u>1 (1)^b</u>		<u>7 (6)</u>	
0.25	<u>73 (58)</u>		1 (1)	
0.5	<u>51 (41)</u>	<u>3 (2)</u>		
1		<u>114 (91)</u>		
2		<u>8 (6)</u>		
4				

^a Data from common lot and test lots combined

^b Values underlined and bold-faced are included in NCCLS-approved ranges

The limits were set as a three dilution range surrounding the mode or a four dilution range if no "clear-cut" mode is seen. The range must include $\geq 95\%$ of all test results.

For *Enterococcus faecalis* ATCC 29212, 100% of the strains were within the three recommended MIC values of 0.12 to 0.5 $\mu\text{g/mL}$, and they were approved as quality control limits by the NCCLS in June 1994. With *Pseudomonas aeruginosa* ATCC 27853, the mode MIC was 1 $\mu\text{g/mL}$; the NCCLS approved limits of 0.5 to 2.0 $\mu\text{g/mL}$. *Staphylococcus aureus* ATCC 29213 gave MICs of 0.03 to 0.25 $\mu\text{g/mL}$ with a mode of 0.06 $\mu\text{g/mL}$. The NCCLS approved a range of 0.03 to 0.12 $\mu\text{g/mL}$ for this organism. This excluded only one test result so 99% of the data was within limits.

Due to the high activity of sparfloxacin against *Escherichia coli* ATCC 25922, two separate studies were needed to obtain a MIC range. In the initial study (87) as indicated in the above TABLE 51, 32% of the values were at or below the lowest concentration studied. An additional experiment was performed in 1994 in which ten different laboratories tested the same common lot of sparfloxacin daily for ten days, generating 100 values (88). Ofloxacin and ciprofloxacin were run as controls and all results with these two antibiotics were within limits. In this experiment, sparfloxacin MICs ranged from $\mu\text{g/mL}$ with a mode of 0.008 $\mu\text{g/mL}$. Only one test was outside of the range of $\mu\text{g/mL}$, which was approved by NCCLS in January 1995.

The following limits have been set for sparfloxacin MIC Quality Control Limits for aerobes:

ORGANISM	SPARFLOXACIN ($\mu\text{g/mL}$)
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5
<i>Escherichia coli</i> ATCC 25922	0.004-0.016
<i>Pseudomonas aeruginosa</i> ATCC 27853	0.5-2
<i>Staphylococcus aureus</i> ATCC 29213	0.03-0.12

Since the limits for *Pseudomonas aeruginosa* ATCC 27853 are outside of the susceptible range and sparfloxacin is not indicated for this organism, this quality control strain will not be included in the label. The other three quality control strains will be included even though two of the three organisms (*E. coli* and *E. faecalis*) do not have indications for sparfloxacin. If they were eliminated only one quality control strain would be included and it is recommended that at least two strains be used.

DISK DIFFUSION QUALITY CONTROL STUDIES

To obtain zone diameter quality control ranges with non-fastidious bacteria, replicate tests were performed in a six-laboratory collaborative study, using NCCLS methods (89). Each investigator performed 30 separate tests with a different lot of Mueller-Hinton agar. Each test involved three different lots of 5- μ g sparfloxacin disks. Each participant performed 10 additional tests on a sixth lot of Mueller-Hinton agar common to all participants. Ciprofloxacin disks were used as controls and were within limits.

The results of tests obtained with *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 can be seen in TABLE 52. Analysis of the data showed good interlaboratory agreement, both for the common lot and the individual media test lots. All six unique lots of agar and the common lot gave essentially identical zones of inhibition. The mean zone sizes for the three different lots of disks varied from 33.3 to 33.9 mm for *E. coli*, 29.8 to 30.4mm for *S. aureus*, and from 24.6 to 24.7 mm for *P. aeruginosa*, which shows that all three lots of disks were equivalent.

TABLE 52
 Sparfloxacin disk agar quality control data

Organism	Zone diameter in mm. surrounding 5- μ g sparfloxacin disk				
	Median	Mean	Range	1/2 MR ^a	± 2 SD ^b
<i>E. coli</i> ATCC 25922	34	33.7	11	3	31.6-35.8
<i>S. aureus</i> ATCC 25923	30	30.2	7	2	27.9-32.5
<i>P. aeruginosa</i> ATCC 27853	25	24.7	10	3	22.1-27.3

^a 1/2 MR = 1/2 the median of the ranges.

^b ± 2 SD = ± 2 standard deviations.

For *E. coli* ATCC 25922; the mean ± 2 SD rounded out would be 31-36 mm, the median $\pm 1/2$ MR is 31-37 mm. The 31-37 mm range includes 93.0% of the data, by extending the range 1 mm on each side all but 8 zones are within limits and the recommended $\geq 95\%$ of the data would be included. A range of 30-38 mm was accepted by NCCLS.

For *S. aureus* ATCC 25923; the mean ± 2 SD rounded out would be 27-33 mm, the median $\pm 1/2$ MR is 28-32 mm. The range of _____ mm includes 95.4% of the data. The NCCLS recommended a range of _____ mm, which is the larger of the two ranges listed above. Since the narrower range includes only slightly more than the $\geq 95\%$ limit, the larger range should be accepted.

For *P. aeruginosa* ATCC 27853; the mean $\pm$ 2 SD rounded out would be 22-28 mm, the median $\pm$ 1/2 MR is 22-28 mm. This range includes 95.6% of the data. Since the above range includes only slightly more than the 95% limit, the range should be extended by 1 mm on each side. The NCCLS has recommended a range of 21-29 mm and this should be accepted.

The following agar disk diffusion quality control limits are proposed for the 5 μ g sparfloxacin disk.

ORGANISM	SPARFLOXACIN ZONE DIAMETER (mm)
<i>Escherichia coli</i> ATCC 25922	30-38
<i>Pseudomonas aeruginosa</i> ATCC 27853	21-29
<i>Staphylococcus aureus</i> ATCC 25923	27-33

The limits for *Pseudomonas aeruginosa* will not be included since sparfloxacin does not have an indication for this organism and the MIC limits for this organism extended into the nonsusceptible range. Two other quality control strains will be included as recommended.

Haemophilus Quality Control Studies

Sparfloxacin quality control limits for MIC tests with *Haemophilus influenzae* ATCC 49247 were determined by NCCLS methods by Barry (90) in 1991. A collaborative study was conducted in five laboratories. Antibiotic powders of known potency were provided to each facility where broth microdilution trays were prepared with Haemophilus Test Media (HTM) broth. Each laboratory used a different lot of Mueller-Hinton broth which had previously been found to perform satisfactory as HTM broth when tested with agents that have NCCLS control limits. A sixth lot of trays was distributed to all laboratories and served as an internal control. Each laboratory performed five independent tests with their lot of trays and one with the common lot on each of five days. Each participant generated 20 MICs with their test lot and 5 with the common lot for the bacterial strain. MIC values of 0.002 to 0.016 μ g/mL were obtained with a mode of 0.008 μ g/mL. A range of one dilution on each side of the mode provides a range of μ g/mL. Only one value was outside this range.

Two studies were performed to determine the disk quality control limits for *Haemophilus influenzae* ATCC 49247 (91,92). In Barry's first study (91) in 1992, replicate disk diffusion tests were performed in five laboratories. Six lots of Mueller-Hinton agar were used. All six lots had previously been proven to perform satisfactorily when HTM supplements were added. For additional control purposes one laboratory tested all six lots at one time to document comparability of the HTM agars when sparfloxacin and ofloxacin disks were tested. The participants each performed 30 separate tests. Each test involved two different lots of 5 μ g sparfloxacin disk and a single 5 μ g ofloxacin disk that was added as a

control. Each laboratory performed 20 tests on the medium assigned to them and 10 additional tests on a control lot of HTM agar common to all participants. This experiment showed marked variability between laboratories, although the different media performed uniformly when tested side by side. Zone diameters varied from 31 to 46 mm. Many of the ofloxacin zone diameters were out of control limits. Both lots of sparfloxacin disk gave identical zone diameters. Zone size limits of 35-40 mm were calculated but to avoid unrealistically stringent control guidelines, zone size limits of 33 to 42 mm were recommended (2 mm above and below the calculated limits). These recommended limits included only 92% of the data.

Since the first study produced a large variation between laboratories a second study was performed by Barry (92) in 1994. In the second study six laboratories participated. Each participant performed 20 separate tests on the HTM agar assigned to them and 10 tests on the common lot of HTM agar. This generated 360 sparfloxacin zone diameters since two lots of disk were tested. An ofloxacin disk was run as a control. Zone diameters for sparfloxacin ranged from mm. All ofloxacin zone diameters but two were within limits. The medians statistic defined a 33 to 39 mm limit which included 93% of the data. When limits were expanded by adding 1 mm to either end (32 to 40 mm), 98.3% of the data was included. This ranged was accepted by NCCLS and it should be in the label for this drug since *Haemophilus influenzae* is indicated and this species is tested on different media than most other organisms.

The quality control ranges for *Haemophilus influenzae* ATCC 49247 should be as follows:

ORGANISM	MIC RANGE ($\mu\text{g/mL}$)	ZONE DIAMETER RANGE (MM)
<i>Haemophilus influenzae</i> ATCC 49247		

Streptococcus pneumoniae Quality Control Studies

A five laboratory collaborative study was performed to select quality control limits for testing *Streptococcus pneumoniae* ATCC 49619 by a 5 μg sparfloxacin disk or by broth microdilution (93). The disk tests were performed on Mueller-Hinton blood agar and microdilution tests included Mueller-Hinton broth with 3% lysed horse blood. Two different lots of sparfloxacin disk were tested and a ofloxacin disk was tested as a control. Six lots of agar were used and a preliminary screening tests were performed. All six lots gave similar sparfloxacin zone diameters.

In the disk diffusion tests each day for five days the participants prepared five plates with the unique lot assigned to them and 2 plates with a common lot of agar used by all laboratories. Two sparfloxacin disks and one ofloxacin disk were placed onto each of the seven plates inoculated that day. This generated 330 sparfloxacin zone diameters and 165 ofloxacin zone measurements. Laboratory D reported ofloxacin zone diameters that were outside of the NCCLS control limits when using the unique lot of agar assigned to them, but not with the common lot.

**RHONE-POULENC RORER
SPARFLOXACIN TABLETS**

This laboratory performed additional tests on additional common lot plates so that they generated 50 zones measurements on that medium. The lot of agar that was unique to laboratory D performed satisfactorily in the preliminary screening tests, but was not acceptable when tested more thoroughly in laboratory D. Ofloxacin zone determinations on the common lot were all within the 16-21mm control limits. Laboratory D reported zones to be 2 to 4 mm larger than those recorded by the other participants, even though they used the common lot of agar. The unique lot of agar assigned to laboratory D was not used and the 50 zones generated on the common lot in this laboratory were used for the test results from this laboratory.

The median statistic calculated controls limits of 21-25 mm and that would exclude 37 of the 50 sparfloxacin zones reported by laboratory D and 1 of 70 zones reported by laboratory A. To include $\geq 95\%$ of all zones, a 7mm range of 21 to 27 mm would be needed. This range is not inconsistent with those accepted for other quinolones. The NCCLS has not approved *S. pneumoniae* quality control ranges at the present time.

In the broth microdilution test serial dilutions of sparfloxacin were prepared in six different broth media all supplemented with 3% lysed horse blood. Each laboratory tested an unique lot and a common lot of medium. All of the data fell within the range of $\mu\text{g/mL}$. The mode was 0.25 $\mu\text{g/mL}$. The proposed range has not yet been accepted by NCCLS.

The following limits for quality control testing of *Streptococcus pneumoniae* ATCC 49619 will be in the label:

ORGANISM	MIC RANGE ($\mu\text{g/mL}$)	ZONE DIAMETER RANGE (MM)
<i>Streptococcus pneumoniae</i> ATCC 49619		

Neisseria gonorrhoeae Quality Control Studies

A five laboratory collaborative study was undertaken to define the acceptable control limits for sparfloxacin when testing *Neisseria gonorrhoeae*. MIC control limits were defined for a standard control strain, *Neisseria gonorrhoeae* ATCC 49226 (94). Ofloxacin was tested as a control. Antibiotic powders of known potency were provided to each laboratory along with an XV supplement devoid of cysteine and two lots of GC agar (one unique and one common lot). Each laboratory generated 30 MICs on its unique lot and 30 more with the common lot. All but one of the ofloxacin MICs generated were within the control limits. The sparfloxacin MICs ranged from $\mu\text{g/mL}$ with the mode at 0.008 $\mu\text{g/mL}$. A one dilution range on each side of the mode takes in 99% of the data. The recommended range is, therefore, $\mu\text{g/mL}$.

Another study (95) was performed to obtain quality control limits for disk diffusion testing. In this study replicate tests were performed in five laboratories. Six different lots of GC agar and two lots of sparfloxacin disks were evaluated along with ofloxacin disk used as controls. The participants each performed 30 separate tests with *Neisseria gonorrhoeae* ATCC 49226. Each test involved two different lots of sparfloxacin disks and a single lot of ofloxacin disks. Each laboratory tested an unique lot of agar and a lot common to all five laboratories. Each laboratory generated 60 zone diameters with the sparfloxacin disks: 40 on the medium unique to them and 20 on the common lot.

One participant (Lab D) reported extremely variable and unusually large zones of inhibition, even when the tests were repeated. With the ofloxacin disk, Lab D reported 17 of 30 zones to be beyond the acceptable 51 mm maximum and another laboratory reported 13 of 30 zones to be smaller than the acceptable 43 mm minimum. Data from all five laboratories were first analyzed and then laboratory D was excluded and the data was analyzed again. The four laboratory analysis gave ranges with upper limits about 3 mm lower. The medians statistic was used to calculate proposed zone limits. Zone size limits were also calculated as the all-laboratory mean zone diameter ± 2 standard deviations. The two statistics gave results within ± 1 mm of each other. Using the five laboratories: the average standard deviation statistic gave a range of mm and medians statistic gave a range of mm. Using only four laboratories: the average standard deviation statistic gave a range of and the medians statistic gave a range of mm. The author proposes a range of mm. This only includes 72.7% of all data or 85.4% of data from 4 of 5 laboratories. If a range of is used then 84.7% of all data or 98% of data from 4 of 5 laboratories would be included. Since this drug has no indication for this organism at the present time Quality Control Ranges are not needed and will not be in the label.

ANAEROBIC STUDIES

Sparfloxacin is not indicated for any anaerobic bacteria, therefore, no anaerobic studies were performed.

HAEMOPHILUS STUDIES

Barry (96) performed a study to obtain tentative breakpoints for *Haemophilus influenzae*. Broth microdilution and disk diffusion tests were carried out with agar or broth versions of HTM, following the procedure defined by the NCCLS. Studies included 150 isolates of *H. influenzae*: 89 ampicillin-susceptible strains, 20 ampicillin-resistant, β -lactamase-negative strains, and 41 ampicillin-resistant β -lactamase-producing strains. Ampicillin MICs and disk diffusion tests were performed at the same time in order to provide internal control data. No major or very major errors were seen with the ampicillin disk tests and 8% of the strains had minor errors.

Seven of the 20 β -lactamase-negative, ampicillin-resistant strains had MICs of 0.06 or 0.12 $\mu\text{g}/\text{mL}$. All others were inhibited by $\leq 0.03 \mu\text{g}/\text{mL}$. The

author defined breakpoints by the following principles: MIC breakpoint one doubling dilution greater than the maximum MIC recorded for 99% of the strains tested (this value would be $\leq 0.25 \mu\text{g/mL}$); zone diameter breakpoint 3 mm less than the smallest zone recorded for 99% of the tested strains (this value would be ≥ 30 mm). No resistant population could be defined. If strains with decreased susceptibility begin to appear in clinical specimens their responsiveness to chemotherapy needs to be evaluated. The distribution of MICs and zone diameters in this study are shown in TABLES 53 and 54.

TABLE 53

Distribution of Sparfloxacin MICs for *H. influenzae* Barry Study

MIC	β -lac-negative			amp ^R - β -lac-neg			β -lac-positive		
	#	Cum #	Cum %	#	Cum #	Cum %	#	Cum #	Cum %
≤ 0.008	75	75	84.3	10	10	50.0	35	35	85.4
0.016	11	86	96.6	1	11	55.0	4	39	95.1
0.03	3	89	100.0	2	13	65.0	2	41	100.0
0.06				5	18	90.0			
0.12				2	20	100.0			

TABLE 54

Distribution of Sparfloxacin Zone Diameters for *H. influenzae* Barry Study

Zone	β -lac-negative			amp ^R - β -lac-neg			β -lac-positive		
	#	Cum #	Cum %	#	Cum #	Cum %	#	Cum #	Cum %
32							1	1	2.4
33	1	1	1.1				0	1	2.4
35	1	2	2.2				3	4	9.8
36	5	7	7.9	3	3	15.0	4	8	19.5
37	7	14	15.7	5	8	40.0	5	13	31.7
38	8	22	24.7	0	8	40.0	7	20	48.8
39	8	30	33.7	5	13	65.0	7	27	65.9
40	14	44	49.4	1	14	70.0	5	32	78.0
41	17	61	68.5	3	17	85.0	3	35	85.4
42	16	77	86.5	2	19	95.0	2	37	90.2
43	5	82	92.1	1	20	100.0	2	39	95.1
44	3	85	95.5				1	40	97.6
45	1	86	96.6				1	41	100.0
46	2	88	98.9						
47	1	89	100.0						

The suggested breakpoints when testing *H. influenzae* on HTM agar or in HTM broth are as follow:

MIC $\leq 0.25 \mu\text{g/mL}$
 Zone ≥ 30 mm

Susceptible (S)
 Susceptible (S)

NEISSERIA GONORRHOEAE STUDIES

Barry (97) performed a study to obtain tentative breakpoints for *Neisseria gonorrhoeae*. Agar dilution and disk diffusion tests were performed as defined by NCCLS documents (GC agar with a defined supplement which is identical to IsoVitalex but without cysteine). Supplemented GC agar plates were inoculated and the results read after 20-24 hours at 5-7% CO₂. Tests were performed with 149 gonococci, including 23 laboratory-trained strains that were previously serially exposed to subinhibitory concentrations of different fluoroquinolones. These strains displayed decreased susceptibility to all fluoroquinolones. The 126 remaining microorganisms included 22 β -lactamase-producing strains, 28 penicillin-resistant β -lactamase-nonproducers, and 76 penicillin-susceptible strains.

A scattergram was constructed to compare the zone of inhibition around a 5- μ g sparfloxacin disk to the agar dilution MIC for each strain. Interpretive breakpoints were selected to describe the susceptible population as distinguished from the more resistant laboratory-trained strains. For the normally susceptible population, sparfloxacin MIC were $\leq 0.03 \mu\text{g/mL}$ and zones of inhibition were ≥ 39 mm in diameter. In the absence of resistant clinical isolates, interpretive breakpoints for the resistant category could not be defined.

Barry proposed the following criteria for *Neisseria gonorrhoeae*:

MIC $\leq 0.03 \mu\text{g/mL}$	Susceptible (S)
Zone ≥ 39 mm	Susceptible (S)

Since the submitted NDA has no indication for this organism, these breakpoints are not needed and will not be placed into the label.

STREPTOCOCCUS PNEUMONIAE STUDIES

Barry (98) also performed a study to obtain tentative breakpoints for testing *Streptococcus pneumoniae*. Broth microdilution and agar disk diffusion testing were performed according to NCCLS methods. Broth microdilution tests were performed against 654 clinical isolates of *S. pneumoniae* from a wide variety of U.S. medical centers. This group of isolates included 510 strains that were penicillin-susceptible, 80 penicillin-intermediate, and 64 strains that were penicillin-resistant. *S. pneumoniae* ATCC 49619 was run as a quality control strain. All MICs for this QC strain were 0.125-0.5 $\mu\text{g/mL}$, which are the proposed limit for this strain. Most of the clinical strains had MICs between 0.12-0.5 $\mu\text{g/mL}$. The results of this study are shown in TABLE 55.

TABLE 55
 Distribution of *S. pneumoniae* sparfloxacin MICs in Barry study

MIC	Pen-I			Pen-R			Pen-S		
	#	Cum #	Cum %	#	Cum #	Cum %	#	Cum #	Cum %
≤0.008							1	1	0.2
0.016							1	2	0.4
0.03							1	3	0.6
0.06				4	4	6.3	1	4	0.8
0.12	19	19	23.8	30	34	53.1	78	82	16.1
0.25	47	66	82.5	27	61	95.3	333	415	81.4
0.5	13	79	98.8	3	64	100.0	89	504	98.8
1.0	1	80	100.0				6	510	100.0

To evaluate disk diffusion tests, 342 of the 654 isolates were selected. Disk diffusion tests were performed with 5- μ g sparfloxacin disks. The resulting zones of inhibition were plotted against broth microdilution MICs. All strains had MICs $\leq 1 \mu\text{g/mL}$ and all but 4 strains had MICs $\leq 0.5 \mu\text{g/mL}$. All but one of the tested isolates produced zones of inhibition of ≥ 19 mm. One isolate had a 16 mm zone of inhibition and a MIC of $0.125 \mu\text{g/mL}$. Barry suggested that the same criteria be used for *S. pneumoniae* testing that were proposed for the non-fastidious organism. The final breakpoint criteria will be determined by comparing MICs and zone diameters to clinical outcome.

CROSS RESISTANCE/CROSS SUSCEPTIBILITY STUDIES

Representative clinical trial isolates from the NDA clinical trials were tested for susceptibility to sparfloxacin and selected currently available quinolones in strict accordance with NCCLS microdilution procedures. When the number of strains was ≥ 100 for a particular species recovered from the clinical trials, representative numbers of these species were chosen at random. These isolates consisted of 530 gram-positive aerobes and 607 gram-negative aerobes. The results are shown in TABLE 56. These data show that sparfloxacin was highly active *in vitro* against clinically isolated species. Sparfloxacin MICs were most often $\leq 0.25 \mu\text{g/mL}$; MIC₉₀s were $\leq 1.0 \mu\text{g/mL}$ for all species tested. Against most gram-positive bacteria sparfloxacin was usually equal to or twice as potent as ciprofloxacin and about 4-fold better than ofloxacin. Staphylococci that were resistant to the other quinolones were also resistant to sparfloxacin. Sparfloxacin appeared to be more active against *S. pneumoniae* than the other quinolones. Sparfloxacin MIC₉₀ values of $0.25 \mu\text{g/mL}$ were uniformly seen against all strains regardless of penicillin-susceptibility, which were 4-fold lower than those seen with ciprofloxacin.

Very low MIC₉₀s of all quinolones were seen with *H. influenzae* (regardless of β -lactamase production) and *Moraxella catarrhalis*. *Pseudomonas aeruginosa* was the only clinically isolated gram-negative species with $>10\%$ of isolates resistant to sparfloxacin. Sparfloxacin's activity against this species was 4-fold less than ciprofloxacin's and about equal to that of ofloxacin. The relative activity of the three agents varied from species to species, but usually, sparfloxacin and ciprofloxacin exceeded ofloxacin in activity; ciprofloxacin was often more active than sparfloxacin.

TABLE 56
 Activity of sparfloxacin and selected commercially available quinolones
 against bacterial isolates from clinical trials

Organism	No. Isolates	Antibiotic	MIC ($\mu\text{g/mL}$)		MIC Range
			MIC ₅₀	MIC ₉₀	
Gram Positive Aerobes:					
<i>Enterococcus faecalis</i>	105	Sparfloxacin	0.5	1	
		Ciprofloxacin	1	1	
		Ofloxacin	2	2	
<i>Staphylococcus aureus</i>	105 ^a	Sparfloxacin	0.06	0.25	
		Ciprofloxacin	0.25	0.5	
		Ofloxacin	0.25	1	
<i>Staphylococcus epidermidis</i>	40 ^b	Sparfloxacin	0.12	4	
		Ciprofloxacin	0.12	4	
		Ofloxacin	0.25	8	
<i>Staphylococcus haemolyticus</i>	20 ^c	Sparfloxacin	0.12	2	
		Ciprofloxacin	0.12	8	
		Ofloxacin	0.25	8	
<i>Staphylococcus hominis</i>	18	Sparfloxacin	0.12	0.25	
		Ciprofloxacin	0.12	0.25	
		Ofloxacin	0.25	0.5	
<i>Staphylococcus saprophyticus</i>	20	Sparfloxacin	0.12	0.25	
		Ciprofloxacin	0.25	0.25	
		Ofloxacin	1	1	
<i>Streptococcus agalactiae</i>	50	Sparfloxacin	0.25	0.5	
		Ciprofloxacin	0.5	1	
		Ofloxacin	1	2	
<i>Streptococcus pneumoniae</i> (Penicillin-susceptible)	62	Sparfloxacin	0.25	0.25	
		Ciprofloxacin	0.5	1	
		Ofloxacin	2	4	
<i>Streptococcus pneumoniae</i> (Penicillin-intermediate)	33	Sparfloxacin	0.12	0.25	
		Ciprofloxacin	0.5	1	
		Ofloxacin	2	2	
<i>Streptococcus pneumoniae</i> (Penicillin-resistant)	7	Sparfloxacin	0.12	-	
		Ciprofloxacin	0.5	-	
		Ofloxacin	2	-	
<i>Streptococcus pyogenes</i>	50	Sparfloxacin	0.25	0.5	
		Ciprofloxacin	0.5	0.5	
		Ofloxacin	1	2	
Viridans streptococci	20	Sparfloxacin	0.25	0.5	
		Ciprofloxacin	1	2	
		Ofloxacin	2	4	

^a 13 of 105 isolates were oxacillin-resistant. MIC₉₀ range of oxacillin-susceptible strains is $\mu\text{g/mL}$

^b 12 of 40 isolates were oxacillin-resistant. MIC₉₀ range of oxacillin-susceptible strains is $\mu\text{g/mL}$

^c 4 of 20 isolates were oxacillin-resistant. MIC₉₀ range of oxacillin-susceptible strains is $\mu\text{g/mL}$

TABLE 56 (continued)
 Activity of sparfloxacin and selected commercially available quinolones
 against bacterial isolates from clinical trials

Organism	No. Isolates	Antibiotic	MIC ($\mu\text{g/mL}$)		MIC Range
			MIC ₅₀	MIC ₉₀	
Gram-Negative Aerobes:					
<i>Acinetobacter anitratus</i>	20	Sparfloxacin	0.03	0.06	
		Ciprofloxacin	0.12	0.25	
		Ofloxacin	0.25	0.5	
<i>Citrobacter diversus</i>	20	Sparfloxacin	0.03	0.06	
		Ciprofloxacin	0.015	0.06	
		Ofloxacin	0.06	0.25	
<i>Enterobacter aerogenes</i>	20	Sparfloxacin	0.03	0.06	
		Ciprofloxacin	0.03	0.06	
		Ofloxacin	0.06	0.25	
<i>Enterobacter cloacae</i>	21	Sparfloxacin	0.06	0.25	
		Ciprofloxacin	0.03	0.06	
		Ofloxacin	0.12	0.25	
<i>Escherichia coli</i>	105	Sparfloxacin	0.03	0.06	
		Ciprofloxacin	0.03	0.03	
		Ofloxacin	0.12	0.12	
<i>Haemophilus influenzae</i> (β -lactamase negative)	40	Sparfloxacin	0.015	0.015	
		Ciprofloxacin	0.015	0.015	
		Ofloxacin	0.03	0.5	
<i>Haemophilus influenzae</i> (β -lactamase positive)	40	Sparfloxacin	0.015	0.015	
		Ciprofloxacin	0.015	0.015	
		Ofloxacin	0.03	0.03	
<i>Haemophilus parainfluenzae</i>	20	Sparfloxacin	0.03	0.06	
		Ciprofloxacin	0.015	0.12	
		Ofloxacin	0.03	0.06	
<i>Klebsiella pneumoniae</i>	50	Sparfloxacin	0.06	0.06	
		Ciprofloxacin	0.03	0.06	
		Ofloxacin	0.12	0.25	
<i>Moraxella catarrhalis</i>	50	Sparfloxacin	0.015	0.03	
		Ciprofloxacin	0.03	0.06	
		Ofloxacin	0.06	0.12	
<i>Proteus mirabilis</i>	21	Sparfloxacin	0.25	0.25	
		Ciprofloxacin	0.03	0.06	
		Ofloxacin	0.12	0.25	
<i>Pseudomonas aeruginosa</i>	100	Sparfloxacin	0.5	8	
		Ciprofloxacin	0.12	1	
		Ofloxacin	1	8	
<i>Serratia marcescens</i>	20	Sparfloxacin	0.25	0.5	
		Ciprofloxacin	0.06	0.12	
		Ofloxacin	0.25	0.5	

Sparfloxacin and comparators were tested to determine their relative activities against all 273 isolates of *Streptococcus pneumoniae* that were recovered from patients during the course of clinical trials. The following additional antibiotics were tested for reference; ceftriaxone, chloramphenicol, ciprofloxacin, erythromycin, penicillin, tetracycline, trimethoprim/sulfamethoxazole (trimeth/sulfa), and vancomycin. The results are shown in TABLE 57. As shown in this TABLE sparfloxacin was active against all pneumococcal isolates; regardless of the susceptibility status of the isolates to penicillin or erythromycin. Sparfloxacin MIC₅₀ and MIC₉₀ were 0.25 and 0.5 µg/mL, respectively, overall; and 99% (270) of the isolates had MICs ≤0.5µg/mL. All 7 penicillin-resistant isolates were susceptible to 0.25 µg/mL of sparfloxacin and against 34 isolates with intermediate susceptibility to penicillin, sparfloxacin MIC₅₀ and MIC₉₀ values were 0.12 and 0.25 µg/mL, respectively. Identical results were seen with 11 erythromycin-intermediate and 4 erythromycin-resistant isolates.

TABLE 57
 Susceptibility of clinical trial isolates of *Streptococcus pneumoniae* to sparfloxacin
 and a variety of comparator agents

Susceptibility Category (No. Isolates)	Antibiotic	MIC ₅₀	MIC (µg/mL)	
			MIC ₉₀	MIC Range
Total (273)	Sparfloxacin	0.25	0.5	
	Ceftriaxone	<0.06	0.25	
	Chloramphenicol	1	2	
	Ciprofloxacin	0.5	1	
	Erythromycin	<0.015	0.12	
	Penicillin	0.03	0.12	
	Tetracycline	0.5	1	
	Trimeth/Sulfa	0.25/4.8	8/152	
	Vancomycin	0.5	0.5	
Penicillin- susceptible (232)	Sparfloxacin	0.25	0.5	
	Ceftriaxone	<0.06	<0.06	
	Chloramphenicol	1	2	
	Ciprofloxacin	0.5	1	
	Erythromycin	<0.015	0.06	
	Penicillin	0.03	0.06	
	Tetracycline	0.5	1	
	Trimeth/Sulfa	0.25/4.8	0.5/9.5	
	Vancomycin	0.5	0.5	
Penicillin- intermediate (34)	Sparfloxacin	0.12	0.25	
	Ceftriaxone	0.25	1	
	Chloramphenicol	1	2	
	Ciprofloxacin	0.5	1	
	Erythromycin	<0.015	0.5	
	Penicillin	0.12	1	
	Tetracycline	0.5	16	
	Trimeth/Sulfa	4/76	8/152	
	Vancomycin	0.5	0.5	
Penicillin- resistant (7)	Sparfloxacin	0.12	-	
	Ceftriaxone	1	-	
	Chloramphenicol	16	-	
	Ciprofloxacin	0.5	-	
	Erythromycin	2	-	
	Penicillin	4	-	
	Tetracycline	32	-	
	Trimeth/Sulfa	8/152	-	
	Vancomycin	0.5	-	

TABLE 57 (continued)
 Susceptibility of clinical trial isolates of *Streptococcus pneumoniae* to sparfloxacin
 and a variety of comparator agents

Susceptibility Category (No. Isolates)	Antibiotic	MIC ₅₀	MIC (µg/mL)	
			MIC ₉₀	MIC Range
Erythromycin- susceptible (258)	Sparfloxacin	0.25	0.5	
	Ceftriaxone	<0.06	0.12	
	Chloramphenicol	1	2	
	Ciprofloxacin	0.5	1	
	Erythromycin	<0.015	0.06	
	Penicillin	0.03	0.12	
	Tetracycline	0.5	1	
	Trimeth/Sulfa	0.25/4.8	0.5/9.5	
	Vancomycin	0.5	0.5	
Erythromycin- intermediate (11) & -resistant (4)	Sparfloxacin	0.12	0.25	
	Ceftriaxone	0.5	2	
	Chloramphenicol	2	16	
	Ciprofloxacin	0.5	1	
	Erythromycin	2	4	
	Penicillin	0.25	4	
	Tetracycline	2	>32	
	Trimeth/Sulfa	8/152	8/152	
	Vancomycin	0.5	1	

BACTERIOLOGICAL EFFICACY

CORRELATION OF TEST RESULTS WITH OUTCOME STATISTICS

In the clinical trials, patients with infections in non-urinary sites all received the same oral dosage regimen of sparfloxacin. An oral dose of 400 mg was taken on the first day followed by 200 mg daily for two additional days. Since the dosing and overall responses were similar from protocol to protocol, the data have been combined. A separate analysis was conducted for each fastidious species in the event that unique MIC breakpoints were needed. Isolates of *Pseudomonas aeruginosa* were not included in the tabulations to select MIC breakpoints because the species was not a target pathogen. TABLE 58 shows the relationship between MICs and pathogen bacteriological response in the non-urinary tract infections. TABLE 58A shows the relationship between MICs and pathogen bacteriological response for only those pathogens in the Indications and Usage section. TABLE 59 shows the relationship between MICs and eradication rates for the fastidious organisms and for all others. As can be seen from these tables there were very few isolates with MICs ≥ 1 µg/mL. There were a significant number of isolates, however with MICs of 0.5 µg/mL. The eradication rate for these isolates was only slightly less than those for isolates

Cs ≤ 0.25 $\mu\text{g/mL}$, and all isolates with MICs of 1.0 $\mu\text{g/mL}$ were eradicated. the vast majority of isolates with MIC of 0.5 $\mu\text{g/mL}$ were eradicated, the susceptible breakpoint must be at least equal to 0.5 $\mu\text{g/mL}$. Since sparfloxacin and ciprofloxacin have similar pharmacokinetics and the spectrum of activity of sparfloxacin is usually equal to or slightly superior to that of ciprofloxacin, this reviewer feels that both drugs should have equal susceptible breakpoints. The breakpoint for ciprofloxacin is ≤ 1 $\mu\text{g/mL}$. Since the few isolates obtained an MIC of 1 $\mu\text{g/mL}$ were eradicated, this reviewer feels that a susceptible breakpoint of 1.0 $\mu\text{g/mL}$ should be set for sparfloxacin. There were a very few isolates with higher MICs, which in most cases, were also eradicated. From *in vitro* studies it can be seen that resistant organisms (i.e. staphylococci) do exist, and, therefore, an intermediate and resistant breakpoint should be used.

Since *Streptococcus pneumoniae* isolates have MICs that are all ≤ 0.5 $\mu\text{g/mL}$, applying the rule of setting a susceptible breakpoint of one dilution higher than 99% of the isolates with the highest MIC value would give us a breakpoint of 1 $\mu\text{g/mL}$. Since there were only three evaluable isolates with MICs of 0.5 $\mu\text{g/mL}$, this reviewer feels that a breakpoint of 1 $\mu\text{g/mL}$ is not justified at the present time. There were no isolates with a MIC of 1 $\mu\text{g/mL}$ and very few at 0.5 $\mu\text{g/mL}$. Isolates with MICs of 1.0 $\mu\text{g/mL}$ might not be eradicated. **Since there are no resistant isolates at the present time only a susceptible breakpoint should be set.**

Since *Haemophilus influenzae* isolates have MICs that are all ≤ 0.12 $\mu\text{g/mL}$, a susceptible breakpoint of 0.25 $\mu\text{g/mL}$ should be set at the present time. **Since there are no resistant isolates at the present time only a susceptible breakpoint should be set.** This breakpoint is the same as that proposed by Barry in his study using preclinical isolates.

TABLE 60 shows that clinical success rates were very similar to bacteriological eradication rates when compared to the MICs of the isolates.

The following MIC criteria should be used when testing sparfloxacin:

For testing aerobes other than *Haemophilus influenzae* and *Streptococcus pneumoniae*:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 1	(S) Susceptible
2	(I) Intermediate
≥ 4	(R) Resistant

For testing *Haemophilus influenzae*:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 0.25	(S) Susceptible

For testing *Streptococcus pneumoniae*:

<u>MIC ($\mu\text{g/mL}$)</u>	<u>Interpretation</u>
≤ 0.5	(S) Susceptible

No testing of *Neisseria gonorrhoeae* is needed since sparfloxacin is not indicated for this organism.

TABLE 58

Relationship Between Individual MICs and Pathogen Responses

Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Population: All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Acinetobacter anitratus</i>	0.008		1(100)	1		1(100)	1
	0.015	3(100)		3	5(100)		5
	0.03	8(89)	1(11)	9	8(89)	1(11)	9
	0.06	1(100)		1	1(100)		1
	0.12	1(100)		1	1(50)	1(50)	2
<i>Acinetobacter lwoffii</i>	0.008	2(100)		2	2(67)	1(33)	3
	0.015	4(100)		4	4(100)		4
	0.03	1(100)		1	1(100)		1
	0.12				1(100)		1
<i>Aeromonas hydrophilia</i>	0.03	1(100)		1	1(100)		1
<i>Citrobacter freundii</i>	0.015	1(100)		1	1(100)		1
	0.06	1(100)		1	1(100)		1
<i>Comamonas acidovorans</i>	0.06	1(100)		1	1(100)		1
<i>Enterobacter aerogenes</i>	0.015	2(100)		2	2(100)		2
	0.03	3(100)		3	4(100)		4
	0.06	4(100)		4	5(100)		5
<i>Enterobacter agglomerans</i>	0.03				1(100)		1
	0.06	2(100)		2	3(100)		3
<i>Enterobacter cloacae</i>	0.015	2(100)		2	2(100)		2
	0.03	5(100)		6	8(100)		8
	0.06	12(92)	1(8)	13	14(88)	2(13)	16
<i>Enterobacter intermedius</i>	0.06	1(100)		1	1(100)		1

TABLE 58(continued)
 Relationship Between Individual MICs and Pathogen Responses
 RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Enterococcus faecalis</i>	0.25	6(75)	2(25)	8	7(78)	2(22)	9
	0.5	7(78)	2(22)	9	9(82)	2(18)	11
	8				1(100)		1
<i>Enterococcus faecium</i>	0.5				1(100)		1
<i>Escherichia coli</i>	0.008	2(100)		2	3(100)		3
	0.015	7(100)		7	8(100)		8
	0.03	3(100)		3	3(100)		3
	0.06	2(100)		2	2(100)		2
	0.06				1(100)		1
<i>Escherichia hermannii</i>	0.06				1(100)		1
<i>Haemophilus influenzae</i>	0.004	4(100)		4	6(100)		6
	0.008	25(86)	4(14)	29	44(86)	7(14)	51
	0.015	49(91)	5(9)	54	71(91)	7(9)	78
	0.03	7(100)		7	10(91)	1(9)	11
	0.06	2(100)		2	4(100)		4
	0.12		1(100)	1		1(100)	1
	0.004	20(100)		20	26(96)	1(4)	27
<i>Haemophilus parainfluenzae</i>	0.008	18(100)		18	28(100)		28
	0.015	54(98)	1(2)	55	71(97)	2(3)	73
	0.03	39(91)	4(9)	43	57(92)	5(8)	62
	0.06	31(94)	2(6)	33	40(91)	4(9)	44
	0.12	2(100)		2	2(67)	1(33)	3
	0.5	1(100)		1	1(100)		1

TABLE 58(continued)
 Relationship Between Individual MICs and Pathogen Responses

Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Population: All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Klebsiella oxytoca</i>	0.004	1(100)		1	1(100)		1
	0.03	2(100)		2	3(75)	1(25)	4
	0.06	2(100)		2	5(100)		5
	0.25	1(100)		1	1(100)		1
<i>Klebsiella pneumoniae</i>	0.03	5(83)	1(17)	6	5(83)	1(17)	6
	0.06	25(100)		25	30(94)	2(6)	32
	0.12	1(100)		1	1(100)		1
	0.25					1(100)	1
	0.5	1(100)		1	1(100)		1
<i>Micrococcus sp</i>	0.25		1(100)	1		1(100)	1
	1	1(100)		1		1(100)	1
<i>Moraxella catarrhalis</i>	0.004	1(100)		1	1(100)		1
	0.008	4(100)		4	4(100)		4
	0.015	29(91)	3(9)	32	33(92)	3(8)	36
	0.03	16(100)		16	17(100)		17
<i>Morganella morganii</i>	0.12					1(100)	1
	0.25	1(100)		1	1(100)		1
<i>Neisseria meningitidis</i>	0.004	5(71)	2(29)	7	5(71)	2(29)	7
	0.008				1(100)		1
	0.12	1(100)		1	1(100)		1
<i>Neisseria mucosa</i>	0.015	1(100)		1	1(100)		1
<i>Neisseria sicca</i>	0.015	1(100)		1	1(100)		1

TABLE 58(continued)
 Relationship Between Individual MICs and Pathogen Responses

Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Population: All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Neisseria subflava</i>	0.004	2(100)		2	2(100)		2
	0.008	1(100)		1	1(100)		1
	0.015	5(100)		5	6(100)		6
	0.03	1(100)		1	1(100)		1
	0.06	1(100)		1	1(100)		1
<i>Pasteurella multocida</i>	0.015	1(100)		1	1(100)		1
<i>Proteus mirabilis</i>	0.06	1(100)		1	2(100)		2
	0.12	2(67)	1(33)	3	2(67)	1(33)	3
	0.25	3(75)	1(25)	4	4(67)	2(33)	6
<i>Proteus vulgaris</i>	0.12	1(100)		1	1(100)		1
<i>Pseudomonas acidovorans</i>	0.03	1(100)		1	1(100)		1
<i>Pseudomonas aeruginosa</i>	0.008				1(100)		1
	0.015					1(100)	1
	0.03	2(100)		2	2(100)		2
	0.06				1(33)	2(67)	3
	0.12	1(50)	1(50)	2	1(50)	1(50)	2
	0.25	2(67)	1(33)	3	6(75)	2(25)	8
	0.5	11(79)	3(21)	14	14(74)	5(26)	19
	1		1(100)	1		1(100)	1
4					1(100)	1	
<i>Pseudomonas maltophilia</i>	0.12	1(100)		1	1(100)		1
<i>Pseudomonas stutzeri</i>	0.03	1(100)		1	1(100)		1

TABLE 58(continued)
 Relationship Between Individual MICs and Pathogen Responses

Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Population: All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Pseudomonas vesicularis</i>	0.06	1 (100)		1	1 (100)		1
<i>Salmonella arizonae</i>	0.03	1 (100)		1	1 (100)		1
<i>Serratia marcescens</i>	0.06				1(50)	1(50)	2
	0.12	1(50)	1(50)	2	2(67)	1(33)	3
	0.25		1(100)	1		2(100)	2
	0.5				1(100)		1
<i>Staphylococcus aureus</i>	0.03	2 (100)		2	2 (100)		2
	0.06	100(87)	15(13)	115	125(87)	18(13)	143
	0.12	28(97)	1(3)	29	38(93)	3(7)	41
	4				1(100)		1
	8				4(80)	1(20)	5
<i>Staphylococcus auricularis</i>	0.06	1 (100)		1	1 (100)		1
<i>Staphylococcus capitis</i>	0.12	1(100)		1	1(100)		1
<i>Staphylococcus epidermidis</i>	0.06	1 (100)		1	2(100)		2
	0.12	7(100)		7	9(90)	1(10)	10
<i>Staphylococcus haemolyticus</i>	0.12	1 (100)		1	1 (100)		1
<i>Staphylococcus hominis</i>	0.25	1(100)		1	1(100)		1
<i>Staphylococcus simulans</i>	0.06	1(100)		1	1(100)		1
<i>Staphylococcus warneri</i>	0.06	1 (100)		1	1 (100)		1
	0.12	4(100)		4	6(86)	1(14)	7
	0.25	1(100)		1	1(100)		1
<i>Staphylococcus agalactiae</i>	0.12	4(100)		4	5(83)	1(17)	6

TABLE 58(continued)
 Relationship Between Individual MICs and Pathogen Responses

Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Population: All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Streptococcus agalactiae</i>	0.25	15(79)	4(21)	19	20(83)	4(17)	24
	0.5	3(75)	1(25)	4	5(63)	3(38)	8
<i>Streptococcus bovis</i>	0.25	1(100)		1	1(100)		1
<i>Streptococcus equisimilis</i>	0.004	1(100)		1	1(100)		1
<i>Streptococcus grp G</i>	0.015		1(100)	1		1(100)	1
	0.12				1(100)		1
<i>Streptococcus intermedius</i>	0.25	5(100)		5	7(100)		7
	0.5	1(100)		1	2(100)		2
	0.25	3(100)		3	3(100)		3
<i>Streptococcus mitis</i>	0.5		1(100)	1		1(100)	1
	0.06	1(100)		1	1(100)		1
<i>Streptococcus pneumoniae</i>	0.12	2(100)		2	4(100)		4
	0.25	6(100)		6	6(100)		6
	0.004	1(100)		1	1(100)		1
	0.015	3(75)	1(25)	4	3(75)	1(25)	4
	0.03	1(100)		1	1(100)		1
	0.06	4(100)		4	6(100)		6
	0.12	33(94)	2(6)	35	42(93)	3(7)	45
	0.25	35(88)	5(13)	40	51(89)	6(11)	57
	0.5	3(100)		3	5(83)	1(17)	6

TABLE 58(continued)
 Relationship Between Individual MICs and Pathogen Responses

Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Population: All-Treated/Evaluable: (Total)N=2412/1211, (Sparfloxacin)N=1333/668, (Comparator)N=1079/543
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Streptococcus pyogenes</i>	0.008	1(100)		1	1(100)		1
	0.12	1(33)	2(67)	3	2(40)	3(60)	5
	0.25	9(90)	1(10)	10	12(92)	1(8)	13
	0.5	13(87)	2(13)	15	14(88)	2(13)	16
	1	2(100)		2	2(100)		2
<i>Streptococcus salivarius</i>	0.25	1(100)		1	1(100)		1
	0.5				2(100)		2
<i>Streptococcus sanguis I</i>	0.06	1(100)		1	1(100)		1
	0.25	1(100)		1	2(100)		2
	0.5	1(100)		1	1(100)		1
<i>Streptococcus sanguis II</i>	0.12	1(100)		1	1(100)		1
	0.25	3(75)	1(25)	4	3(75)	1(25)	4
	0.5	3(100)		3	3(100)		3
<i>Xanthomonas maltophilia</i>	0.25	1(100)		1	1(100)		1

TABLE 58A
 Relationship Between Individual MICs and Pathogen Responses for Indicated Pathogens
 Protocol: RP64206-301/352/353/356/359 - Sparfloxacin vs Erythromycin/Cefaclor/Ciprofloxacin/Ofloxacin
 Treatment: Sparfloxacin

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total * Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>Enterobacter cloacae</i>	0.015	2(100)		2	2(100)		2
	0.03	6(100)		6	8(100)		8
	0.06	12(92)	1(8)	13	14(88)	2(13)	16
<i>Haemophilus influenzae</i>	0.004	4(100)		4	6(100)		6
	0.008	25(86)	4(14)	29	44(86)	7(14)	51
	0.015	49(91)	5(9)	54	71(91)	7(9)	78
	0.03	7(100)		7	10(91)	1(9)	11
	0.06	2(100)		2	4(100)		4
	0.12		1(100)	1		1(100)	1
	0.5						
<i>Haemophilus parainfluenzae</i>	0.004	20(100)		20	26(96)	1(4)	27
	0.008	18(100)		18	28(100)		28
	0.015	54(98)	1(2)	55	71(97)	2(3)	73
	0.03	39(91)	4(9)	43	57(92)	5(8)	62
	0.06	31(94)	2(6)	33	40(91)	4(9)	44
	0.12	2(100)		2	2(67)	1(33)	3
	0.5	1(100)		1	1(100)		1
<i>Klebsiella pneumoniae</i>	0.03	5(83)	1(17)	6	5(83)	1(17)	6
	0.06	25(100)		25	30(94)	2(6)	32
	0.12	1(100)		1	1(100)		1
	0.25					1(100)	1
	0.5	1(100)		1	1(100)		1
<i>Moraxella catarrhalis</i>	0.004	1(100)		1	1(100)		1
	0.008	4(100)		4	4(100)		4
	0.015	29(91)	3(9)	32	33(92)	3(8)	36
	0.03	16(100)		16	17(100)		17
<i>Staphylococcus aureus</i>	0.03	2(100)		2	2(100)		2
	0.06	100(87)	15(13)	115	125(87)	18(13)	143
	0.12	28(97)	1(3)	29	38(93)	3(7)	41
	4				1(100)		1
	8				4(80)	1(20)	5

TABLE 59
 Relationship between sparfloxacin MICs against baseline pathogens
 and pathogen eradication responses

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>H. influenzae</i>	≤ 0.12	87(90)	10(10)	97	135(89)	16(11)	151
<i>H. parainfluenzae</i>	≤ 0.12	164(96)	7(4)	171	224(95)	13(5)	237
	0.5	1(100)		1	1(100)		1
<i>S. pneumoniae</i>	≤ 0.25	77(91)	8(9)	85	104(91)	10(9)	114
	0.5	3(100)		3	5(83)	1(17)	6
All others	≤ 0.25	402(91)	41(9)	443	493(89)	61(11)	554
	0.5	29(83)	6(17)	35	39(83)	8(17)	47
	1	3(100)		3	3(100)		3
	2			0			0
	4				1(100)		1
	≥ 8				5(83)	1(17)	6

TABLE 60
 Relationship between sparfloxacin MICs against baseline pathogens
 and clinical responses

Pathogen	MIC ($\mu\text{g/mL}$)	-----Evaluable-----			-----All-Treated-----		
		Success # (%)	Failure # (%)	Total Isolates	Success # (%)	Failure # (%)	Total Isolates
<i>H. influenzae</i>	≤ 0.12	84(87)	13(13)	97	131(87)	20(13)	151
<i>H. parainfluenzae</i>	≤ 0.12	158(92)	13(8)	171	212(89)	25(11)	237
	0.5	1(100)		1	1(100)		1
<i>S. pneumoniae</i>	≤ 0.25	78(92)	7(8)	85	106(93)	8(7)	114
	0.5	3(100)		3	6(100)		6
All others	≤ 0.25	398(90)	45(10)	443	486(88)	68(12)	554
	0.5	29(83)	6(17)	35	38(81)	9(19)	47
	1	2(67)	1(33)	3	2(67)	1(33)	3
	2			0			0
	4			0	1(100)		1
	≥ 8				6(100)		6

Sparfloxacin zone diameters against baseline pathogens were correlated with bacteriological and clinical outcome. Since the dosing and overall responses in the non-urinary sites were similar from protocol to protocol, the data were combined. Separate analysis was conducted for each fastidious species to determine if unique zone breakpoints were needed. Isolates of *Pseudomonas aeruginosa* were not included in the analysis.

TABLE 61 shows the relationship between each of the two sets of provisional zone diameter breakpoints suggested in preclinical studies and bacteriological outcome in the non-urinary clinical trials.

The overall correlation (69%) between zone diameters of 16-18 mm with the non-fastidious pathogens and satisfactory pathogen responses in the bacteriologically evaluable patients was somewhat less than the correlation (90%) seen with stains with zones of ≥ 19 mm. The number of observations in the intermediate category (16-18 mm) were small, however, and thus the results were difficult to interpret. There were very few zones (9 strains) in the intermediate category in the bacteriologically evaluable population and no strains had smaller zones. Patients in the all-treated population who were excluded only on the basis of having isolates with resistant zone diameters to comparator drugs were also evaluated. Even with strains having zones at or below the proposed resistant breakpoint, there were 7 or 8 satisfactory pathogen responses. All corresponding clinical responses were satisfactory.

Using the alternate disk diffusion criteria, ≥ 20 mm S/ ≤ 16 mm R, gave very similar correlations between zone diameters and outcome.

Figure 1 shows the scattergram of zone diameters versus MICs for the non-urinary site isolates. A meaningful regression analysis could not be performed since the correlation coefficient was only 0.5720. An error-rate bounded analysis was performed to determine the most appropriate set of zone diameter criteria. Both sets of provisional zone diameter criteria were applied to the zone diameter data obtained from the clinical trial isolates using the MIC breakpoints of ≤ 1 μ g/mL for susceptible, 2 μ g/mL for intermediate, and ≥ 4 μ g/mL for resistant. Application of the 19/15 set of disk criteria produced the lowest interpretive errors (TABLE 62). No very major errors were seen. Since there were fewer errors with the 19/15 breakpoint criteria this set should be the one that is used and will be listed in the label.

For the indicated organisms other than *Streptococcus pneumoniae* and *Haemophilus* species the following zone diameters and responses were seen:

Enterobacter cloacae: one at 21 mm; 1 at 24 mm; 19 at ≥ 25 mm--all eradicated except 1 at ≥ 25 mm.

Klebsiella pneumoniae: 1 at 22 mm; 4 at 23 mm; 9 at 24 mm; 19 at ≥ 25 mm--all eradicated except 1 at ≥ 25 mm.

Moraxella catarrhalis: 1 at 23 mm; 1 at 24 mm; 55 at ≥ 25 mm--all eradicated except for 2 at ≥ 25 mm.

Staphylococcus aureus: 3 at 21 mm; 4 at 23 mm; 15 at 24 mm; 124 at ≥ 25 mm--2 at 21 mm persisted, 1 at 23 mm persisted; 12 at ≥ 25 mm persisted.

Since almost all pathogens that persisted for the indicated organisms had zones that were ≥ 25 mm the breakpoints set above do not need to be altered.

Figure 1

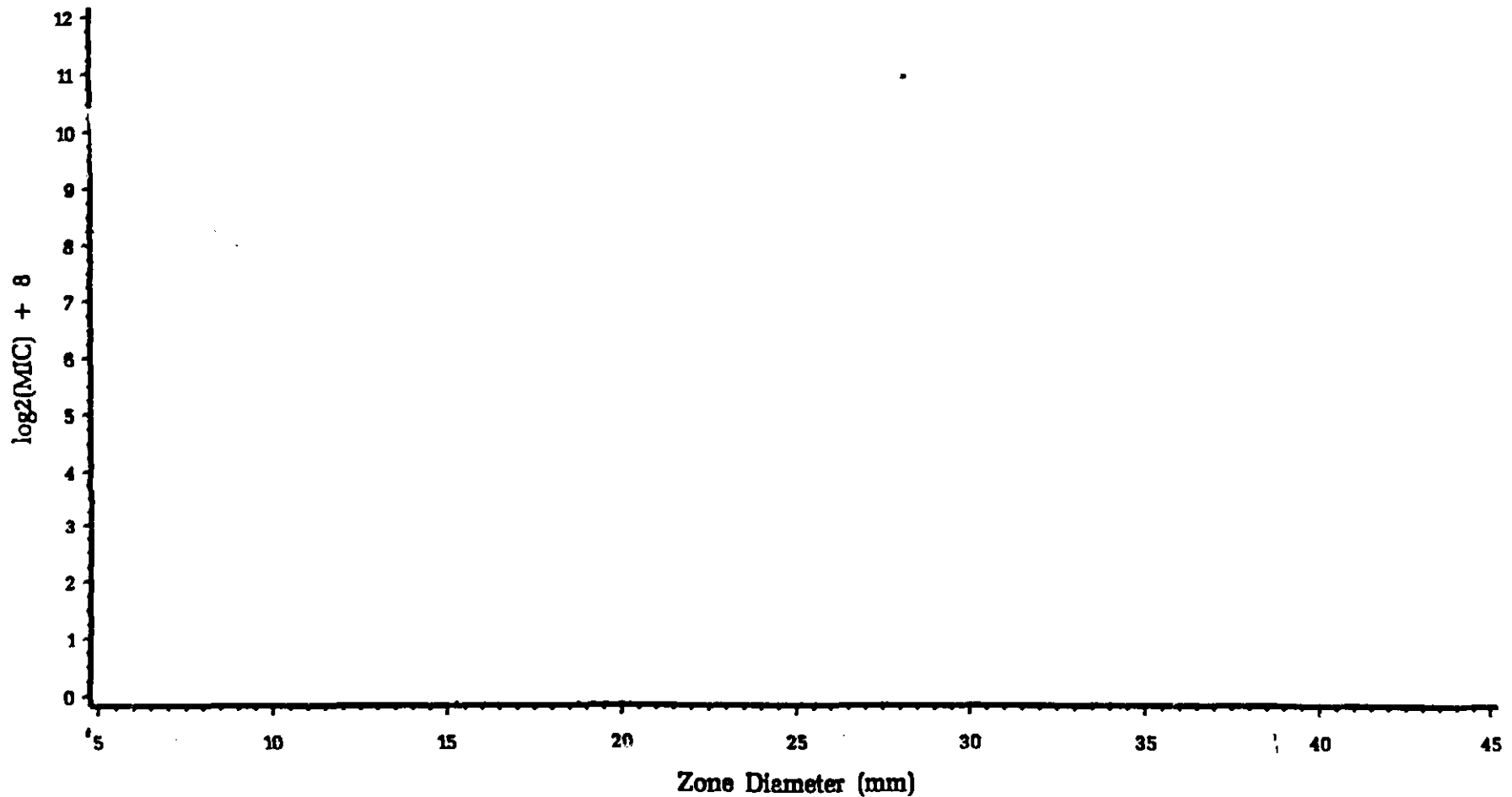
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SPORP_PROJECT_DIRECTORY_TREE\Figure 1 Error Rate Bounded Analysis of MICs and Zone Diameters of Rapidly-Growing Clinical Trial Pathogens

Appendix A - Figure 1 : Error Rate-Bounded Analysis of MICs and Zone Diameters of Rapidly-Growing Clinical Trial Pathogens from the All-Treated Sparfloxacin Treatment Group

Zone Diameters: <=15, 16-18, >=19 mm; MICs: <=1, 2, >=4 ug/ml

Protocol: KP64206_301/352/353/354/359 - Sparfloxacin vs Erythromycin/Cladator/Ciprofloxacin/Ofloxacin
Treatment: Sparfloxacin
Population: All-Treated



7-4-179

Numbers in plot represent number of observations.
MIC Values (ug/ml) corresponding to (log2(MIC) + 8): 0=0.500; 1=1.000; 2=2.000; 3=4.000; 4=8.000; 5=16.000; 6=32.000; 7=64.000; 8=128.000; 9=256.000; 10=512.000; 11=1024.000; 12=2048.000

TABLE 61
 Relationship between sparfloxacin zone diameters against baseline pathogens
 and pathogen eradication responses

Pathogen	ZONE (mm)	Evaluable			All-Treated			
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates	
<i>H. influenzae</i>	≤15			0			0	
	16-18	1(100)		1	1(100)		1	
	≥19	87(90)	10(10)	97	140(89)	17(11)	157	
	≥30	83(89)	10(11)	93	130(88)	17(12)	147	
	≤16			0			0	
	17-19	1(100)		1	1(100)		1	
	≥20	87(90)	10(10)	97	140(89)	17(11)	137	
	<i>H. parainfluenzae</i>	≤15			0			0
16-18		1(100)		1	1(100)		1	
≥19		164(96)	7(4)	171	249(93)	18(7)	267	
≥30		90(96)	4(4)	94	141(93)	10(7)	151	
≤16				0			0	
17-19		1(100)		1	1(100)		1	
≥20		164(96)	7(4)	171	249(93)	18(7)	267	
<i>S. pneumoniae</i>		≤15			0			0
	16-18	3(100)		3	4(100)		4	
	≥19	80(89)	10(11)	90	110(89)	13(11)	123	
	≤16			0			0	
	17-19	4(100)		4	5(100)		5	
	≥20	79(100)	10(11)	89	109(89)	13(11)	122	
	All others	≤15			0	7(88)	1(13)	8
		16-18	9(69)	4(31)	13	13(76)	4(24)	17
≥19		439(90)	47(10)	486	541(89)	69(11)	610	
≤16		1(50)	1(50)	2	9(82)	2(18)	11	
17-19		16(80)	4(20)	20	21(84)	4(16)	25	
≥20		431(90)	46(10)	477	531(89)	68(11)	599	

TABLE 62
 Error rate-bounded analyses of sparfloxacin zone diameter data
 for the clinical trial isolates using provisional disk diffusion criteria

Organism Group	Criteria	No. (%) Discrepancies		No. (%) Agreement
		Major Errors	Minor Errors	
Streptococci	19/15	0 (0)	20 (8.1)	227 (91.9)
	20/16	3 (1.2)	25 (10.1)	219 (88.7)
Fastidious aerobes	19/15	0 (0)	8 (1.4)	556 (98.6)
	20/16	1 (0.2)	10 (1.8)	553 (98)
Other rapid-growing aerobes	19/15	2 (0.2)	18 (1.8)	975 (98.0)
	20/16	3 (0.3)	22 (2.2)	970 (97.5)

Figure 2 and TABLE 63 show the correlation between *Streptococcus pneumoniae* zone diameters and therapeutic efficacy. These data show that except for six isolates with zone diameters of 21 mm, eradication rates were all at least 85-90%. Isolates with zone diameters of 17-20 mm were all eradicated and all patients had a successful clinical response. Since only a susceptible MIC breakpoint is to be used, only a susceptible zone diameter breakpoint should also be given. It appears that the ≥ 19 mm criteria would work well for this organism. Zone diameters of ≥ 19 mm indicates susceptible. There were three evaluable patients with *S. pneumoniae* isolates with zone diameters of 17-18 mm. These isolates had MICs of 0.5 μ g/ml. which indicates they should be susceptible. These zone diameter criteria should be in the label.

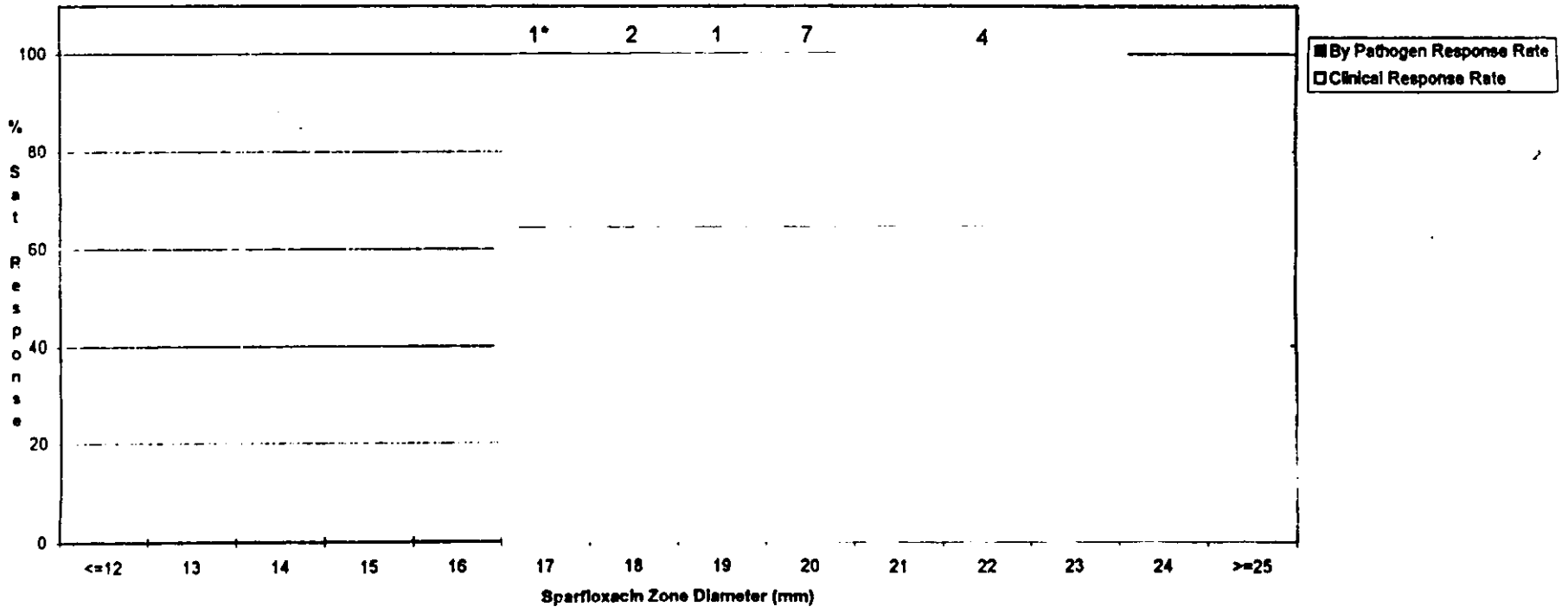
Figure 3 and TABLE 64 show the correlation between *Haemophilus influenzae* zone diameters and therapeutic efficacy. These data show that most zones were larger than 30 mm and that all the isolates that persisted had zone diameters ≥ 30 mm. Most of the persisting isolates had zone diameters of 36-38 mm. It appears that at the present time all isolates are susceptible and that the size of the zone does not correlate well with bacteriological outcome. This reviewer feels that zone diameter criteria should not be set for this species and that MIC testing be performed. The sponsor has suggested that a ≥ 30 mm zone diameter, determined in preclinical testing, be used as a susceptible breakpoint. If this criteria is used then all the isolates with zones between 18-29 mm, which were eradicated in the clinical trials would be left in limbo (since there is no category set except for susceptible). **No zone diameter criteria for *Haemophilus influenzae* will be in the label.** It will be stated that an MIC should be determined for these isolates.

Since this drug is not approved for *Neisseria gonorrhoeae* no breakpoint criteria will be listed for this species in the label.

Figure 2

Appendix A - Figure 2: Correlation of Therapeutic Efficacy Data with Reference Laboratory Zone Diameters for Selected Organisms from Indications

Organism: Streptococcus pneumoniae



7-4-168

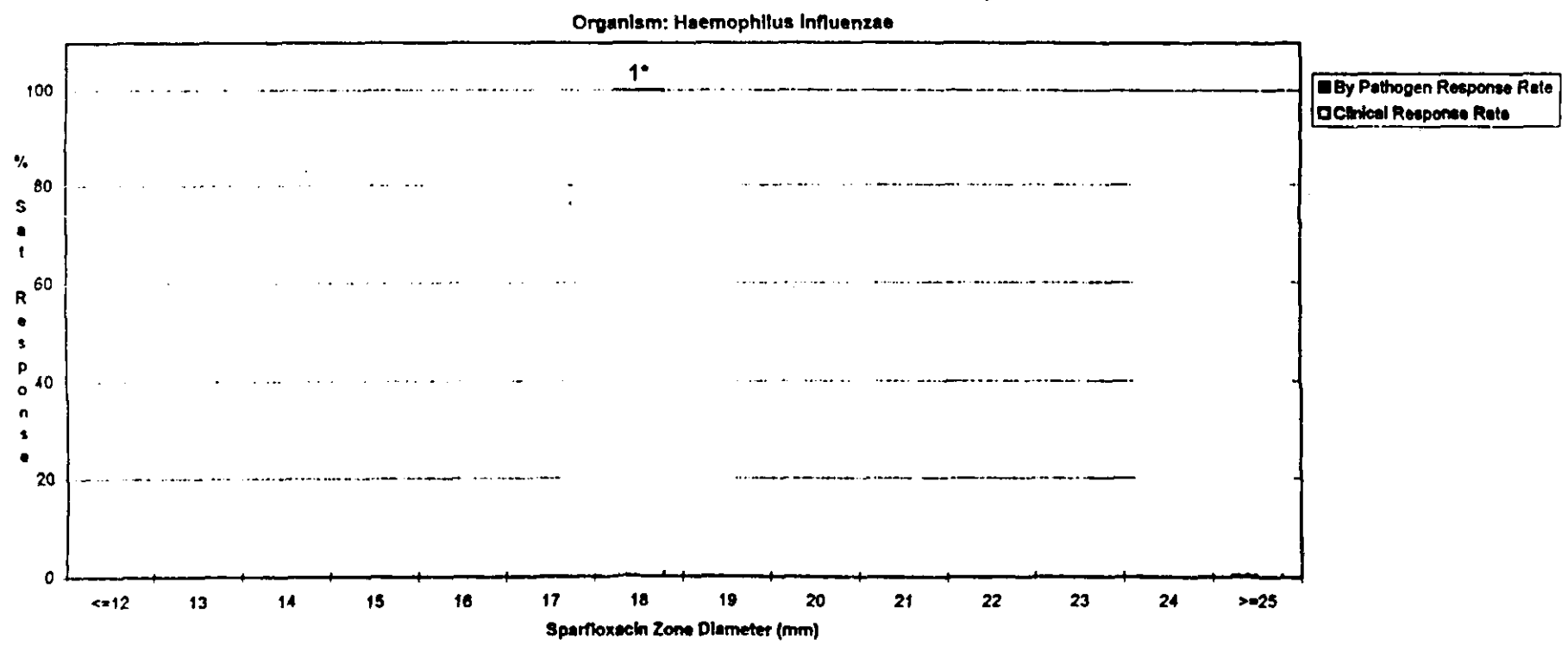
* Number of Strains

TABLE 63
 Relationship between sparfloxacin zone diameters against *S. pneumoniae*
 and pathogen eradication responses

Pathogen	ZONE (mm)	Evaluable			All-Treated		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>S. pneumoniae</i>	17	1(100)		1	1(100)		1
	18	2(100)		2	3(100)		3
	19	1(100)		1	1(100)		1
	20	7(100)		7	8(100)		8
	21	4(67)	2(33)	6	7(70)	3(30)	10
	22	4(100)		4	7(100)		7
	23	16(84)	3(16)	19	20(87)	3(13)	23
	24	8(89)	1(11)	9	13(87)	2(13)	15
	25	19(95)	1(5)	20	24(96)	1(4)	25
	26	4(100)		4	8(89)	1(11)	9
	27	9(82)	2(18)	11	10(83)	2(17)	12
	28	2(100)		2	4(100)		4
	29	1(100)		1	1(100)		1
	30	4(80)	1(20)	5	5(83)	1(17)	6
	31	1(100)		1	1(100)		1
	32				1(100)		1

Figure 3

Appendix A - Figure 3: Correlation of Therapeutic Efficacy Data with Reference Laboratory Zone Diameters for Selected Organisms from Non-UTI Indications



7-4-171

* Number of Strains

TABLE 62
 Relationship between sparfloxacin zone diameters against *H. influenzae*
 and pathogen eradication responses

Pathogen	ZONE (mm)	Evaluable			All-Treated		
		Eradicated # (%)	Persisted # (%)	Total Isolates	Eradicated # (%)	Persisted # (%)	Total Isolates
<i>H. influenzae</i>	18	1(100)		1	1(100)		1
	21				1(100)		1
	25	1(100)		1	1(100)		1
	26	1(100)		1	2(100)		2
	28	1(100)		1	3(100)		3
	29	1(100)		1	3(100)		3
	30	11(100)		11	14(93)	1(7)	15
	31	5(83)	1(17)	6	8(80)	2(20)	10
	32	7(88)	1(13)	8	13(87)	2(13)	15
	33	4(100)		4	8(89)	1(11)	9
	34	4(100)		4	9(90)	1(10)	10
	35	11(92)	1(8)	12	21(95)	1(5)	22
	36	7(78)	2(22)	9	11(73)	4(27)	15
	37	6(100)		6	7(100)		7
	38	6(67)	3(33)	9	9(75)	3(25)	12
	39	2(67)	1(33)	3	3(75)	1(25)	4
	40	15(94)	1(6)	16	17(94)	1(6)	18
	41	1(100)		1	3(100)		3
	42	4(100)		4	6(100)		6
	43				1(100)		1

The following zone diameter criteria should be used when testing sparfloxacin:

For testing aerobes other than *Haemophilus* species and *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	(S) Susceptible
16-18	(I) Intermediate
≤ 15	(R) Resistant

For testing *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	(S) Susceptible

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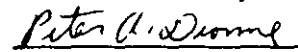
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6 Pages 152-159
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Draft Labeling

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Peter A. Dionne
Microbiologist, HFD-520

cc: Orig. NDA 20-677
HFD-520/Division File
HFD-520/MO/NMoledina
HFD-520/Pharm/Ellis
HFD-520/Chem/BShetty
HFD-520/Micro/PDionne
HFD-520/CSO/FLesane
HFD-520/GLMO/Albaerhe

Concurrence Only:
HFD-520/DepDir/LGavrilov.ch
HFD-520/GLMicro/ATSheldon
Anil B.D. 10/28/96

AS 10/29/96

E A + Fonsi

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT**

FOR

ZAGAM®

(sparfloxacin)

200 mg Tablets

NDA 20-677

**Division of Anti-Infective Drug Products
(HFD-520)**

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FINDING OF NO SIGNIFICANT IMPACT

for

ZAGAM®

(sparfloxacin)

200 mg Tablets

NDA 20-677

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

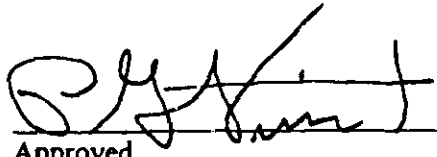
The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

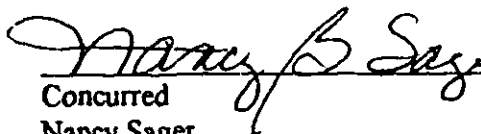
In support of their new drug application for ZAGAM®, Rhône-Poulenc Rorer Pharmaceuticals, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Sparfloxacin is a chemically synthesized drug which is administered as a 200 mg tablet in the treatment of patients with bacterial infections resulting in pneumonia and bronchitis. The drug substance is manufactured by the The finished dosage form is manufactured by Rhône-Poulenc Rorer, Republic of Ireland, and packaged by Rhône-Poulenc Rorer, Puerto Rico. The finished drug product will be used in hospitals and by out-patients throughout the United States.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

07/25/96 
DATE Approved
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

7/25/96 
DATE Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

Zagam® (sparfloxacin)

TITLE: Environmental Assessment for Zagam® NDA

Non-Confidential (FOI) Version

Section 1: **Date** **March 4, 1996**

Section 2: **Applicant** **Rhône-Poulenc Rorer
Pharmaceuticals, Inc.**

Section 3: **Address** **500 Arcola Road
Collegeville, PA 19426-0107**

Section 4: **Description of the Proposed Action**

4.A) **Requested Approval**

Rhône-Poulenc Rorer is submitting a new drug application (NDA) for Zagam® (sparfloxacin) for the treatment of bacterial infections resulting in pneumonia and bronchitis. The drug product is a round white film-coated tablet containing 200 mg of sparfloxacin drug substance. The tablets are packaged into blisters or HDPE bottles.

4.B) **Need for the Action**

Clinical studies have demonstrated that Zagam® offers an effective treatment for certain serious bacterial infections. Approval of this NDA would make this treatment available to patients in the United States.

4.C) Production Locations

1. The drug substance sparfloxacin will be manufactured by manufacturing facility.

2. The drug product, Zagam® will be manufactured and packaged into blisters at the Rhône-Poulenc Rorer facility in Nenagh, Ireland.

Rhône-Poulenc Rorer
Linsbunny Industrial Estate
Nenagh, Co. Tipperary
Republic of Ireland

3. For drug product to be packaged into bottles, the finished tablets received in bulk from Rhône-Poulenc Rorer Nenagh will be packaged into HDPE bottles at the Rhône-Poulenc Rorer facility in Manati, Puerto Rico.

Rhône-Poulenc Rorer
Road 604 Coto Norte Industrial Park
Manati
Puerto Rico

4.D) Locations of Use

Zagam® will be used in hospitals for in-patient use and by patients for out-patient use throughout the United States.

4.E) Disposal Sites

Returned drug product (Zagam®) will be sent from the Rhône-Poulenc Rorer Distribution Centers for disposal via incineration at the permitted incineration facility of

Incineration Site:

Air Quality Permit No: 4953-025-9154
Expiration Date: No. Expiration Date
Solid Waste Permit Number: 025-059P (INC)
Expiration Date: No Expiration Date
Permitting Authority: Georgia Department of Natural Resources
Environmental Protection Division

Section 5: Identification of Chemical Substances

5.A) Introduction

Basic information concerning the drug substance sparfloxacin and the excipients in the drug product Zagam® is provided in this section.

5.B) Drug Substance - Sparfloxacin

5.B.I) Names and Codes

USAN/INN: Sparfloxacin

Drug Product: Zagam®

Code Numbers: RP 64206, CI-978, AT-4140

Chemical Names:

CA Index Name: 3-quinolinecarboxylic acid, 5-amino-1-cyclopropyl-7-(cis-3,5-dimethylpiperazinyl) - 6,8-difluoro-1,4-dihydro-4-oxo-

Systematic Name: 5-amino-1-cyclopropyl-7-(cis-3,5-dimethylpiperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

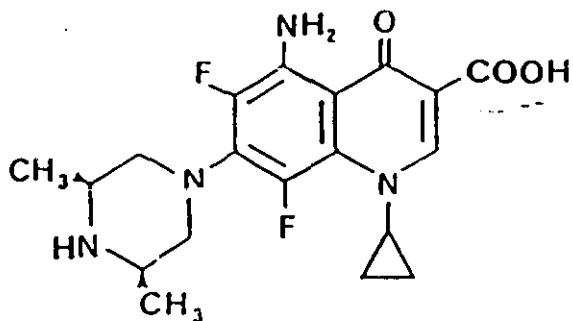
CAS Number: 110871-86-8

5.B.II) Structural Information and Description

Molecular Formula: C₁₉H₂₂F₂N₄O₃

Molecular Weight: 392.41

Chemical Structure:



RP 64206, Sparfloxacin

Physical Description: Odorless, yellow crystalline powder

5.C) Drug Product Excipients

The drug product excipients for Zagam® are identified in Table I (Confidential, Attachment I) along with the corresponding CAS registration numbers for each excipient. The amount of each excipient relative to the amount of drug substance sparfloxacin is provided in Table I. The drug product Zagam® is a coated tablet which contains 200 mg of the drug substance sparfloxacin. Based upon the nature of the excipients, all of which are common compendial products, no further information is provided for the excipient materials.

5.D) Drug Substance Impurities

The impurities in the drug substance sparfloxacin are controlled at levels well below one percent and therefore there is no further information provided for the individual impurities in this environmental assessment.

Section 6: Introduction of Substances into the Environment

6.A) Production of Drug Substance - Sparfloxacin

1. Substances Expected to be Emitted

The drug substance sparfloxacin is prepared via a five step synthetic process by site. The Sparfloxacin manufacturing is carried out in a dedicated production building designed for the process. The Confidential Attachment II lists by name the chemical materials used in the process to produce sparfloxacin. Along with the name of each material is the quantity in grams of each chemical per kilogram of sparfloxacin produced. The Attachment III declaration certifies that none of the materials utilized in the process is in the category of OSHA regulated substances. The Confidential Attachment IV describes the overall process in a stepwise manner. For each step the waste streams generated are designated by type of waste, chemical constituents and destination. Each waste stream is identified by a number for correlation with the confidential table of waste volumes provided in Attachment V. As indicated in the table, the volume of each waste is given relative to a "Confidential" Kg. lot of sparfloxacin. As noted in the Attachment V, the waste streams are directed to the site sewage and activated sludge treatment, for removal by for incineration or for removal as solid waste by for landfill. Attachment VI provides two statements of compliance, by the Health Center Director for the Prefecture, for the with respect to the proper disposal of industrial waste and compliance with environmental standards.

2. Controls Exercised

Engineering controls are in place in the to minimize emissions to the environment. As indicated previously, there is a site waste water treatment facility with a total capacity of 800 tons/day. The treatment is by an activated sludge process that operates to the standard described in Attachment VII. operates with a set of "Standard Codes" or operating procedures that include the disposal of wastes and the monitoring of emissions. See Confidential Attachment VIII for a description of the environmental monitoring plan for the twelve months of 1995.

3. Compliance with Applicable Emission Requirements

Attachment VI contains two statements of compliance for the site. These statements were prepared by the Director of the Prefecture that includes the site, both original version and English Translation are provided. The MSDS for sparfloxacin is provided as Attachment IX.

4. Effect of Approval on Compliance with Current Emission Requirements

Production of sparfloxacin has been carried-out at the facility for approximately two years. The incremental change resulting from approval of this application is not expected to have an adverse impact on the ability of to comply with existing emission requirements.

6.B) Drug Product - Zagam®

1. Substances Expected to be Emitted.

The bulk drug substance sparfloxacin is processed at the RPR Pharmaceuticals, LTD site in Nenagh, Republic of Ireland to produce drug product tablets and the tablets are coated to prepare Zagam®. The process is a normal pharmaceutical manufacturing process which employs pharmacopeal excipients (see Confidential Attachment I). The process does not include any chemical modification or treatment of the sparfloxacin drug substance and it does not involve the use of any organic solvents. None of the materials used at the Nenagh site in the production of Zagam® tablets are in the category of OSHA regulated substances as defined by SARA 313. Provided in Attachment X is a summary of the governmental permit and license numbers applicable to the disposal of waste water and solid waste streams from the Zagam® tablet, tablet coating and blister packaging processes at the RPR Nenagh site. As a normal pharmaceutical tablet process the primary waste generated is the result of equipment cleaning. Damaged or rejected drug substance will be returned to the sparfloxacin production site for proper disposition via recovery or disposal. Rejected or returned drug product are expected to be minimal. Drug product that must be sent for disposal will be sent for incineration. The following information is provided with respect to the disposal of solid waste by the contractor identified in Attachment X.

Waste Handler: O'Brien Waste Disposal & Recycling Co.
Permit Number: Letter issued August 9, 1994 in accordance with Article 5 of the EC waste regulations of 1979

Expiration Date: No Expiration Date
Permitting Authority: Tipperary (North Riding) County Council
Landfill Facility: County Landfill
Facility Operator: Tipperary (North Riding) County Council

2. Controls Exercised

Provided as Confidential Attachment XI is a description of the engineering and procedural controls in place at the Nenagh site to insure minimization of emissions from the Zagam® process. As a part of the description, there is also a listing of operating procedures which are relevant to the control of waste emissions from the site.

3. Compliance with Applicable Emission Requirements

Provided as Attachment XII is a statement of compliance for the RPR Nenagh site by the responsible RPR official for the site. The statement applies to the production of Zagam® drug product tablets at the site.

4. Effect of Approval on Compliance with Current Emission Requirements

The volume of Zagam® tablets produced at the Nenagh site will not have a significant impact on the utilities consumption or upon the ability of the site to meet current emission requirements.

6.C) Drug Product HDPE Bottle Packaging

1. No sparfloxacin drug substance is processed at the RPR Manati site, and therefore disposal will not be required. Drug product bulk tablets will be packaged and labeled at the Manati site. The operations of packaging and labeling are strictly controlled by inventory and shipping procedures. The need for disposal of drug product is anticipated to be minimal. Any drug product for disposal will be sent for incineration by Savannah Energy Systems Company, as described for returned drug product in Section 4.E above. Liquid wastes from the packaging of Zagam® tablets will be from equipment washing, these wastes will be discharged to the process lines to be treated appropriately. The facility currently operates under extensions of the permit number GDA-92-210-037 with the Puerto Rico Aqueducts and Sewage Authority until completion of modifications to the pretreatment facility. Rhône-Poulenc Rorer Puerto Rico adheres to the National Pollutant Discharge Elimination System (NPDES) storm water discharge associated with industrial activity, general Permit No. RPR 00A047 and Best

Management Practices for pollution prevention and spill management.

There is expected to be no hazardous waste material generated as a result of the Zagam® packaging and labeling. Non-hazardous solid waste generated in the process will be sent for incineration:

Waste Handler: Commercial Incineration Corporation
Licensee Number: SR-0057 (Renewal of DS-1)
Expiration Date: January 19, 1998
Permitting Authority: Committee for Environmental Quality, PR

Incineration Facility: Commercial Incineration Corp., Carolina, PR
Permit Number: SI-93-0002
Expiration date: January 19, 1997
Permitting Authority: Committee for Environmental Quality, PR

2. Compliance with Applicable Emission Requirements

Provided as Attachment XIII is a statement of compliance related to the Zagam® packaging and labeling operations at the Manati site.

3. Effect of Approval on Compliance with Current Emission Requirements

The packaging and labeling of Zagam® tablets at the Manati site will not have an adverse impact on the ability of the site to meet current emission requirements.

6.D) Expected Introduction Concentrations

In the fifth year of commercial production, the total quantity of sparfloxacin drug substance projected to be produced for the preparation of Zagam® drug product for use in the United States is "Confidential" Kg. The total drug substance quantity would be expected to enter public and private sewage systems as a result of drug product use. Based on these assumptions, an EIC of "Confidential" ppm or "Confidential" ppb can be calculated. The EIC calculation has been made in accordance with the example shown in Section III.D.6.E.i. of the "Guidance for Industry" document provided by CDER in November of 1995. Based upon the calculated EIC which is below 1 ppb, the Tier 0 approach is adopted for this application and the information, related to sparfloxacin drug substance and Zagam drug product, for format items 7, 8, 9, 10, and 11 is not included in this application. Format item 15 information is provided only as it applies to the format items 1 to 6, 12 and 13 of this application.

Section 7: Fate of Emitted Substances in the Environment

The Tier 0 approach is taken for this application and the information for format item 7 is excluded.

Section 8: Environmental Effects of Released Substances

The Tier 0 approach is taken for this application and the information for format item 8 is excluded.

Section 9: Use of Resources and Energy

The Tier 0 approach is taken for this application and the information for format item 9 is excluded.

Section 10: Mitigation Measures

The Tier 0 approach is taken for this application and the information for format item 10 is excluded.

Section 11: Alternatives to the Proposed Action

The Tier 0 approach is taken for this application and the information for format item 11 is excluded.

Section 12: List of Preparers

The following individual has prepared this environmental assessment for Zagam®. A copy of the preparer's CV is provided as Attachment XIV.

William L. Studt, Director, Global Process Chemistry/Regulatory Liaison
Ph.D., Organic Chemistry
Rhône-Poulenc Rorer Pharmaceuticals, Inc.

Section 13: Certification

Attachment XV contains a certification as to the veracity of this document.

Section 14: References

None

Section 15: Attachments

- I. Zagam® Drug Product Excipients - Confidential
- II. Sparfloxacin Process Materials List - Confidential
- III. Process Materials Declaration
- IV. Sparfloxacin Process Waste Streams - Confidential
- V. Waste Streams Volume and Destination - Confidential
- VI. Suzuka Site Compliance with Emissions Requirements
- VII. Waste Water Treatment Standards
- VIII. Suzuka Site Environmental Monitoring - Confidential
- IX. Sparfloxacin - MSDS
- X. Nenagh - Disposal Permits
- XI. Nenagh - Environmental Controls - Confidential
- XII. Nenagh - Certification of Environmental Compliance
- XIII. Manati - General Compliance Statement
- XIV. CV of Preparer - William Studt
- XV. Certification

ATTACHMENT I

Zagam® Drug Product Excipients

Confidential

ATTACHMENT II

Sparfloxacin Process Materials List

Confidential

ATTACHMENT III

Process Materials Declaration

DECLARATION

I, Hiroaki Kinugasa, Director of

DECLARE

that none of chemical materials used by
to prepare SPARFLOXACIN at the site are
in the category of OSHA regulated substances.

H. Kinugasa
Hiroaki Kinugasa

Date: 1995. 6. 8.

(June 8, 1995)

ATTACHMENT IV

Sparfloxacin Process Waste Streams

Confidential

ATTACHMENT V

Waste Streams Volume and Destination

Confidential

ATTACHMENT VI

Suzuka Site Compliance with Emissions Requirements

November 14, 1994

Re: Proper disposal of industrial waste

Based on the inspection performed on November 2nd, 1994 in accordance with Article 19 of the Disposal and Cleaning of Industrial Waste Act, I hereby confirm that the
of _____ has complied with the disposal method of industrial
waste in accordance with Article 19 of the above mentioned Act for the last 2 years.

Name of the Facility:
Address of the Facility:

Director,

(Ref. no. 227-3)

November 14, 1994

Re: **Certificate of compliance with environmental standards in accordance with the Anti-Pollution laws**

Based on the inspection of _____ performed on November 2nd, 1994 in accordance with Article 22 of the Anti-Water Pollution Act and Article 26 of the Anti-Air Pollution Act, I hereby confirm that _____ has complied with the Anti-Pollution laws for the last 2 years as follows:

- 1) Sewage specifications and amount limit as outlined in the Anti-Water Pollution Act
- 2) Specifications outlined in Item 1 of Article 4 of the Anti-Air Pollution Act and outlined in the Ordinance based on the Item 3 of Article 3 of Anti-Water Pollution laws
- 3) Air pollutant specifications as outlined in the Anti-Air Pollution Act and Pollution Control Ordinance set forth by the Mie Prefectural Government

Name of the Facility:
Address of the Facility:

Director,

(Ref. no. 227-3)

ATTACHMENT VII

Waste Water Treatment Standards

Environmental Assessment

The Environmental Assessment is not requested by the Environmental Control Laws of Japan. However, overall operation and any manufacturing practice in this plant are performed in compliance with the National and Local Government Laws concerned to the Environmental Controls.

Waste water generated in this plant is treated by the systems with a total capacity of 800t / day to the standard designated as follows :

Systems : Activated sludge process

Capacity : 800 t/day

Disposal water standard : pH 5.8 ~ 8.6

BOD 130(100) mg/L

SS 130(100) mg/L

Solid waste materials are removed by _____ to a landfill.
Waste solvent, sewage and solvent distilled residue are stored in tanks,
carried out by _____ and incinerated.
_____ provide
written assurance as to final disposal of all waste materials, and these
company's capability to safely dispatch waste materials and disposal sites
were confirmed by our inspection.

ATTACHMENT VIII

Suzuka Site Environmental Monitoring

Confidential

ATTACHMENT IX

Sparfloxacin - MSDS

1. IDENTIFICATION**SPARFLOXACIN****1.1 Manufacturer****1.2 Emergency contact**

: RHONE-POULENC RORER PHARMACEUTICALS, Ltd. -
Libbunny Industrial Estate NENAGH - Co. TIPPERARY
REPUBLIC of IRELAND

Phone

: (353) 67 32 222

2. CHEMICAL CHARACTERIZATION

CAS Number

: 110871-88-8

Chemical Name : Sparfloxacin

Molecular Formula : $C_{19}H_{22}F_2N_4O_3$

Relative molecular mass: 392.41

3. HAZARDS IDENTIFICATION

NONE

4. FIRST AID MEASURES

Skin contact

: flood exposed skin with water immediately

Eye contact

: irrigate immediately with clean water for at least 15 minutes.

Ingestion

: get medical help immediately and show container or label

5. FIRE-FIGHTING MEASURES

5.1 Fire extinguishing agents

: waterspray, foam, dry chemical

5.2 Fire extinguishing agents-not suitable

: hosepipe

5.3 Specific hazards fire or explosion

: combustible; toxic fumes are emitted

5.4 Special protective equipment for firefighters : wear breathing apparatus

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal Precautions

: protective dust mask, impervious gloves, chemical safety goggles

6.2 Environmental Precautions

: picking up and incineration in an approved installation.

6.3 Methods for cleaning up

: wash with plenty of water.

7. HANDLING AND STORAGE

7.1 Handling

: use with adequate ventilation

7.2 Storage

: stable material under normal storage conditions.

RHONE D.P.C. EUROPE

 RHÔNE-POULENC

8. EXPOSURE CONTROLS / PERSONAL PROTECTIVE EQUIPMENT

8.1 Respiratory Protection	: protective dust mask
8.2 Hand Protection	: impervious gloves (latex)
8.3 Eye Protection	: chemical safety goggles
8.4 Skin Protection	: resistant protective clothing
8.5 Personal protection comments	: shower after working

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Appearance	: yellow crystal or crystalline powder
9.2 Odour	: odorless
9.3 pH	: not applicable
9.4 Boiling point	: not applicable
9.5 Melting point	: 266°C with decomposition
9.6 Flash point	: not applicable
9.7 Flammability (solid)	: no
9.8 Auto-ignition temperature	: no
9.9 Explosion properties	: no
9.10 Oxidizing properties	: no
9.11 Vapour Pressure	: not applicable
9.12 Density	: 0.65 (apparent)
9.13 Water Solubility	: practically insoluble
Ethanol, Methanol	: 0.8 g/l and 1.4 g/l respectively
Dimethylsulfoxide	: 3 g/l at 25°C
9.14 Partition coefficient n-octanol/buffer solution pH 7.4	: 2 to 2.6
9.15 Partition coefficient chloroforme/buffer solution pH 7.4	: 50

10. STABILITY AND REACTIVITY

10.1 Conditions to avoid	: heat, light, naked flame and moisture
10.2 Materials to avoid	: none to our knowledge
10.3 Hazardous decomposition products	: on combustion, product is decomposed and toxic fumes are emitted : carbon and nitrogen oxides, fluor compounds.

11. TOXICOLOGICAL INFORMATION

LD 50 p.o. rat : greater than 5000 mg/kg
(CHEMOTHERAPY, TOKYO, 1991 (39))

Toxicity in repeated administration : electrocardiographic modifications were observed in the dog (increased QT and QTc intervals) at 25 mg/kg, which represented Cmax and AUC values 4 to 5 fold higher than those observed in man after repeated administration of 200 mg/day.

Teratogenesis (reproduction) : gives cardiac anomaly in the rat from 250-300 mg/kg. At 300 mg/kg, Cmax and AUC₀₋₂₄ were about 7 fold higher than the values observed in man after repeated administration of 200 mg/day. Such anomalies were not observed in the rabbit and the monkey.

Phototoxicity test : positive.

(F. ROUET expert report 5/07/93)

RHONE D.P.C. EUROPE

 RHÔNE-POULENC

12. ECOLOGICAL INFORMATION

- 12.1 Mobility : no data available
 12.2 Persistence and degradability : no data available
 12.3 Bioaccumulation : no data available
 12.4 Ecotoxicity : not applicable

13. DISPOSAL CONSIDERATIONS

Appropriate Methods: (chemical product and/or contaminated packaging)

- incineration : yes
 recycling : no
 landfilling : no

14. TRANSPORT INFORMATION

Not restricted

15. REGULATORY INFORMATION

no classification, no labeling

N.B. : Comply with national legislation.

16. OTHER INFORMATION

- 16.1 Warning Statements : based on currently available data, this product does not meet the OSHA definition of a hazardous substance. However, good industrial hygienic practice should be used in handling it.
 16.1 Use : pharmaceutical use, antibacterial.
 The trade name of the drug product obtained is Zagam in the European countries.
 16.2 Main literature references Rhône D.P.C. Europe

IMPORTANT

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication and is in our opinion consistent with the state of general scientific and technical knowledge at that date but we cannot accept liability for any loss, injury or damage which may result from its use. In compiling the Data Sheet we have taken into account all proper applications of the substance of which we are aware and any user of the substance should consult us before applying it to any novel or unusual use. We shall use our best endeavours to ensure that any revision of this Safety Data Sheet is sent to all customers to whom we have directly supplied this substance, but we must point out that it is the responsibility of any intermediate supplier to ensure that such revision is passed to the ultimate user. If any such ultimate user wishes to make arrangements for revisions to be sent to him direct, we shall, if so notified, be glad to make the necessary entry in our records. The information given in this Safety Data Sheet is designed only as a guidance for the safe handling, storage and use of the substance. It is not a specification nor does it guarantee any specific properties.

ATTACHMENT X

Nenagh - Disposal Permits



Rhône-Poulenc Rorer Pharmaceuticals Limited

Supplying the World from Ireland

Lisburny Industrial Estate, Nenagh, Co. Tipperary, Republic of Ireland
Telephone 067 32222 (National) +353 67 32222 (International) Fax +353 67 32249

Permits for the Disposal of Waste Water and Solid / Liquid Wastes

The following permits are applicable for the disposal of waste water from the Rhone Poulenc Rorer site at Nenagh, Co. Tipperary, Ireland.

- Nenagh Urban District Council, Licence To Discharge Trade of Sewage Effluent, Licence No. 20/168C(1/1) dated 28th February 1984.

The disposal of solid waste is contracted to a licenced waste disposal company. The company has been issued with the appropriate permit.

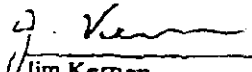
- Tipperary (North Riding) County Council, Permit To Collect, Transport and Tip Refuse, issued to O'Brien Waste Disposal & Recycling Co.

Hazardous waste for incineration (principally organic liquids) is disposed of in the UK. The appropriate contractor registrations are as follows:

- Waste disposal contractor - Licence Number ESX/298003/B issued by East Sussex County Council (UK)
- Haulage contractor - Licence Number LAN/490364 issued by Lancashire County Council (UK)
- Transfer site operator - Toxic and Dangerous Waste Storage and Treatment Permit, dated 16th September 1994, issued by Clare County Council (IRL)
- Incineration Site - Authorization Number AG7946 issued by E.P.A. (UK)

The Nenagh plant does not as yet require an air emissions licence, however, in preparation for same a base line study has been carried out and indicates that the plant would satisfy the appropriate regulatory limits. It is expected that the Nenagh site will be required to apply for a new Integrated Pollution Control Licence within the next couple of years and this will include a stipulation on air emissions.

For and on behalf of
Rhône Poulenc Rorer


Jim Kerman
Engineering Manager

19/12/95
Date

ATTACHMENT XI

Nenagh - Environmental Controls

Confidential

ATTACHMENT XII

Nenagh - Certification of Environmental Compliance



Rhône-Poulenc Rorer Pharmaceuticals Limited

Supplying the World from Ireland

Lisburny Industrial Estate, Nenagh, Co. Tipperary, Republic of Ireland
Telephone 067 32222 (National) -353 67 32222 (International) Fax +353 67 32249

Certification of Environmental Compliance

Rhone-Poulenc Rorer certifies that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in applicable local, national and European environmental regulations applicable to the formulation of Zagam tablets at its facility in Nenagh, Ireland.

For and on behalf of
Rhone Poulenc Rorer

C. Kerran

Jim Kerran
Engineering Manager

19/12/95
Date

ATTACHMENT XIII

Manati - General Compliance Statement



RHÔNE-POULENC RORER INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA. 19426-0107
TEL 610-454-8000

GENERAL COMPLIANCE STATEMENT

Rhone-Poulenc Rorer, Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the product Zagam at its facilities in Manati, Puerto Rico as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the packaging of Zagam at its facilities in Manati, Puerto Rico.

A handwritten signature in cursive script, reading 'Christine L. Hegedus', written over a horizontal line.

Christine L. Hegedus
Director,
Health, Safety and Environment

ATTACHMENT XIV

CV of Preparer - William Studt

NDA 28-677

8 OF 8

CURRICULUM VITAE

William L. Studt, Ph.D.

Director
Global Process Chemistry & Regulatory Liaison
RHÔNE-POULENC RORER PROCESS CHEMISTRY & BIOCHEMISTRY

EDUCATION:

- 1969 BA Eastern Michigan University, Ypsilanti, Michigan (Chemistry)
- 1973 Ph.D. The University of Michigan, Ann Arbor, Michigan (Organic Chemistry)
- 1974 Postdoctoral Fellow, Sterling Chemistry Laboratory, Yale University, New Haven, Ct.

EXPERIENCE:

- 1/95 - present Director, Global Process Chemistry/Regulatory Liaison, Rhône-Poulenc Rorer Process Chemistry & Biochemistry
- 10/89 - 12/94 Director, Process Research and Development (US), Rhône-Poulenc Rorer Central Research
- 3/86 - 10/89 Department Director, Process Research & Development, Rhône-Poulenc Rorer Central Research
- 1/84 - 3/86 Department Manager, Exploratory Chemistry and Development Support, William H. Rorer, Inc.
- 1/81 - 1/84 Section Manager, Medicinal Chemistry, William H. Rorer, Inc.
- 5/75 - 1/81 Section Head, Medicinal Chemistry, William H. Rorer, Inc.
- 9/74 - 5/75 Group Leader, Medicinal Chemistry, William H. Rorer, Inc.
- 7/74 - 9/74 Senior Organic Chemist, Medicinal Chemistry, William H. Rorer, Inc., Fort Washington, PA.

ATTACHMENT XV

Certification

Certification

The undersigned certifies that the information contained in this environmental assessment is true, accurate and complete to the best of his knowledge and that of Rhône-Poulenc Rorer.



William Studt, Ph.D.
Process Chemistry & Biochemistry
Rhône-Poulenc Rorer.

March 4, 1996
March 4, 1996

Co Corres

ORIGINAL

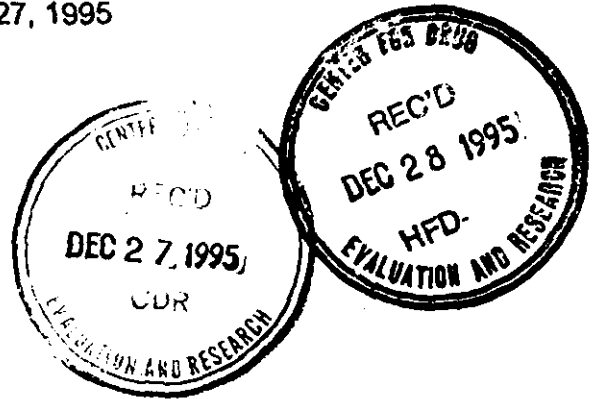


RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

December 27, 1995

Mary Fanning, M.D., Director
Division of Anti-Infective Drug Products
(HFD-520)
Center for Drug Evaluation and Research
Office of Drug Review II
Document Control Room #12B-30
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857



NDA #20-677
Zagam® (sparfloxacin)
Serial #
ORIGINAL NEW DRUG
APPLICATION

Dear Dr. Fanning:

In accordance with 21 CFR 314.50 (b)(1) of the Federal Food, Drug and Cosmetic Act, Rhone-Poulenc Rorer Pharmaceuticals Inc. is submitting an Original New Drug Application for Zagam® (sparfloxacin) which demonstrates the efficacy and safety of the product in the treatment of patients with community acquired pneumonia, acute bacterial exacerbations of chronic bronchitis

In accordance with 21 CFR 314.08 (b)(2), RPR believes that, upon approval of this application, they will be entitled to five years of marketing exclusivity during which no person may submit a 505 (b)(2) application or abbreviated new drug application under section 505 (j) of the Act for a drug containing the same active moiety. To the best of our knowledge, a drug has not previously been approved under section 505 (b) of the Act containing any active moiety in the drug Zagam®. Therefore, in accordance with 21 CFR 314.50 (j) RPR is claiming such exclusivity as described in 21 CFR 314.108 (b)(2).

Mary Fanning, M.D.

Page -2-

Case report form tabulations for the individual medical reports are included in the appendices of each report when available and are located in the Clinical Data and Statistical sections of the application. An index to these tabulations is provided in Item 11: Case Report Form tabulations.

The format and content of the various sections of the NDA were discussed and agreed to at a May 15, 1995 pre-NDA meeting, the minutes of which we have previously submitted to the IND.

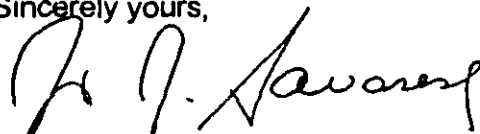
In accordance with the Prescription Drug User Fee Act of 1992, a check (Check No. 762849, in the amount of _____ was sent to the Food and Drug Administration, Philadelphia, Pennsylvania on December 21, 1995. The application was assigned the User Fee Identification Number 2941.

As required by Section 306 (k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application, Rhone-Poulenc Rorer did not and will not use in any capacity the services of any person disbarred under subsections 3-6(a) or (b) of the act.

Rhone-Poulenc Rorer Pharmaceuticals Inc. considers the information in this application to be confidential and proprietary and we request that no portions thereof be disclosed to third parties, under FOI or otherwise, without first obtaining written consent from Rhone-Poulenc Rorer.

If you have any questions or require any additional information during review of this application, please contact me at (610) 454-5471.

Sincerely yours,



John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs Liaison

JJS/dps

Attachment

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

New Drug Application:#20-677
Form FDA 356h
Item 1

Zagam®(sparfloxacin)

Item 1.3: Statement of Organization

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete archival copy (blue binder) which is 610 volumes and one additional copy each of the relevant technical sections for review.

<u>ITEM</u>	<u>REVIEW VERSION</u>	<u>BINDER COLOR</u>	<u>VOLUMES</u>
--	Archives	Blue	610
3.	Chemistry Manufacturing and Control	Red	8
4.	Methods Validation	Red	1
5.	Preclinical Data	Yellow	48
6.	Human Pharmacokinetics	Orange	53
7.	Microbiology	White	14
8.	Clinical Data	Tan	387
10.	Statistical Data	Green	387
11.	Case Report Form	Tan	1
	Tabulations/ Comments	Green	1

Volume numbers were assigned in a consecutive fashion from 2.2 to 2.34. Page numbers reflect the Item number, the volume within that Item, and the consecutive page within that volume. For example, page 8-2-50 is the 50th page in the second volume of Item 8, which in this submission is the 128th overall volume (Volume 1.128).

Item 1.3: Statement of Organization (continued)



The following gives a brief hierarchical representation of the dossier.

Item(s)	Volume(s)	Subject(s)	Volume(s)
1 and 2: Index and Application Summary	1.1-1.2		
3. Chemistry, Manufacturing and Control	1.3-1.10	CMC Summary	1.3
		Drug Substance	1.3
		Drug Product	1.3
		Environmental Assessment	1.9
4. Samples, Methods Validation and Labeling	1.11		
5. Nonclinical Pharmacology and Toxicology	1.12-1.59	Summary Volume	1.12
		Pharmacology	1.13
		Toxicology	1.14
		ADME	1.52
6. Human Pharmacokinetics and Bioavailability	1.60-1.112	Summary Volume	1.60
7. Microbiology Section	1.113-1.126	Summary Volume	1.113
8. Clinical Data Section	1.127-1.513	Summary Volume	1.127
		Tables/Background Overview	1.127
		ISE	1.491 - 1.495
		ISS	1.496 - 1.512
		Clinical Trials	1.128 - 1.487
9. Safety Update Report	1.1		
10. Statistical Data Section: Same as Item 8			
11. Case Report Form Tabulations - Located in Item 8			
Stray Comments Listings	1.514		
12. Case Report Forms	1.515-1.610		
13 and 14: Patent Information and Certification	1.1		
15: Other - Not Applicable			



RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ANCOLA HONAY
P.O. BOX 1200
COLLEGEVILLE, PA 19426 0107
TEL. 610-454-8000

October 15, 1996

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
3rd Floor, Room N303
9201 Corporate Boulevard
Rockville, MD 20857

Zagam® (sparfloxacin 200 mg tablets)
NDA 20-677

Re: CMC questions

Dear Dr. Feigal:

On July 8, 1996, Dr. Shetty phoned RPR and described five minor deficiencies uncovered during his review of the Zagam NDA. We were also notified by Dr. Shetty on July 29, 1996, about five questions raised by the chemists reviewing the methods validation package. RPR clarified these issues with Richard Needham in your Philadelphia District Office on August 12, 1996. During recent conversations with Drs. Shetty and Moledina we have been encouraged to submit responses to these chemistry questions as soon as possible. Therefore, enclosed please find RPR's responses to Dr. Shetty's five deficiencies (Attachment 1) and to the five methods validation questions (Attachment 2).

Because the issues addressed in this submission relate to 21CFR §314.50(d)(1), RPR is sending a copy of this submission to our home FDA District Office.

If you have any questions about this submission, please feel free to contact me at (610) 454-5471 or Mr. Mark Learn at (610) 454-3053.

Sincerely,

John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

JJS:ML/dps
Attachments

cc: Vithal Shetty, Ph.D.
Ms. Debra Pagano; Philadelphia District Office



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Center for Drug Evaluation and Research
Office of Training and Communication
Freedom of Information Staff HFD-205
5600 Fishers Lane 12 B 05
Rockville, Maryland 20857

May 8, 1998

In Response Refer to File : F98-05533

S.S. HAU
P. O. BOX 391557
CAMBRIDGE, MA 02139-0016

Dear Requester;

This is in response to your request of February 20, 1998, in which you requested the approval package for NDA 20677, MIRAPEX. Your request was received in the Center for Drug Evaluation and Research on February 26, 1998.

The documents you have requested (Mirapex) are enclosed. "In order to help reduce processing time and costs, certain material has been deleted from the record(s) furnished to you because a preliminary review of the record(s) indicated that the deleted information is not required to be publicly disclosed. If, however, you desire to review the deleted material, please make an additional request at the following address:

Food and Drug Administration
Freedom of Information Staff, HFI-35
5600 Fishers Lane
Rockville, MD 20857

Should the Agency then deny this information, you would have the right to appeal such denial. Any letter of denial will explain how to make this appeal." SMG 2460.7(3)

Charges of \$223.50 (Search \$14.50, Review \$140.00, Reproduction \$69.00, Computer time \$0.00) will be included in a monthly invoice. **DO NOT SEND ANY PAYMENT UNTIL YOU RECEIVE AN INVOICE.**

If there are any problems with this response, please notify us in writing of your specific problem(s). Please reference the above file number.

Sincerely,

J. Santford Williams, R.Ph.

J. Santford Williams, R.Ph.

Freedom of Information Officer

Office of Training and Communications

Freedom of Information Staff, HFD-205

Direct Line (301)827-3456

Enclosure:

690 pages, of approval package for MIRAPEX, NDA 20667

PARTIAL RESPONSE

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020667

Trade Name: MIRAPEX

Generic Name: PRAMIPEXOLE DIHYDROCHLORIDE

Sponsor: PHARMACIA & UPJOHN, INC

Approval Date: 07/01/97

**INDICATION(s): PROVIDES FOR THE TREATMENT
OF THE SIGNS AND SYMPTOMS OF IDIOPATHIC
PARKINSON'S DISEASE.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020667

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology	X			
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020667

APPROVAL LETTER



Registered Mail
Return Receipt Requested

NDA 20-667

JUL 1 1997

Pharmacia & Upjohn, Inc.
Attention: Ms. Julianna Stewart
Regulatory Affairs Department
7000 Portage Road
Kalamazoo, MI 49001-0199

BEST POSSIBLE COPY

Dear Ms. Stewart:

Please refer to your new drug application dated December 26, 1995, and your January 7, 1997 resubmission received January 10, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex, (pramipexole dihydrochloride), tablets, 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg.

We also refer to an Agency Approvable letter dated December 23, 1996, and we acknowledge receipt of your submissions dated:

January 6, 1997	January 8, 1997	January 10, 1997
January 24, 1997	January 27, 1997	February 5, 1997
February 10, 1997	February 11, 1997	March 6, 1997
June 12, 1997	June 17, 1997	

The User Fee goal date for this application is July 10, 1997.

This new drug application provides for the treatment of the signs and symptoms of idiopathic Parkinson's Disease.

We have completed the review of this application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-667. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ENCLOSURE

APPEARS THIS WAY
ON ORIGINAL

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE
ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE
PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

FEB 27 1997

Safety Review

Application Information

NDA 20-667

Pharmacia & Upjohn

NDA Safety Update Submission Date: January 10, 1997

Drug Name

Generic: Pramipexole

Proposed Trade Name: Mirapex™

Drug Characteristics

Pharmacological Category: Dopamine agonist

Proposed Indications: 1) Primary symptomatic treatment of Parkinson's disease.
2) Adjunctive treatment of Parkinson's disease.

Dosage Forms: Oral tablets in 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg

Proposed Use:

Pramipexole should be given T.I.D.. Dosages should be increased gradually from a starting dose of 0.375 mg/day and should not be increased any sooner than every 5-7 days. In most studies a 7 week dose escalation scheme was followed: 0.125 T.I.D., 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D., 1.25 T.I.D., and at the 7th week to the maximum dose of 1.5 T.I.D. Withdrawal should occur gradually over a 7-day period.

Safety Update Reviewer: John D. Balian, M.D.

Date of Review: February 27, 1997

1 Summary of Pramipexole Safety Update Review

The original ISS summarized the safety experience for 1408 patients with about 815 person-years (PYs) of pramipexole use, most of it (800 PYs) coming from the Parkinson's Disease (PD) trials. This safety update brings the total to 2146 patients with 1925 PYs of pramipexole exposure, most of it (1878 PYs) coming from the PD trials. This increased exposure does not change the findings, add new clinically significant adverse events (AEs), or new safety issues to the original review.

In the safety update, there is doubling of the number of deaths (15 new cases) in the pramipexole patients, but this is a reflection of more than doubling of the exposure, as noted above. The reports on serious AEs, dropouts, and common AEs were much of the same when compared to the original review. Since most of the new information comes from open-label uncontrolled trials, and most of the patients are not uniquely exposed, incidence rates are not presented here. There were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, or aplastic anemia. No new cases of rhabdomyolysis were reported (there was one case in the original review).

In summary, pramipexole use is not associated with increased risk for deaths, serious AEs, or dropouts in PD patients. While there was a clear increase in CV effects (syncope and OSH) attributable to pramipexole in the phase 1 healthy volunteers, no significant differences from placebo were observed in the phase 2/3 trials.

APPEARS THIS WAY
ON ORIGINAL

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APPEARS THIS WAY
ON ORIGINAL

2 Background

Following the review of NDA 20-667 (submitted by Pharmacia & Upjohn on Dec 26, 1995), the agency informed the sponsor, with a letter dated Dec 23, 1996, that the application is approvable for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), upon the submission and favorable review of a safety update. The present submission is the safety update report on pramipexole using 2/29/96 as the cutoff date.

2.1 Overview of the Safety Update

The present submission is a compilation of data from the original submission and data analyzed since that submission. The sponsor's presentation of the information follows the same format as the original submission, unfortunately, there is no separation of the new data from the old, thus making a clear identification of the new data very cumbersome. As in the case of the original Integrated Safety Summary (ISS), the sponsor provides pooled descriptions and analyses of the treatment emergent adverse events (AEs), but upon special request, a supplement with separate tables of early-treatment (ET) and advanced-treatment (AT) PD patients was also submitted.

3 Methods of Safety Update Review

This review will follow the format used in reviewing the original submission: stratification of patients into ET and AT populations with a separate review and analysis of the RCTs in the ET and AT patient populations (3 studies from the ET trials and 5 from the AT trials), and wherever pertinent, mention the findings from the other studies (open-label PD, schizophrenia, and depression).

The majority of the new safety data comes from the uncontrolled ongoing PD trials and newly completed trials in schizophrenia and depression. Since this update does not include any further completed RCTs in ET patients, the comparative information on the ET patients presented in the NDA review has not changed. There is one new completed RCT in the AT patient population and this review will update all pertinent tables in this patient population to reflect the addition of the newly completed RCT.

It is not practical to discuss incidence rates for the overall database, since most of the new information comes from open-label, uncontrolled trials, and most of the patients are not uniquely exposed (they were counted in the original NDA review, and they simply have continued their participation in the uncontrolled trials). For this reason, denominators are left out of most tables to avoid confusion.

3.1 Review of Safety Issues Identified in The Sponsor's Proposed Labeling

The sponsor's most recent updated proposed label, 1/27/97, is a very close approximation of

the division's revised version forwarded to the sponsor with the approvable letter. The sponsor has completed the missing sections requested by the division and has responded to outstanding issues. Besides few language changes (for clarity), the only glaring difference between the division's version and the sponsor's, is the sponsor's deletion of the item pertaining to rhabdomyolysis in the precautions section. The sponsor's rationale is that it brings undue attention to a case that the sponsor considers a "unique circumstance". Of minor consequence, the sponsor has not incorporated the data from the newly completed RCT in AT population in the presentation of the 1% AE table in the adverse events section.

4 Review of Findings

4.1 Description of the Pramipexole Development Program

The original ISS described pramipexole treatment emergent AEs based upon observations from 19 Clinical Pharmacology studies, 16 completed phase II-III clinical trials, and 15 ongoing trials.

Of the 19 clinical pharmacology studies involving 297 (260 PPX and 37 placebo) subjects, 17 were conducted in healthy volunteers, 1 (protocol 60) was conducted in volunteers with impaired renal function, and 1 (n=3) was conducted in APD patients.

Of the 16 completed phase II-III clinical trials (i) 9 (studies---#1, 4, 17, and 21 in ET, and studies---#10, 18, 19, 20, and 22 in AT) were PD studies involving 1253 (702 PPX and 551 placebo) patients; and (ii) 7 were completed studies in schizophrenia involving 322 (177 PPX, 50 comparator, and 95 placebo) patients. There were also 15 ongoing studies: (i) 10 ongoing PD studies (controlled and open label); (ii) 3 schizophrenia studies; and (iii) 2 depression studies.

This Safety Update Report provides additional safety data from (i) one newly completed study in PD (protocol 36); (ii) 2 studies in depression (protocols 37 and 43); (iii) 2 studies in schizophrenia (protocols 7 and 67); and (iv) safety data from the open-label ongoing studies. Data from the unfinished controlled studies are not available due to the blind. A tabulation of an updated patient accountability of the completed studies is detailed in table 4.1.1:

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Table 4.1.1 Patient Accountability (All Completed Studies)				
	Number of Patients			
	Pramipexole	Placebo	Comparator	Total
Phase I (Clinical Pharmacology)	260	37	-	297
Phase II/III				
PD Total	794	633	-	1511
EPD	416	262	-	678
APD	366	371	84	821
Other*	12	-	-	12
Schizophrenia	201	95	50	346
Depression	231	69	-	300
Total	1226	797	134	2157

*Protocol 55, an Italian study was prematurely terminated (Jan. 96), because the investigator was not able to recruit enough patients.

The newly completed study in PD, protocol 36 is a randomized, double-blind, placebo-controlled study in AT involving 247 patients (80 PPX, 83 placebo, and 84 bomocriptine). This multi-center, Non-US study was similarly designed as the other AT RCTs, except for the addition of an active control arm. No major differences in the findings (exposure, demographics, deaths, serious AEs, dropouts, and other AEs) were noted between this protocol and the others, hence no separate tables of data will be presented here for this study alone, but new data tables will be presented that incorporate this study.

4.2 Description of the Population

The updated demographic information of the RCTs is not different from the demographics tables of the original review. There were no statistically significant differences between the pramipexole and placebo groups with respect to age, sex, or race. The demographic characteristics of the ET and AT population were generally representative of the expected demographics of PD patients.

4.3 Extent of Exposure

4.3.1 Extent of Exposure, Overall and Stratified by Duration of Use

The exposure in the original review was based on 1408 pramipexole patients for a total of 274.4 patient years. This safety update adds 738 pramipexole patients from newly completed and ongoing studies in all treatment groups. Table 4.6.1.1 displays the updated exposure in patient years:

Table 4.6.1.1. Number of Patients and Estimated Person-Years (PYs) in Patients with pramipexole Use up to 2 Years				
	Completed Trials		Completed + Ongoing Trials	
	N	PYs	N*	PYs
Phase I				
Healthy Volunteers+	250	--	276	--
PD Patients (0023)	3	--	3	--
Phase 2/3 (PD, Schizophrenia and Depression)				
All Patients@	1213	351.46	2146**	1924.67**
0-24 Months	1213	351.46	1924	1358.92
>6-24 Months	353	223.71	939	1196.63
>12-24 Months	2	2.84	671	986.54
All PD Patients#	782	305.72	1715	1878.94
0-24 Months	782	305.72	1493	1313.19
>6-24 Months	350	219.93	936	1192.85
>12-24 Months	0	--	669	983.70
ET Patients&	388	134.59	777	867.56
0-24 Months	388	134.59	702	699.28
>6-24 Months	137	84.66	493	662.31
>12-24 Months	0	--	401	588.26
AT Patients&&	340	161.73	884	1001.98
0-24 Months	340	161.73	737	604.50
>6-24 Months	213	135.27	443	530.54
>12-24 Months	0	--	268	395.45
Schizophrenia Patients!	200	17.77	200	17.77
0-24 Months	200	17.77	200	17.77
>6-24 Months	0	--	--	--
>12-24 Months	0	--	--	--
Depression Patients!!	231	27.96	231	27.96
0-24 Months	231	27.96	231	27.96
>6-24 Months	3	3.78	3	3.78
>12-24 Months	2	2.84	2	2.84

* Patients were counted only once

** Includes 147 AT PPX patients with continued use beyond 24 months (total of 105.48 additional PY) and 75 ET PPX patients with continued use beyond 24 months (total of 38.28 additional PY).

+ All completed Studies are 3, 25, 26, 27, 28, 29, 30, 31, 47, 51, 61, 62,63, 64, 65, 69, and 73; one ongoing study (0060)

@ All completed studies are: 1,4,7, 10, 15, 17, 18, 19, 20, 21, 22, 24, 33, 34, 36, 37, 43, 48, 49, and 67; all open-label ongoing studies are: 2, 6, 11, 13, 14, 16, and 52.

All AT + All ET studies

& All completed ET studies are 1, 4, 17, and 21; all open-label ongoing ET studies are 2, 6, and 16.

&& All completed AT studies are 10, 18, 19, 20, 22, and 36; all open-label ongoing AT studies are 11, 13, 14, and 52.

! All completed schizophrenia studies are 7, 15, 24, 33, 34, 48, 49, and 67.

!! All completed depression studies are 37 and 43.

Overall (including the extension trials that are ongoing), a total of 2146 patients with 1924.67 PYs of pramipexole use are included in the exposure data, most of it (1878.94 PYs) coming from the PD trials.

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4.4 Mortality in Phase 2/3 Studies

4.4.1 Pramipexole Mortality Compared to Placebo

Fifteen additional pramipexole patients and one placebo patient died during study participation between the NDA (cut-off January 31, 1995) and this safety update report (cut-off February 2, 1997). Therefore, the total number of pramipexole patients who died is 29 (14 deaths observed in the original review), and all 29 came from PD patients. Table 4.8.1.1 shows the estimated mortality rates for pramipexole and placebo separately in ET and AT patients, and in Schizophrenia and depression patients:

Table 4.8.1.1. Rate of Mortality Observed					
	Deaths	N	PYs	Rate / 100 PYs	RR** 95% CIs
PD Completed RCTs					
ET Patients (studies 1, 4, 21)					
Pramipexole	1	388	134.60	0.74	0.79 (0.05, 12.5)
Placebo	1	235	106.5	0.90	
AT Patients (studies 10, 19, 20, 22, 36)					
Pramipexole	4	340	161.7	2.5	1.9 (0.36, 10.3)
Placebo	2	347	154.9	1.3	
Schizophrenia (studies 7, 15, 24, 33, 34, 48, 49, 67)					
Pramipexole	0	200	17.8	0	
Placebo	0	95	9.2	0	
Depression (studies 37, 44)					
Pramipexole	0	231	28.0	0.0	
Placebo	0	69	9.5	0.0	
Completed and Open-Label Ongoing Trials					
ET Patients (studies 1, 4, 21, 2, 6, 16)					
Pramipexole	8	777	867.6	0.9	not applicable#
Placebo	1	235	106.5	0.9	
AT Patients (studies 10, 19, 20, 22, 36, 11, 13, 14, 52)					
Pramipexole	18	884	1002.0	1.8	not applicable#
Placebo	2	347	154.9	1.3	

** Rate Ratio (Relative Risk) of Pramipexole is defined as: (Death/100 PYs of PPX) / (Death/100 PYs of Placebo)
Because all patients in the ongoing part received pramipexole.

Four patients in study 0012 died but are not included in this table because the randomization codes, # of patients, and drug exposure data were not available. Among these patients, three (#23, 599 and 424) received PPX, one (#118) received placebo.

The increase in absolute numbers of deaths (29 from 14) is simply a reflection of greatly increased exposure. The pramipexole mortality rate per 100 PYs was 3.5 fold greater in AT compared to ET pramipexole exposed patients, but equivalent in the placebo patients.

There were no deaths reported in the schizophrenia and depression (completed or ongoing) studies. There were no deaths reported in the 19 Phase 1 studies.

4.4.2 Description of Deaths Observed During Pramipexole's Use

The table below presents a summary of deaths reported in the safety update:

Table 4.4.2.1 Patients deaths which occurred between 1/31/95 and 2/29/96			
Study	Patient	Days on study	Cause of death
Pramipexole			
2	2128	406	Myocardial Infarction
	2333	359	Cardiac arrest
	2334	425	Suicide (secobarbital O.D.)
11	1181	396	Pulmonary Carcinoma
	1227	237	Sudden Death
	1296	152	Cardiac failure
	1170	481	Myocardial Infarction
12	599	196	Sudden Death
13	500	62	? (lost to follow-up)
	89	87	Arrythmia/cardiogenic shock
	478	105	pneumonia
16	16128	185	accidental injury (gunshot)
36	229	238	Multi-system failure
52	423	241	Prostate carcinoma
	642	254	Myocardial Infarction
Placebo			
36	430	263	Cerebral Infarct/UTI

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A complete review of the death cases did not reveal any apparent association to the use of PPX.

4.5 All-Cause and AE Dropout Risks

A tabulation of the number of patients that dropped out due to serious AEs reported in the safety update is detailed in table 4.5.2:

	Number of Patients	
	Pramipexole	
PD Total	32	
EPD	13	
APD	19	
Schizophrenia	1	
Depression	2	
Total	35	

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4.5.1 ET Studies

As mentioned earlier, no new ET RCTs were completed and hence there are no changes to the original review.

4.5.2 AT Studies

Table 4.5.2.1 shows the reasons for study dropout in AT patients (completed double-blind, placebo-controlled PD trials including the newly completed study #36) by treatment groups.

Reason For Discontinuation	Number (%) of Patients					
	Pramipexole (N=340)		Placebo (N=347)		Bromocriptine (N=84)	
	N	%	N	%	N	%
Adverse Events	46	13.5	77	22.2	17	20.2
Lack of efficacy	3	0.9	5	1.4	1	1.2
Protocol Violation	2	0.6	1	0.3	0	0.0
Lost to Follow-up	0	0	2	0.6	0	0.0
Other	13	3.8	9	2.6	1	1.2
Total Patients	64	18.8	94	27.1	19	22.6

This reveals no overall changes from the original review.

4.6 Clinical Characteristics of AEs that were Associated with Dropout

4.6.1 Most Common AEs associated with Dropout in ET Patients

No new ET RCTs were completed and hence there are no changes to the original review.

4.6.2 Most Common AEs associated with Dropout in AT Patients

Table 4.6.2.1 is an updated list of AEs, irrespective of severity, that were associated with dropout in more than 1% of AT patients:

Table 4.6.2.1
AT Patients
Adverse Events with PPX Which Caused Study Termination
Occurring with Frequency $\geq$ 1%

Adverse Event	Number (%) of Patients		
	Pramipexole N(%)	Placebo N(%)	Bromocriptine N(%)
Total Patients (N)	340	347	84
CONFUS	8 (2.35)	7 (2.02)	1 (1.2)
DIZZINESS	4 (1.2)	5 (1.4)	0
DYSKINESIA	6 (1.8)	4 (1.2)	0
EXTRAPYR SYND	7 (2.1)	34 (9.8)	7 (8.3)
HALLUCIN	8 (2.4)	3 (0.86)	0
HYPOTENS POST	7 (2.1)	4 (1.2)	0

Studies included M/2730/0010, M/2730/0019, M/2730/0020, M/2730/0022, and M/2730/0036

Only hallucinations were associated with dropout in more than 1% of pramipexole patients and occurred 2 times more frequently than with placebo.

4.7 Serious AEs Associated with Pramipexole

A tabulation of the number of serious AEs reported in the safety update is detailed in table 4.7.1:

	Number of Serious AEs
	Pramipexole
PD Total	288
EPD	121
APD	167
Schizophrenia	2
Depression	5
Total	583

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A tabulation of the number of patients with serious AEs reported in the safety update is detailed in table 4.7.2:

Table 4.7.2 Number of patients with serious AEs	
	Number of Patients with Serious AEs
	Pramipexole
PD Total	171
EPD	72
APD	99
Schizophrenia	2
Depression	3
Total	176

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As most serious AEs reported come from open-label trials, there is no basis of comparison. A complete review of all serious AEs leading to death or discontinuation did not reveal any apparent association to the use of PPX. There were no serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, seizures, or new cases of rhabdomyolysis. There were 2 cases of syncope in the depression trials and 1 case from the PD trials.

4.8 AE Risks Associated with Pramipexole Use Irrespective of Severity

4.8.1 Overall

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4.8.1.1 ET Patients

No new ET RCTs were completed, and hence there are no changes to the original review.

4.8.1.2 AT Patients

Table 4.8.1.2.1 lists the AEs that were reported at $\geq 1\%$ in the PPX arm and twice the rate of placebo in the safety update:

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Table 4.8.1.2.1
AT Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	340	348
Peripheral Edema	7 (2.1)	2 (0.6)
Weight Decrease	4 (1.2)	2 (0.6)
Arthritis	10(2.9)	3(0.9)
Twitching	6 (1.8)	1(0.3)
Bursitis	5 (1.5)	2 (0.6)
Hallucination	55 (16.2)	21(6.0)

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Paranoid Reaction	6 (1.8)	1 (0.3)
Hypesthesia	8(2.4)	5(1.4)
Delusions	4 (1.2)	2 (0.6)
Rhinitis	9 (2.7)	3 (0.9)
Pruritis	4 (1.2)	2(0.6)
Accomodation Abnormality	12 (3.5)	6(1.7)
Vision Abnormality	10 (2.9)	3 (0.9)

Studies included M/2730/0010, M/2730/0019, M/2730/0020, M/2730/0022, and M/2730/0036

Only hallucinations (16.2%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

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4.9 Changes in Laboratory Parameters Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

4.10 Changes in Vital Signs Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

4.11 Changes in ECG Parameters Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5 Summary of the Safety Experience in the Pramipexole Development Program

5.1 General Comments

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Overall, there are no new significant clinical findings or safety concerns in the 8 month safety update.

5.2 Cardiovascular System

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Aside from the 3 new cases of syncope (2 from the depression trials and 1 from the PD trials), there are no new significant clinical findings or safety concerns in the 8 month safety update.

5.3 Central Nervous System

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.4 Dermatological

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.5 Gastrointestinal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.6 Genitourinary/Renal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.7 Hematologic

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.8 Metabolic Endocrine

There are no new significant clinical findings or safety concerns in the 8 month safety update.
No new cases of rhabdomyolysis are reported.

5.9 Musculoskeletal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.10 Respiratory

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.11 Special Senses

There are no new significant clinical findings or safety concerns in the 8 month safety update.

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6 Conclusion

Review of the data in the safety update indicates that pramipexole is relatively safe. There were no occurrences of adverse events that were not reported previously and no general increase in incidence rates from previously reported rates.

In conclusion, when the dose of pramipexole is slowly titrated and individualized to obtain optimum response, pramipexole is a safe treatment for patients with Parkinson's disease.

7 Labeling Recommendations

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Adverse Events section:

(1) The 1% table should be redone to reflect newly available data from the RCT of the AT patient population.

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Precautions section:

(1) The sponsor should note the occurrence of rhabdomyolysis even if the circumstances were unique.

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John D. Balian, M.D.

Date

2/27/97

Clinical Reviewers, Safety Group
Div. of Neuropharmacologic Drug Products

Orig. NDA 20-667
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Safety Team Leader's Review of Clinical Data

NDA: NDA 20-667
Response to Approvable Letter

Date of Submission: January 07, 1997

Sponsor: Pharmacia & Upjohn

Drug: Pramipexole 0.125 mg, 0.25 mg, 0.5 mg,
1.0 mg, 1.25 mg and 1.5 mg
Tablets

Route of Administration: Oral Titration

Proposed Indication: Symptomatic Treatment of Parkinson's Disease

Material Reviewed: January 07 Submission that Responding to the
FDA approvable letter; January 10 Amendment
41; January 13 Amendment 42, and Medical
Officer's Review of the Safety Update in
amendments 41 and 42.

Date of Review: 5/13/97

Summary

Pramipexole's sponsor responded to the approvable letter with a safety update, draft labeling and narrative responses to several queries raised by the agency in the letter and proposed labeling. There were no new safety issues raised by the safety update, and its findings were consistent with those in the NDA safety review. New analyzes conducted to evaluate the effects of dose and duration of use on AE events rates were not helpful because of limited number of events in most dose categories, and confounding of dose with duration of use.

The sponsor changed the pregnancy category from "C" to "B" arguing that the findings from animal reproductive studies were sufficient to conclude that pramipexole had no teratogenic risk in rats or rabbits. The sponsor further argued that its effects on implantation and embryo survival were similar to those with bromocriptine which is labeled pregnancy category "B". The review team, however, considers the reproductive study in rats to have failed because the embryotoxicity markedly limited the number of litters in the high dose group. Thus, until the study is repeated a pregnancy category of "C" is justified as per 201.57.

The sponsor also proposed different language in labeling to describe the retinal toxicity that was observed in albino rats. In my opinion, the effect of that language is to accentuate the uncertainty of the finding's relevance to human users of pramipexole. The FDA proposed language tells the reader not to discount the finding because the potential mechanism of the effect generalizes to humans. Such caution seems justified since there is little data addressing the long-term effects of pramipexole use in humans.

Finally, the precaution that the FDA recommended to describe the one case of rhabdomyolysis was removed from labeling by the sponsor. Since pramipexole's use was associated with slight increase in the mean CPK, the precaution seems justified.

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Background

The FDA issued an approvable letter for pramipexole on December 23, 1996. In that letter, the agency requested a safety update and suggested the conduct of in vitro studies to evaluate potential drug interactions with pramipexole. Also included with the letter was proposed labeling that made several requests of the sponsor, most notably a request to conduct dose-response and time since first exposure analyses of the safety data for events that were numerically more frequent than with pramipexole and occurring in more than 1% of patients. On January 7, the sponsor responded by providing a safety update, new labeling, additional analyses and a discussion of the issues raised in the approvable letter.

Dr. Balian, who was the safety reviewer for the NDA, reviewed the safety update and concluded that the findings were consistent with those in the NDA and that there were no new issues to address. After reviewing the safety update, I concur with Dr. Balian.

Dr. Steele, who was the pharmacology reviewer for the NDA, has reviewed the sponsor's proposed changes to the clinical pharmacology, animal toxicology and pregnancy sections of labeling. His comments and recommendations are considered further below. Dr. Ibrahim reviewed the in vitro studies submitted to address the FDA request for in vitro data to address potential for drug interactions. It is her opinion that these data are sufficient to conclude that pramipexole is unlikely to affect important cytochrome P450 isoenzymes.

Based upon changes to the labeling that were proposed by the sponsor, there are still three issues to consider where there may be some disagreement between the FDA and the sponsor. First, the sponsor has proposed a pregnancy category of "B" while the FDA had concluded that a pregnancy category of "C" is justified based upon the available data. Second, there is some disagreement over the nature of the language to be used to describe the uncertain relevance to humans of the retinal toxicity that was observed in albino rats. Finally, the sponsor removed the precaution that described the one patient with rhabdomyolysis that had been added by the FDA. These issues are discussed further below along with the validity of the dose response and time since first exposure analyses conducted by the sponsor at the FDA's request.

Pregnancy Category

In rabbits, there were no adverse reproductive effects observed at 10 mg/kg/day which the sponsor states is 71 times the AUC in humans. In the animal reproductive studies in rats, three effects were associated with pramipexole exposure: (1) When pramipexole was administered throughout pregnancy at 2.5 mg/kg/day, implantation was impaired. (2) In the organogenesis rat study, significant embryonic loss occurred in the high dose group (1.5 mg/kg). (3) Postnatal growth and development was impaired at doses as low as 0.5 mg/kg/day.

While the effects on implantation, and postnatal growth and development were considered by Dr. Steele to be possibly related to pramipexole's effect on prolactin, which if true may limit the relevance of these findings to humans, the embryotoxicity prevented a complete evaluation of teratogenicity by markedly reducing the number of litters available for observation in the high dose group. While the sponsor states that the AUC resulting from the exposures in the two lower dose groups covered the expected human exposure, Dr. Steele considers the high dose group to be paramount to evaluating the teratogenic potential of pramipexole because several rare birth defects were observed in the two lower dose groups. Since the findings in the highest dose group were critical in interpreting the study, Dr. Steele considers this organogenesis study to have failed and, in fact, recommended repeating it.

The sponsor argues that the effects observed with pramipexole were the same as those with bromocriptine which is labeled "B". However, the bromocriptine labeling suggests that the number of litters available for review were sufficient in the high dose bromocriptine group. The labeling also describes the birth outcomes from prospective follow-up of maternal exposures which may or may not have contributed to the decision to label it "B".

Thus, it seems that without even considering the relevancy of the findings that may be attributable to prolactin, a consideration that may be complex because of potential difficulties in directly attributing any effects to decreases in prolactin, pramipexole should be labeled "C" at least until the sponsor conducts the appropriate studies.

Retinal Toxicity in Albino Rats

While there is some disagreement about whether the effects (loss of photoreceptor cells, degeneration of retinal pigment epithelium) should be referred to as "retinal degeneration" or "retinotoxicity", the sponsor prefers language that does not mention any link to humans. The FDA, however, used the following wording "The potential significance of this effect in humans has not been established, but cannot be disregarded since retinal disk shedding is a universal vertebrate mechanism." Since no human data has been collected on retinal changes with long-term treatment, the FDA wording seems more prudent since the potential mechanism of the effect may generalize to humans.

Rhabdomyolysis

In the sponsor's discussion about the one case of rhabdomyolysis observed with pramipexole, more history was provided, in that the event occurred after rigorous exercise. Rigorous exercise is generally accepted as being a risk factor for rhabdomyolysis. While I would tend to agree with the sponsor in that one case of any rare event is usually not a justification for a precaution, there is more to the signal in this case.

In Dr. Balian's original review of the NDA, there was a mean increase of about u/L in CPK across several studies, with the difference from placebo having reached statistical significance in two studies. While the evidence of a slight increase in the mean seemed compelling, there was no increase in the percentage of patients who had increases that were of clinical concern. Thus, the slight increase in the mean CPK was, by itself, not considered to be clinically significant. Nevertheless, since there was one accepted case of rhabdomyolysis, a precaution seemed appropriate. In fact, if there had been increases of CPK that were clinically significant, a warning statement could be justified. Thus, a precaution seems consistent with the safety findings.

Effect of Dose and Time Since First Exposure on AE Rates

Based upon the FDA comments contained in the proposed labeling included with the approvable letter, the sponsor has conducted more specific analyses to evaluate dose response. These analyses were used to clarify the role of dose and time on the risk associated with pramipexole use. However, the analyses of dose, while confounded with time since the studies allowed titration to clinical endpoints, contained are too few events in dose groups to reach a conclusion about the effect of increasing dose. Thus, I would recommend not mentioning these issues in labeling.

Conclusion and Recommendation

Review of the pramipexole safety update and the sponsor's response to the approvable letter did not identify any new safety issues for consideration. The embryotoxicity observed in the rat reproductive studies justifies a pregnancy category "C". Because the potential mechanism for the retinal toxicity observed in albino rats generalizes to humans, language should clearly articulate this potential risk. A precaution describing the one case of rhabdomyolysis is justified given the slight increase in mean CPK observed in the clinical studies.

/S/

APPEARS THIS WAY
ON ORIGINAL

Greg Burkhardt, M.D., M.S.
Safety Team Leader, Neuropharmacological Drug Products, HFD-120

cc:HFD-120\Burkhardt\Katz\Leber

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: June 16, 1997

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I/HFD-101

SUBJECT: Review of Sponsor's Response to Approvable Letter for
Pramipexole, NDA 20-667

On December 23, 1996, the Agency sent an Approvable letter to Pharmacia & Upjohn, Inc. for NDA 20-667, Pramipexole in patients with Parkinson's Disease. The letter asked only for the sponsor to accept specific dissolution specifications and methodology as well as submit a safety update. In addition, of course, there were multiple questions embedded in the draft labeling that accompanied the letter.

The sponsor responded to the letter in a submission dated 1/7/97. In that response, the sponsor 1) made a number of changes to the proposed draft labeling, 2) responded to the questions and requests embedded in the draft, 3) submitted a safety update, and 4) agreed to the dissolution specifications and methodology described in the letter.

The sponsor's response has been reviewed by Drs. Balian and Burkhart of this Division, in reviews dated 2/27/97 and 5/13/97, respectively, and by Dr. Baweja of OCPB, in a review dated 4/30/97. No new safety issues emerged. Of note, however, Dr. Burkhart concluded that a reliable analysis of dose response of ADRs could not be performed because 1) dose and time were confounded (due to the fact that the studies used a titration design), and 2) there were too few events of interest in any dose group. This conclusion is important because we asked the sponsor to include in labeling a description of those ADRs, if any, that were dose related. Based on Dr. Burkhart's review, no such statements will be included (see below).

The division reviewed the sponsor's draft labeling, and had a number of areas of disagreement with the firm. The division constructed revised draft labeling, and "faxed" this revised version to the sponsor on 5/28/97. The company informed us of their continued disagreement with some of our proposed language and, as a result, these residual issues were discussed

in a telephone call on 6/10/97.

At this meeting, the Agency and sponsor came to agreement on essentially all issues (minor wording in a few areas was left to the firm to draft). A revised draft of labeling was sent to the Division on 6/12/97. This draft is acceptable with a few minor changes. This most recent draft (again, which we find acceptable) differs from the draft label accompanying the Approvable letter in several important ways:

1) **CLINICAL PHARMACOLOGY:** The sponsor has proposed a sentence at the end of the 1st paragraph that describes relative binding affinities at D₃, D₂, and D₄ receptor sub-types, but that describes (at the Division's urging) the relevance of this binding for Parkinson's Disease as being unknown.

Also, they have removed the last sentence of this section, which discussed the effects of pramipexole on neuronal dopamine metabolism in animals.

2) **CLINICAL STUDIES:** The sponsor corrected the number of placebo controlled double blind trials described to 7, not 8, as had been originally (and incorrectly) stated.

3) **WARNINGS:** We asked the sponsor to re-calculate the comparative incidence of objective orthostatic events (we were concerned with misclassification of events that they included as being manifestations of orthostasis). No additional language was added to that proposed in the draft that accompanied the Approvable letter.

4) **PRECAUTIONS:** The language in the sub-section called **Retinotoxicity in Albino Rats** has been changed to be somewhat more detailed and to include a statement about the potential relevance to humans. The sub-section itself has been re-named; it is now called **Retinal pathology in albino rats**.

5) **ADVERSE EVENTS:** In the draft labeling accompanying the Approvable letter, we asked the sponsor to draft statements about the dose relatedness of ADRs for both early and late PD patients. Upon review of this data, we realized that it was impossible to determine which ADRs might be dose related, because the studies all used a titration design, and dose and time were confounded. Hence, we removed any statements designed to list those ADRs which were dose related, and instead included a statement about this confounding after the first paragraph in this section (before the sub-section "**Early**" Parkinson's Disease).

6) **DOSAGE AND ADMINISTRATION:** In this section, we included a table of dosing adjustments necessary for patients with renal impairment. In this table, for the last category of patients (those with severe impairment), we had written WARNING in the space for the proposed dosing. Upon further reflection, we decided that this was cryptic, at best. The revised version now reads "The use of MIRAPEX has not been adequately studied in this group of patients".

In addition to these changes, the sponsor has adequately responded to all the questions we asked in the body of the draft labeling.

RECOMMENDATIONS

The application should be approved and the attached Approval letter should be sent to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

Cc:
NDA 20-667
HFD-120
HFD-120/Leber/Katz/Burkhart/Feeney/Fitzgerald/Steele/Wheelous
HFD-860/Baweja

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CLINICAL REVIEW AND EVALUATION OF EFFICACY

NDA 20-667

Mirapex (pramipexole)

**APPEARS THIS WAY
ON ORIGINAL**

Reviewer: John Feeney, M.D.
James Sherry, M.D., Ph.D. (Studies 19 & 22)

Date: September 13, 1996

Sponsor: Pharmacia & Upjohn

Indication: Parkinson's Disease

NDA Submission Date: December 28, 1995

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Introduction:

Overview of Studies Pertinent to Efficacy

There have been 9 completed controlled trials addressing the efficacy of pramipexole in Parkinson's Disease.

Four of the 9 were conducted in patients with early PD and did not allow concomitant L-dopa therapy: Studies 1,4,17, and 21.

Five of the 9 were conducted in patients with advanced PD, including patients on concomitant L-dopa therapy: Studies 10,18,19,20, and 22.

Early disease was defined as Hoehn and Yahr stages 1-3. Patients in these studies could not be on concomitant L-dopa, but could take some other drugs use to treat symptoms, including amantadine, deprenyl, and anticholinergics. Advanced PD was defined as Hoehn and Yahr stages 2-4, requiring concomitant L-dopa and experiencing some of the adverse events associated with longterm use of L-dopa, including "on-off" periods and dyskinesias.

Studies 1,4, and 10 are the most recent studies (completed around January 1995) and the largest. The sponsor considers these 3 studies the "pivotal" studies. However, **Studies 19 and 22** (both in advanced PD) are not small. Study 19 randomized 78 patients to 2 groups and Study 22 randomized 69 patients to 2 groups. These 2 studies are reviewed by Dr. James Sherry, incorporated into this document.

Study 20 is a very small, double-blind, placebo-controlled trial in advanced PD. It showed no difference between groups, but it really is too small to lead to any generalizations. It stopped enrollment prematurely.

Study 21 is a very small, double-blind, placebo-controlled trial in early PD. It showed a difference in favor of pramipexole. It stopped enrollment prematurely.

Studies 17 and 18 were both single-blind studies, but seem capable by design of demonstrating a difference in favor of the active agent, pramipexole. However, Study 18 in advanced PD showed no difference

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MODIFIED HOEHN AND YAHR SCALE		RATER'S INITIALS (3): _____
Indicate the patient's Parkinson stage for both 'on' and 'off' periods by checking one box for 'on' and one box for 'off' below.		
STAGE	ON	OFF
0	☐	☐ No signs of disease
1	☐	☐ Unilateral disease
1.5	☐	☐ Unilateral plus axial involvement
2	☐	☐ Bilateral disease, without impairment of balance
2.5	☐	☐ Mild bilateral disease, with recovery on pull test
3	☐	☐ Mild to moderate bilateral disease; some postural instability; physically independent
4	☐	☐ Severe disability; still able to walk or stand unassisted
5	☐	☐ Wheelchair bound or bedridden unless aided

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Pramipexole			
Study No.	Study Description	Number of Centers	Number of Patients Studied (Pramipexole / Placebo)
Completed Studies in Parkinson's Disease			
Adequate and Well-Controlled Studies			
1	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	26	335 (164 / 171)
4	Multicenter, Dose response, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	20	264 (213 / 51)
10	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	25	360 (181 / 179)
Other Double-Blind Controlled Studies			
19	Multicenter, Ascending dose, Prospective, Randomized, Double-blind, Placebo-controlled Study	9	77 (43 / 34)
20	Randomized, Double-blind, Placebo-controlled, Parallel-group Study	1	19 (9 / 10)
21	Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	6	24 (11 / 13)
22	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	9	69 (36 / 33)
Single-Blind Controlled Studies			
17	Multicenter, Ascending dose, Prospective, Randomized, Single-blind, Placebo-controlled, Parallel-group Study	4	55 (28 / 27)
18	Multicenter, Ascending dose, Prospective, Randomized, Single-blind, Placebo-controlled, Parallel-group Study	6	50 (26 / 24)

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Pramipexole			
Study No.	Study Description	Number of Centers	Number of Patients Studied (Pramipexole / Placebo)
Ongoing Studies in Parkinson's Disease			
Controlled Studies			
M/2730/0005	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	33	176 (1/31/95)
M/2730/0012	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	52	236 (1/31/95)
M/2730/0036	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	36	124 (1/31/95)
M/2730/0055	Randomized, Double-blind, Placebo-controlled, Parallel-group Study	1	6 (1/31/95)
Uncontrolled Studies			
M/2730/0002	Open-label extension of 1	26	281 (1/31/95)
M/2730/0006	Open-label extension of M/2730/0005	33	41 (1/31/95)
M/2730/0011	Open-label, Ascending-dose Study Extension of 10	25	305 (1/31/95)
M/2730/0013	Open-label, Ascending-dose Study Extension of M/2730/0012	52	88 (1/31/95)
M/2730/0014	Open-label, long-term, safety Study Extension of 19, 20, 22	19	89 (1/31/95)
M/2730/0016	Multi-center, Open-labeled, Non-comparative, Safety Study	19	22 (1/31/95)

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between drug and placebo, despite a reasonable enrollment. Study 17 in early PD did demonstrate a difference in favor of pramipexole.

The sponsor maintains that all 4 studies conducted in early PD showed a difference between pramipexole and placebo. Study 4, a dose-comparison trial, showed no benefit of doses greater than 1.5 mg/day.

Of the 5 studies in advanced PD, the sponsor maintains that 3 demonstrate a difference in favor of pramipexole, 1 demonstrates no difference between pramipexole and placebo, and 1 study stopped enrollment so early as to preclude any meaningful interpretation of the results.

Reviews of the individual studies follow.

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Unified Parkinson's Disease Rating Scale (UPDRS)

All the studies in this NDA specified the UPDRS (or components) as primary outcome assessments. Studies 1 and 10 required a dual outcome, a positive effect on Part II and a positive effect on Part III of the UPDRS. Study 4 used the sum of Parts I-III as a primary outcome assessment.

A copy of the scale is attached. Part I rates mentation, mood, and behavior. Part II rates ADLs during the past week. Part III is a motor exam. Part IV rates complications of therapy, including dyskinesias.

Part II has 13 items scored from 0 (best) to 4 (worst) for a worst total score of 52. In advanced Parkinson's Disease where unpredictable shifts from states of good functioning to states of poor functioning occur throughout the day, Part II is scored twice, once for the so-called "on" state and once for the so-called "off" state. The total score on Part II then becomes the average of the "on" score and the "off" score. (This will be discussed in more detail in my review of Study 10.) In early Parkinson's Disease, where the "on-off" phenomenon is not occurring, Part II is scored only once and this averaging technique does not apply.

Part III has 14 items scored from 0-4, but some of the items are scored several times for different body regions (right body vs left body; right arm, left arm, right leg, vs left leg) so that the worst total score is 108. Part III is scored only once in both early and advanced Parkinson's Disease.

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Boehringer Ingelheim Pharmaceuticals, Inc.
 Trial No.: 248.320

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UNIFIED PARKINSON'S DISEASE RATING SCALE Pramipexole 00679A - M2730/0010						
PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
		2			1001	14

The same person should conduct a given part of this evaluation throughout the trial.

When completing this section, indicate the patient's best level of function during the past week.

PART I. MENTATION, BEHAVIOR AND MOOD

RATER'S INITIALS (3): _____

The worsening of a patient's disease symptom(s) will be recorded on the Adverse Event Report form only if their frequency has increased and/or severity has worsened since baseline or if, in the opinion of the investigator, they do not represent the patient's usual clinical state prior to study entry.

1. Intellectual impairment: ☐ 0 = None ☐ 1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties. ☐ 2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting. ☐ 3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems. ☐ 4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.	2. Thought disorder (DUE TO DEMENTIA OR DRUG INTOXICATION): ☐ 0 = None. ☐ 1 = Vivid dreaming. ☐ 2 = "Benign" hallucinations with insight retained. ☐ 3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities. ☐ 4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.
3. Depression: ☐ 0 = Not present. ☐ 1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks. ☐ 2 = Sustained depression (1 week or more). ☐ 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest). ☐ 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.	4. Motivation/Initiative: ☐ 0 = Normal. ☐ 1 = Less assertive than usual; more passive. ☐ 2 = Loss of initiative or disinterest in elective (nonroutine) activities. ☐ 3 = Loss of initiative or disinterest in day-to-day (routine) activities. ☐ 4 = Withdrawn, complete loss of motivation.

PART II. ACTIVITIES OF DAILY LIVING DURING THE PAST WEEK
 (score for both 'on' and 'off' periods)

RATER'S INITIALS (3): _____

5. Speech: ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Mildly affected. No difficulty being understood. ☐ ☐ 2 = Moderately affected. Sometimes asked to repeat statements. ☐ ☐ 3 = Severely affected. Frequently asked to repeat statements. ☐ ☐ 4 = Unintelligible most of the time.	6. Salivation: ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Slight but definite excess of saliva in mouth; may have nighttime drooling. ☐ ☐ 2 = Moderately excessive saliva; may have minimal drooling. ☐ ☐ 3 = Marked excess of saliva with some drooling. ☐ ☐ 4 = Marked drooling, requires constant tissue or handkerchief.
7. Swallowing ON OFF ☐ ☐ 0 = Normal ☐ ☐ 1 = Rare choking. ☐ ☐ 2 = Occasional choking ☐ ☐ 3 = Requires soft food. ☐ ☐ 4 = Requires NG tube or gastrostomy feeding.	8. Handwriting: ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Slightly slow and small. ☐ ☐ 2 = Moderately slow or small; all words are legible. ☐ ☐ 3 = Severely affected; not all words are legible. ☐ ☐ 4 = The majority of words are not legible.

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UPDRS (CONT.)			Pramipexole 00679A - M2730/0010			
PATIENT INITIALS	VISIT	INVEST NO.	SHEET NO.	PATIENT NO.	PAGE	
(S) [] [] []	2			1001	15	

PART II. - (Continued)

9. Cutting food and handling utensils: ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Somewhat slow and clumsy, but no help needed. ☐ ☐ 2 = Can cut most foods, although clumsy and slow, some help needed. ☐ ☐ 3 = Food must be cut by someone, but can still feed slowly. ☐ ☐ 4 = Needs to be fed.	10. Dressing ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Somewhat slow, but no help needed. ☐ ☐ 2 = Occasional assistance with buttoning, getting arms in sleeves. ☐ ☐ 3 = Considerable help required, but can do some things alone. ☐ ☐ 4 = Helpless.
11. Hygiene: ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Somewhat slow, but no help needed. ☐ ☐ 2 = Needs help to shower or bathe; or very slow in hygienic care. ☐ ☐ 3 = Requires assistance for washing; brushing teeth, combing hair, going to bathroom. ☐ ☐ 4 = Foley catheter or other mechanical aids.	12. Turning in bed and adjusting bedclothes. ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Somewhat slow and clumsy, but no help needed. ☐ ☐ 2 = Can turn alone or adjust sheets, but with great difficulty. ☐ ☐ 3 = Can initiate, but not turn or adjust sheets alone. ☐ ☐ 4 = Helpless.
13. Falling (unrelated to freezing): ON OFF ☐ ☐ 0 = None. ☐ ☐ 1 = Rare falling. ☐ ☐ 2 = Occasionally falls, less than once per day. ☐ ☐ 3 = Falls an average of once daily. ☐ ☐ 4 = Falls more than once daily.	14. Freezing when walking: ON OFF ☐ ☐ 0 = None. ☐ ☐ 1 = Rare freezing when walking; may have start-hesitation. ☐ ☐ 2 = Occasional freezing when walking. ☐ ☐ 3 = Frequent freezing. Occasionally falls from freezing. ☐ ☐ 4 = Frequent falls from freezing.
15. Walking: ON OFF ☐ ☐ 0 = Normal. ☐ ☐ 1 = Mild difficulty. May not swing arms or may tend to drag leg. ☐ ☐ 2 = Moderate difficulty, but requires little or no assistance. ☐ ☐ 3 = Severe disturbance of walking, requiring assistance. ☐ ☐ 4 = Cannot walk at all, even with assistance.	16. Tremor: ON OFF ☐ ☐ 0 = Absent. ☐ ☐ 1 = Slight and infrequently present. ☐ ☐ 2 = Moderate; bothersome to patient. ☐ ☐ 3 = Severe; interferes with many activities. ☐ ☐ 4 = Marked; interferes with most activities.
17. Sensory complaints related to parkinsonism: ON OFF ☐ ☐ 0 = None. ☐ ☐ 1 = Occasionally has numbness, tingling, or mild aching. ☐ ☐ 2 = Frequently has numbness, tingling, or aching, not distressing. ☐ ☐ 3 = Frequent painful sensations. ☐ ☐ 4 = Excruciating pain.	

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UPDRS (CONT.)		Pramipexole 00679A - M2730/0010					
PATIENT INITIALS B		VISIT 2	INVEST NO	SHEET NO	PATIENT NO 1001	PAGE 16	

PART III - MOTOR EXAMINATION (This exam **MUST** be completed when the patient is in an 'on' period)
This examination should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

TIME OF EXAMINATION: _____ (24-hour clocktime)

RATER'S INITIALS (3): _____

18. Speech: ☐ 0 = Normal. ☐ 1 = Slight loss of expression, diction, and/or volume. ☐ 2 = Monotone, slurred but understandable; moderately impaired. ☐ 3 = Marked impairment, difficult to understand. ☐ 4 = Unintelligible.	19. Facial expression: ☐ 0 = Normal ☐ 1 = Minimal hypomimia, could be normal "Poker Face". ☐ 2 = Slight but definitely abnormal diminution of facial expression. ☐ 3 = Moderate hypomimia; lips parted some of the time. ☐ 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.
20. Tremor at rest: (F=Face, LH=Left Hand, RH=Right Hand, LF=Left Foot, RF=Right Foot) F LH RH LF RF ☐ ☐ ☐ ☐ ☐ 0 = Absent. ☐ ☐ ☐ ☐ ☐ 1 = Slight and infrequently present. ☐ ☐ ☐ ☐ ☐ 2 = Mild in amplitude and persistent, or moderate in amplitude, but only intermittently present. ☐ ☐ ☐ ☐ ☐ 3 = Moderate in amplitude and present all the time. ☐ ☐ ☐ ☐ ☐ 4 = Marked in amplitude and present most of the time.	21. Action or postural tremor of hands: L R ☐ ☐ 0 = Absent. ☐ ☐ 1 = Slight present with action. ☐ ☐ 2 = Moderate in amplitude, present with action. ☐ ☐ 3 = Moderate in amplitude, with posture holding as well as action. ☐ ☐ 4 = Marked in amplitude, interferes with feeding.
22. Rigidity (judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.) LLE = Left upper extremities, RUE = Right Upper extremities LLE = Left lower extremities, RLE = Right lower extremities ☐ ☐ ☐ ☐ 0 = Absent ☐ ☐ ☐ ☐ 1 = Slight or detectable only when activated by mirror or other movements. ☐ ☐ ☐ ☐ 2 = Mild to moderate. ☐ ☐ ☐ ☐ 3 = Marked, but full range of motion easily achieved. ☐ ☐ ☐ ☐ 4 = Severe, range of motion achieved with difficulty.	23. Finger taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.): L R ☐ ☐ 0 = Normal. ☐ ☐ 1 = Mild slowing and/or reduction in amplitude. ☐ ☐ 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. ☐ ☐ 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. ☐ ☐ 4 = Can barely perform the task.
24. Hand movements (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.): L R ☐ ☐ 0 = Normal. ☐ ☐ 1 = Mild slowing and/or reduction in amplitude. ☐ ☐ 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. ☐ ☐ 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. ☐ ☐ 4 = Can barely perform the task.	25. Rapid alternating movements of hands (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.): L R ☐ ☐ 0 = Normal. ☐ ☐ 1 = Mild slowing and/or reduction in amplitude. ☐ ☐ 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. ☐ ☐ 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. ☐ ☐ 4 = Can barely perform the task.

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UPDRS (CONT.)		Pramipexole 00679A - M2730/0010			
PATIENT INITIALS (S)		VISIT	INVEST NO	SHEET NO	PATIENT NO
		2			1001
					PAGE 17

PART III. - (continued)

26. Leg agility (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.):

L	R	
☐	☐	0 = Normal.
☐	☐	1 = Mild slowing and/or reduction in amplitude.
☐	☐	2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐	☐	3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐	☐	4 = Can barely perform the task.

27. Arising from chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.):

0 = Normal.

1 = Slow, or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture:

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait:

0 = Normal.

1 = Walks slowly, may shuffle with short steps; but no festination or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.):

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body bradykinesia and hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude and poverty of movement in general.):

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

TR No.: 9158-95-023

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 Trial No.: 248.320

Page: CRF 19

UPDRS (CONT.)		Pramipexole 00679A - M2730/0010						
PATIENT INITIALS (3)		VISIT 2	INVEST NO	SHEET NO	PAGE 18			
<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 33%;"></td> <td style="width: 33%;"></td> <td style="width: 33%;"></td> </tr> </table>							1001	

PART IV. - COMPLICATIONS OF THERAPY* (during the past week).

A. DYSKINESIAS*

RATER'S INITIALS (3): _____

32. Duration: What proportion of the waking day are dyskinesias present? (historical information):

- 0 = None.
- 1 = 1-25% of day.
- 2 = 25-50% of day.
- 3 = 51-75% of day.
- 4 = 75-100% of day.

34. Painful dyskinesias: How painful are the dyskinesias?

- 0 = No painful dyskinesias.
- 1 = Slight.
- 2 = Moderate.
- 3 = Severe.
- 4 = Marked.

33. Disability: How disabling are dyskinesias? (historical information; may be modified by office examination):

- 0 = Not disabling.
- 1 = Mildly disabling.
- 2 = Moderately disabling.
- 3 = Severely disabling.
- 4 = Completely disabled.

35. Presence of early morning dystonia: (historical information):

- 0 = No.
- 1 = Yes.

B. CLINICAL FLUCTUATIONS

36. Are any 'off' periods predictable as to timing after a dose of medication?

- 0 = No.
- 1 = Yes.

38. Do any of the 'off' periods come on suddenly, e.g., over a few seconds?

- 0 = No.
- 1 = Yes.

37. Are any 'off' periods unpredictable as to timing after a dose of medication?

- 0 = No.
- 1 = Yes.

39. What proportion of the waking day is the patient 'off' on average?

- 0 = None.
- 1 = 1-25% of day.
- 2 = 25-50% of day.
- 3 = 51-75% of day.
- 4 = 75-100% of day.

C. OTHER COMPLICATIONS*

40. Does the patient have anorexia, nausea, or vomiting?

- 0 = No.
- 1 = Yes. If yes, check appropriate box(es) below:
 1 Anorexia 2 Nausea 3 Vomiting

42. Does the patient have symptomatic orthostasis?

- 0 = No.
- 1 = Yes. List symptoms: _____

41. Does the patient have any sleep disturbances, e.g., insomnia?

- 0 = No.
- 1 = Yes. Describe: _____

* The worsening of a patient's disease symptom(s) will be recorded on the Adverse Event Report form only if their frequency has increased and/or severity has worsened since baseline or if, in the opinion of the investigator, they do not represent the patient's usual clinical state prior to study entry.

Study 1

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of pramipexole vs. placebo. Randomization was stratified for concurrent L-deprenyl use. The treatment periods were designed to be at least 6 months in duration.

300 patients were to be entered, 150 per treatment group. A total of 24 centers in the U.S. and Canada were planned with up to 30 patients per center.

Inclusion criteria were:

1. Patients with early, symptomatic, idiopathic Parkinson's disease, Hoehn and Yahr Scale scores of I-III, age 25 years and older. Patients could not be taking L-dopa currently.

Exclusion criteria were:

1. Previous treatment with L-dopa for more than 180 days (6 months) and/or within 60 days of Visit 2.
2. Previous treatment with amantadine within 21 days of Visit 2.
3. Previous treatment with direct-acting dopamine receptor agonists.
4. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.
5. Dementia or active psychosis.
6. Second or third degree AV block or sick sinus syndrome; resting heart rate below 50; CHF Class III or IV; MI within 6 months; other clinically significant heart conditions.
7. Occurrence of a seizure within 2 years.

8. Renal or hepatic impairment. Neoplastic disease.
9. Surgery within 6 months which the investigator believes could impact patient's participation.
10. History of stereotactic brain surgery.
11. SBP less than 100 or a symptomatic drop in SBP of 20 or greater upon standing.
12. Neuroleptics within 60 days; alpha-methyl dopa within 60 days; metoclopramide within 60 days; flunarizine, cinnarizine, parenteral ergots, MAO inhibitors other than deprenyl, methylphenidate, amphetamine, beta blockers if used to treat tremor, or reserpine within 30 days.
13. Adequate contraception and a negative pregnancy test for all women of childbearing potential.
14. Electroconvulsive therapy within 90 days.

Note that the Inclusion/Exclusion criteria do not specifically address the issue of prior or current use of anticholinergic drugs, but the protocol (p11) states that patients may be treated with one concurrent anticholinergic medication at a fixed daily dose.

The schedule of time and events is attached. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria, patients were **randomized** to receive the first dose of study medication. An **ascending-dose phase** followed and could last as long as 7 weeks. If patients experienced dose-limiting toxicity prior to reaching the maximal dose, they entered the **maintenance phase** at that point (prior to 7 weeks). A patient who moved into the maintenance phase after only 1 or 2 weeks of the ascending-dose phase was considered to have missing data for the additional 5-6 weeks of the ascending-dose phase, resuming entries with visit 9. The maintenance phase was 6 months in duration and was followed by a 1 week **dose reduction phase**.

M/2730/0001

PRAMIPEXOLE PHASE III TRIAL IN EARLY PARKINSON'S DISEASE
 PROTOCOL SUMMARY - PART I (Double-Blind, Placebo-Controlled)

TR No.: 9158-95-025

	S	Ascending-Dose Interval ¹							Maintenance-Dose Interval ²									
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 ³
Days since the last visit		1-14	5-9	5-9	5-9	5-9	5-9	5-9	5-9	10-16	10-16	10-16	10-16	10-16	10-16	25-35	26-35	25-35
Dose Level		1	2	3	4	5	6	7	M ⁴	M	M	M	M	M	M	M	M	M
History	x																	
Physical Examination*	x																	
Laboratory Tests*	x				x				x				x			x		x
Chest X-ray	x																	
12-Lead ECG*	x				x				x				x			x		x
Disability Ratings ⁵	x	x	x	x	x	x	x	x	x		x		x		x	x		x
Adverse Events* and Concomitant Meds*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization to Treatment		x																
Dispense Study Medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs ⁴	x	x	x	x	x	x	x	x	x		x		x		x	x		x
Medication Compliance			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

1. Duration of the ascending-dose interval varies depending upon the optimal daily dose of study medication that is achieved. The optimal daily dose is defined as the tolerated dose of study medication associated with stable improvement (i.e. lack of further improvement despite up to two additional dose increases). The degree of improvement is based upon the clinical judgement of the investigator without examination of previous scores on various rating scales used in the trial.
 2. Maintenance dose (M) is either the maximally tolerated dose or the optimal dose if adverse events do not prevent dose escalation during the ascending dose interval.
 3. UPDRS Part II (activities of daily living) and Part III (motor examination) start at Visit 2. The motor examination is to be done 2 to 3 hours after study medication is administered except for Visit 2 (done prior to the dose of study medication administered in the clinic). Modified Hoehn and Yahr Scale at Visit 1 only.
 4. Vital signs (supine and 1 minute standing blood pressure and pulse rate) are taken at Visit 1 in triplicate per protocol, prior to study medication at Visit 2 only and at 2 hours post-dose of study medication at all Visits beyond Visit 1 as noted above.
 5. Dose-reduction interval starts with Visit 18 and ends at Visit 19, the final visit in Part 1. See Protocol Summary Part II for specific procedures to be completed for Visit 19.
- 17
 8 - Screening

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The ascending dose schedule is attached. Study medication was to be taken 1 hour before or 2 hours after meals. There were 7 possible fixed dose regimens, ranging from a total daily dose of _____ mg. The dose was to be raised until dose-limiting toxicity was reached, the maximum dose was reached, or there was a lack of further clinical improvement in the judgment of the investigator despite up to two additional increases in the dose of study medication.

The protocol does not have instructions for dose adjustments of study medications if patients developed AEs during the maintenance phase. That is, if a patient developed nausea during the maintenance phase, it is not clear if the dose of study drug could be lowered.

The protocol **does state** (p16) that patients receiving anticholinergic medication should not have dose adjustments. Patients on l-deprenyl were allowed to have dose adjustments.

Patient visits occurred every week during the ascending dose phase. Patient visits occurred every 2 weeks for the first 3 months of the maintenance phase and every month for the last 3 months of the maintenance phase.

Monthly, during the maintenance phase, the investigator completed Parts II (activities of daily living) and III (motor exam) of the UPDRS.

Note that during the ascending-dose phase, patients assigned to the pramipexole group received both pramipexole and placebo tablets; patients assigned to the placebo group were not exposed to pramipexole.

Two primary outcome variables were stated in the protocol: Part II of the UPDRS (ADL) and Part III of the UPDRS (motor exam).

The analysis plan stated that "the primary efficacy endpoint for each of these parts of the UPDRS is the change in the score between baseline and maintenance where the maintenance score is the last available score prior to the dose-reduction interval." The primary analysis plan was not clearly specified in the protocol. In order for the study to be declared positive, both primary endpoints had to achieve statistical significance. The ITT population was to be the primary analysis population with an LOCF technique employed for missing data.

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Pramipexole Ascending-Dose Schedule

Week	Dose Level	Dosage (mg)	Total Daily Dose (mg)
1	1	3 x 0.125	0.375
2	2	3 x 0.25	0.75
3	3	3 x 0.5	1.50
4	4	3 x 0.75	2.25
5	5	3 x 1.0	3.00
6	6	3 x 1.25	3.75
7	7	3 x 1.5	4.50

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A stated secondary endpoint for the study was time-to-failure where failure was defined as requiring treatment with L-dopa.

Subset analyses were also planned based on concomitant use of l-deprenyl and anticholinergic medications.

The sample size was computed using results in the DATATOP study. It was estimated that with 150 patients per treatment group, the study would have 90% power to detect small differences on the order of 2-4 points in change from baseline in Part III of the UPDRS (motor exam).

B. Subject Disposition and Baseline Comparison

The planned enrollment was 300.

335 patients were randomized: 164 pramipexole and 171 placebo. The investigators and centers are listed at the end of this Study 1 review.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics.

	Placebo N=171	Pramipexole N=164
Age	62	63
Sex	98M/73F	105M/59F
Race	94% White	95% White
Parkinson's Duration	1.7 yrs	2 yrs
Deprenyl Use	66%	68%
Anticholinergic Use	14%	12%
Part II Score	8	8
Part III Score	18.7	18.8
Hoehn & Yahr	1.9	1.9

Patient Flow: Only 2 patients (1 in each treatment group) did not meet the ITT definition, i.e. they did not have at least one efficacy assessment. Therefore, 333 patients are included in the efficacy analysis: 163 pramipexole and 170 placebo.

The following table outlines the withdrawals during the study.

Withdrawals

	Pramipexole	Placebo
Ascending Dose Phase	12	10
Maintenance Phase	16	24
TOTAL	28	34
	62	

The reasons for withdrawals are shown in the next table.

Patient Disposition

	Pramipexole	Placebo
Disease Worsening	4	15
Worsening of Pre-existing Disease	0	1
Other AEs	18	8
Poor Therapeutic Resp.	1	7
Protocol Violation	1	0
Lost to Follow-Up	2	0
Withdrew Consent	2	2
Other	0	1

136/164 pramipexole patients completed the trial. 137/171 placebo patients completed the trial.

C. Efficacy Evaluation

All the analyses below are LOCF analyses, unless specifically described otherwise.

There were 2 patients who received drug but did not have any post-baseline efficacy measurements (1 patient per treatment group). Thus, 333 patients (163 pramipexole, 170 placebo) comprise the ITT population.

1. UPDRS Part II

Sponsor's Table 5 on the next page shows the average Part II scores by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant.

	LOCF Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-1.9	-57
Placebo	0.4	-5
p-value	≤ 0.0001	≤ 0.0001

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**Table 5. Adjusted^a Mean Change from Baseline in UPDRS Part II Total Score^b,
Maintenance Interval
Intent-to-Treat - All Patients, LOCF**

Treatment Group	Baseline ^c	Maintenance Week					
		0 ^d	4	8	12	16	24
PPX (N=163)	8.2	-2.5	-2.5	-2.4	-2.3	-2.4	-1.9
PBO (N=170)	8.3	-0.9	-0.7	-0.4	-0.2	0	0.4
P-Value	-	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 9.2.

^a Adjusted by investigator and investigator-by-treatment interaction.

^b Sum of 13 components of UPDRS Part II.

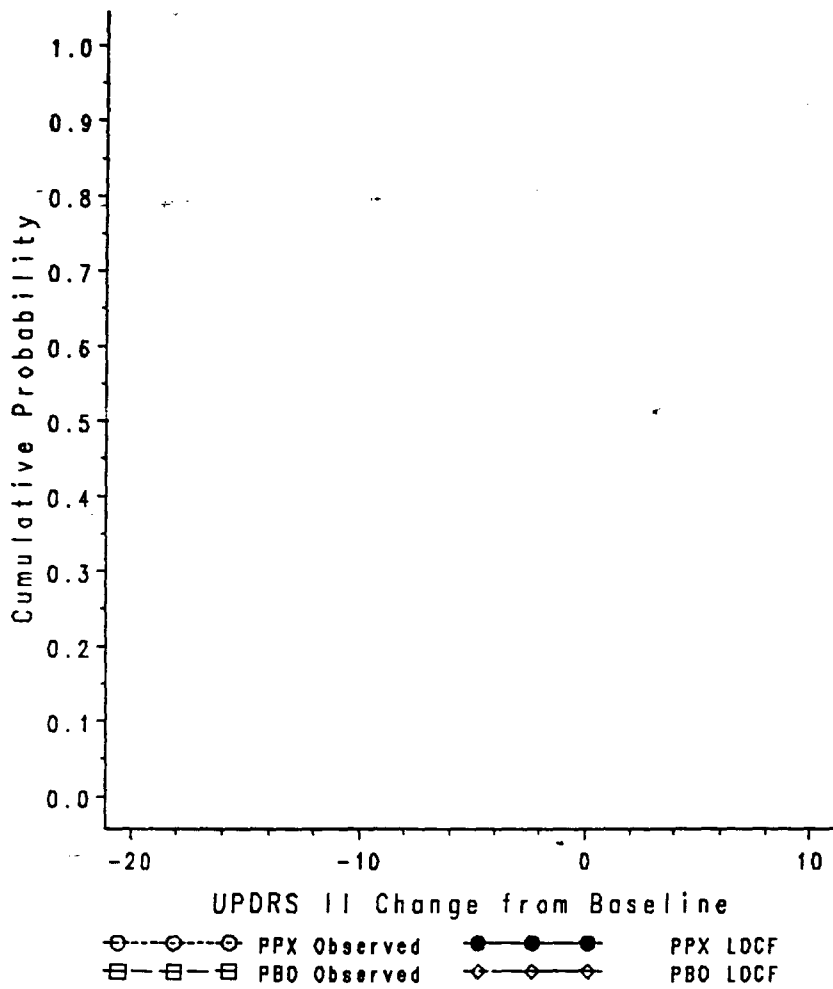
^c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^d Week 0 is the endpoint of the ascending-dose interval.

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Figure 1
 Ogive Curve of UPDRS II Change from Baseline -- M/2730/0001



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2. UPDRS Part III

Sponsor's Table 6 (next page) shows the average Part III scores by visit for the two treatment groups. Cumulative distribution functions are shown on the page after that.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant.

	LOCF Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	- 5	-127
Placebo	0.8	- 11
p-value	≤ 0.0001	≤ 0.0001

3. Modified Hoehn and Yahr Scale

Sponsor's Table 12 (next page) shows the average scores at the beginning and end of the maintenance period for the two treatment groups.

The sponsor also classified patients as: 1) improved, 2) no change, or 3) worsening. The breakdown of patients according to these classifications is presented in Sponsor's Table 13 (next page).

D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are not in the study report.

2. Plasma levels of concomitant deprenyl and anticholinergics were not measured during the conduct of this trial.

Table 6. Adjusted^a Mean Change from Baseline in UPDRS Part III Total Score^b,
Maintenance Interval
Intent-to-Treat - All Patients, LOCF

Treatment Group	Baseline ^c	Maintenance Week					
		0 ^d	4	8	12	16	24
PPX (N=162)	18.8	-6	-5.4	-5.2	-5.2	-5.1	-5
PBO (N=168)	18.8	-2.6	-2.3	-1.6	-0.9	0.4	0.8
P-Value	--	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 10.2

^a Adjusted by investigator and investigator-by-treatment interaction.

^b Sum of 14 components of UPDRS Part III.

^c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^d Week 0 is the endpoint of the ascending-dose interval.

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Table 12. Summary of the Mean Modified Hoehn and Yahr Scale
Classification for All Patients

Mean ± SE	Baseline ^a	Maintenance Week	
		0 ^b	24 ^c
PPX (N=163)	1.92 ± 0.044	1.77 ± 0.049	1.82 ± 0.052
PBO (N=171)	1.89 ± 0.048	1.83 ± 0.047	1.94 ± 0.05

Source: Appendix C: Table 18A.

^a Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^b Week 0 is the endpoint of the ascending-dose interval.

^c Last maintenance-dose visit, prior to dose reduction.

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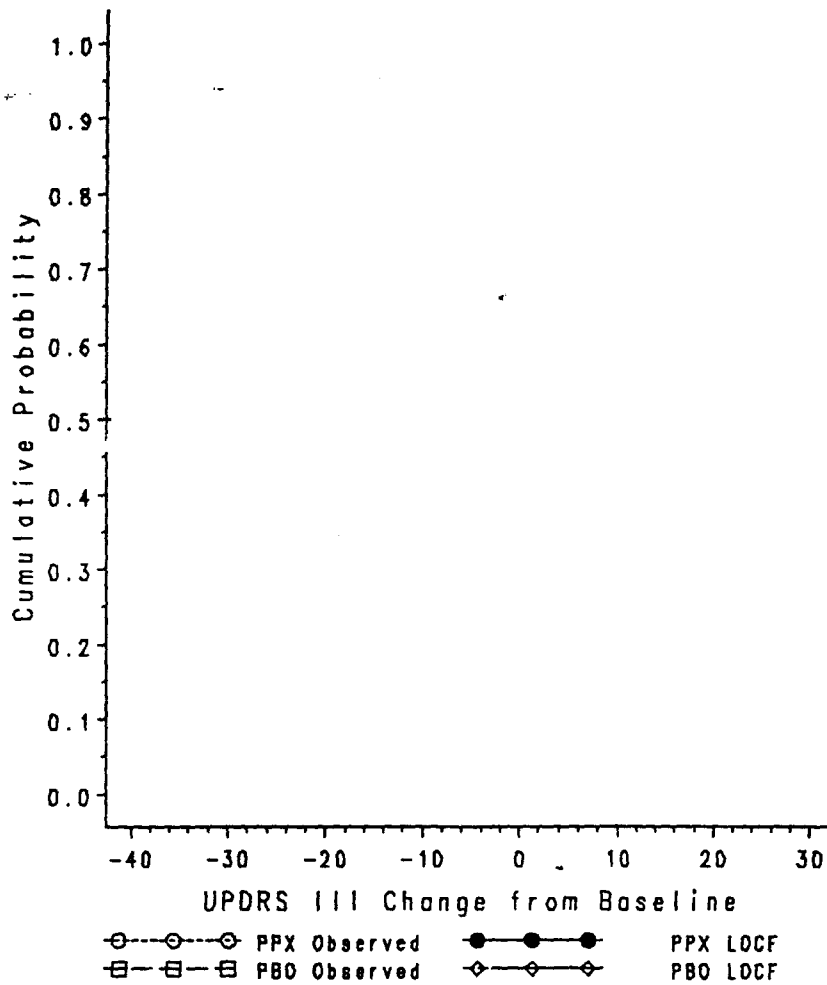
Table 13. Summary of the Change in Modified Hoehn and Yahr
Classification from Baseline to Last Maintenance Visit
All Patients

Classification Change Based on Modified Hoehn and Yahr Scale	Number (%) of Patients	
	PPX N=161	PBO N=170
Improvement	44 (27.2)	28 (16.5)
No Change	90 (55.6)	102 (60)
Worsening of Classification	27 (16.7)	40 (23.5)

Source: Appendix C: Tables 18A, 19.1A and 19.2A.

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Figure 2
 Ogive Curve of UPDRS III Change from Baseline -- M/2730/0001



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E. Subgroup Analyses by Deprenyl and Anticholinergic Use

Sponsor's Table 7 demonstrates that only slight differences in the mean change from baseline for Parts II and III of the UPDRS exist between patients on and off deprenyl. Likewise, only slight differences in these scores exist between patients on and off anticholinergics.

F. Subgroup Analyses by Age, Sex, and Race

Only slight differences in the mean change from baseline for Parts II and III of the UPDRS were shown between male and female patients.

Only 17 patients were non-white so that a subgroup analysis by race is not meaningful.

Only slight differences in the mean change from baseline for Parts II and III of the UPDRS were shown between patients ≥ 65 and < 65 years.

Sponsor's Table 8 demonstrates the results of these analyses.

G. Adverse Events

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Sponsor's Table 17 shows the AEs with an incidence of 10% or greater in the pramipexole group. Of these, nausea, constipation, asthenia, dizziness, insomnia, somnolence, and hallucinations showed the largest differences between the treatment groups.

There was a single death during the study, a pramipexole patient who had a myocardial infarction and died.

There were 10 pramipexole patients and 12 placebo patients with serious AEs. Most of these were malignancies or cardiac-related. No obvious differences between the treatment groups emerged.

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**Table 7. Mean Change From Baseline in UPDRS
Parts II and III, Total Score by L-deprenyl and Anti-cholinergic Usage;
All Patients**

Concomitant Therapy	Treatment Group	Part II ^a				Part III ^b			
		N	Yes	N	No	N	Yes	N	No
l-deprenyl	PPX	112	-1.9	51	-1.5	111	-4.6	51	-4.6
	PBO	112	0.3	58	0.7	112	1.3	57	1.5
Anticholinergic	PPX	19	-1.3	144	-1.9	19	-4.5	143	-4.6
	PBO	24	0.1	146	0.4	24	1.4	145	1.4

Source: Appendix C: Tables 11.1A & 12.1A.

^a Sum of 13 components of UPDRS Part II.

^b Sum of 14 components of UPDRS Part III.

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**Table 8. Mean Change From Baseline in UPDRS
Parts II & III, Total Score by Sex, Age, and Race
All Patients**

Treatment Group		N	Part II ^a	N	Part III ^b
Age					
<65	PPX	75	-2.0	74	-5.4
	PBO	86	0.1	85	0.6
≥65	PPX	88	-1.6	88	-4.0
	PBO	84	0.7	84	2.2
Sex					
Male	PPX	104	-1.8	103	-5.2
	PBO	97	0.4	97	1.3
Female	PPX	59	-1.9	59	-3.6
	PBO	73	0.3	72	1.4
Race					
White	PPX	156	-1.8	155	-4.7
	PBO	160	0.4	159	1.1
Black	PPX	2	0.5	2	3.5
	PBO	4	-0.8	4	2.0
Other	PPX	5	-2.4	5	-6.0
	PBO	6	1.5	6	7.7

Source: Appendix C: Tables 11.2A and 12.2A.

^a Sum of 13 components of UPDRS Part II.

^b Sum of 14 components of UPDRS Part III.

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Table 17. Number (%) of Patients With Adverse Events (TES/Reported in ≥10% of the Patients in the Pramipexole Group) by Body System and Adverse Event Regardless of Relationship to Study Medication

Body System Event ^a	Treatment Group ^b	
	PPX (N=164)	PBO (N=171)
	No. Pts (%)	No. Pts (%)
Body as a Whole		
Infection	44 (26.83)	45 (26.32)
Pain	33 (20.12)	35 (20.47)
Asthenia	31 (18.90)	19 (11.11)
Headache	27 (16.46)	31 (18.13)
Pain back	22 (13.41)	17 (9.94)
Injury accident	21 (12.80)	18 (10.53)
Digestive System		
Nausea	64 (39.02)	35 (20.47)
Constipation	29 (17.68)	11 (6.43)
Dyspepsia	18 (10.98)	12 (7.02)
Nervous System		
Dizziness	57 (34.76)	45 (26.32)
Insomnia	42 (25.61)	22 (12.87)
Somnolence	30 (18.29)	15 (8.77)
Tremor	20 (12.20)	34 (19.88)
Hallucinations	18 (10.98)	5 (2.92)

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Source: Appendix C: Table 21.1.

^a COSTART coding system using preferred term.

^b Number of patients in each treatment group is the number randomized who received at least one dose of study drug.

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H. Conclusions

Pramipexole-treated patients, on average, saw a larger change-from-baseline on Part II of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was small, but highly statistically significant.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline on Part III of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was again small, but highly statistically significant.

The protocol called for a statistically significant result on each of these outcome measures (a dual outcome) in order for a positive result to be declared for the trial as a whole.

The sponsor has shown that the effect was present whether or not concomitant deprenyl and anticholinergic medication were used.

The sponsor has also shown that age (above or below 65 years) and sex do not influence response greatly.

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Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Aminoff, Michael J, M.D. Department of Neurology, Rm. M348 University of California San Francisco San Francisco, CA 94143-0216	7
Bennett, James P, Jr., M.D., Ph.D. Fontaine Research Park Neurology Suite 370 500 Ray C. Hunt Drive Charlottesville, VA 22903	13
Burch, Gordon, M.D. Roanoke Neurological Associates 2601 Franklin Road, S.W., Suite B Roanoke, VA 24014-1049	14
Factor, Stewart A., D.O. Professor of Neurology Department of Neurology (A70) Albany Medical Center New Scotland Avenue Albany, NY 12208	14
Farmer, Stephen, D.O. Grayline Clinical Drug Trials 706 Denver Street Wichita Falls, TX 76301	8
Fazzini, Enrico, D.O., Ph.D. 530 First Avenue 9th Floor, Suite 9Q New York, NY 10016	9
Friedman, Joseph, M.D. Department of Neurology Roger Williams General Hospital 50 Maude Street, 4th Floor Providence, RI 02908	15
Golbe, Lawrence I., M.D. UMDNJ Robert Wood Johnson Medical School Dept. of Neurology, 4th Floor 1 Robert Wood Johnson Plaza, CN-19 New Brunswick, NJ 08903-0019	17

Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Hill, Thomas, M.D. Center for Clinical Research 911 West 38th Street, Suite 301 Austin, TX 78705	11
Hiner, Bradley, M.D. Marshfield Clinic 1000 North Oak Avenue Marshfield, WI 54449-5777	17
Hoehn, Margaret M., M.D. 3535 Cherry Creek North Drive, #303 Denver, CO 80209	8
Hubble, Jean, M.D. Department of Neurology Kansas University Medical Center 39th and Rainbow Blvd. Kansas City, KS 66103	13
Karp, Jeffrey, M.D. Mease Clinic 3253 McMullen Booth Road, Suite 200 Clearwater, FL 34621-2010	10
Kurth, Matthias, M.D. St. Joseph Hospital Barrow Neurological Institute 222 W. Thomas Road, Suite 401 Phoenix, AZ 85013	25
LeWitt, Peter, M.D. Professional Village Clinical Neuroscience Center 5821 West Maple Road, Suite 192 West Bloomfield, MI 48322	14
Nathan, Denis, M.D. Neurological Consultants, S.C. 2002 W. Howard Avenue Milwaukee, WI 53221	11

Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Olanow, C. Warren, M.D. (1/19/93 - 6/12/94) Hauser, Robert A., M.D. (6/13/94 - Present) Assistant Professor of Neurology Department of Neurology Harbour Side Medical Tower 4 Columbia Drive, Suite 410 Tampa, FL 33606	15
Paulson, George, M.D. Chairman, Department of Neurology 452 Means Hall Ohio State Univ. School of Medicine 1655 Upham Drive Columbus, OH 43210	9
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Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
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Study 4

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of 4 different fixed doses of pramipexole and placebo. Randomization was stratified for l-deprenyl use.

The treatment periods incorporated an ascending dose period (as long as 6 weeks) followed by a fixed-dose maintenance period of 4 weeks (and a 1-week dose-reduction period).

250 patients were to be entered, 50 per treatment group. A total of 20 centers in the U.S. and Canada were planned with at least 10 patients per center.

The study was conducted by the
After the study was complete, data sets were provided to the Upjohn Company by the

Inclusion criteria were:

Patients with idiopathic Parkinson's disease of less than 7 years duration, Hoehn and Yahr Scale scores of I-III, age 30 years and older. Patients could not have taken L-dopa within the past 3 months.

Deprenyl, anticholinergics, or amantadine therapy at a stable dose for 30 days prior to the study and throughout the study were allowed.

Exclusion criteria were:

1. L-dopa or dopamine agonist medication in previous 3 months.
2. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.
3. Dementia or active psychosis.
4. Third degree AV block or sick sinus syndrome; CHF Class III or IV; MI

within 6 months.

5. Occurrence of a seizure within 1 year.
6. Renal or hepatic impairment. Neoplastic disease.
7. Symptomatic orthostatic hypotension at screening.
8. History of stereotactic brain surgery.
14. Electroconvulsive therapy within 90 days.

The schedule of time and events is on the next page. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria, patients were **randomized** to receive the first dose of study medication. An **ascending-dose phase** followed and could last as long as 6 weeks. If patients experienced dose-limiting toxicity prior to reaching their target dose, they could be lowered to the previous dose level. The protocol allowed patients to be lowered only 1 or 2 dose levels. Once lowered to a given level, patients were not to be re-challenged at the higher dose level.

The **maintenance phase** was to last 1 month or 4 weeks. This was followed by a 1 week **dose reduction phase**.

The ascending dose schedule is on the next page. Study medication was to be taken 1 hour before or 2 hours after meals.

The protocol states that concomitant deprenyl, amantadine, or anticholinergics could be used, but at a "stable dosage." This implies that changes in dosage of these drugs during the trial would not be allowed.

Patients were seen every 2 weeks during dose-escalation and during maintenance, for a total of 5 scheduled visits post-randomization. At each visit, the following were performed:

1. UPDRS, Parts I-III
2. Supine and standing BP and pulse
3. Adverse events

**APPENDIX E
SCHEDULE OF ACTIVITIES**

	Visit Name		Escalation			Maintenance		Taper
	Screen (14 days)	Baseline (Day 0)	Day 14 (week 2)	Day 28 (week 4)	Day 42 (week 6)	Day 56 (week 8)	Day 70 (week 10)	Day 77 (week 11)
Visit #	1	2	3	4	5	6	7	8
Med/Neuro History	x							
Physical Exam	x							
12-lead EKG	x						x	
Hoehn/Yahr	x	x					x	
Safety Labs	x				x		x	x*
UPDRS I-III		x	x	x	x	x	x	x
Vital Signs		x	x	x	x	x	x	x
NIM's	x	x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x	x
Pharmacokinetics					x		x	
QOL		x					x	
Drug Dispensing		x	x	x	x	x	x	
Compliance Check			x	x	x	x	x	x

*repeat Day 70 abnormal labs

Escalating Pramipexole Dose Schedule

Dose Group	Pramipexole dose - mg/day					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo	pbo	pbo	pbo	pbo	pbo	pbo
1.5 mg/day	pbo	pbo	pbo	0.375	0.75	1.5
3.0 mg/day	pbo	pbo	0.375	0.75	1.5	3.0
4.5 mg/day	pbo	0.375	0.75	1.5	3.0	4.5
6.0 mg/day	0.375	0.75	1.5	3.0	4.5	6.0

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4. Concomitant therapy
5. Safety labs
6. PK blood sample
7. Medication compliance (tablet counts)

At the last visit, the Hoehn and Yahr scale, QOL assessment, and an EKG were additionally performed. The QOL assessments were 1) Functional Status Questionnaire (FSQ) with supplemental questions about employment and 2) EuroQol.

The **FSQ** contains 37 questions. It is designed to be self-administered by the subject in about 10 minutes. The questions are then divided into 6 domains:

- o basic ADLs
- o intermediate ADLs
- o social activities
- o mental health
- o quality of interaction
- o work performance

All questions use the previous month as reference (although it was completed at baseline and at end of maintenance--a 2-month timespan). Responses range roughly from 0-6, with some variation. Higher numbers represented better health. Scores within a domain are added and converted to percent of maximal possible.

There were also several additional questions regarding work (normal work hours, work time lost, or employment changes due to disease), which were analyzed separately.

The **EuroQol** contains 6 health-related questions and an analog scale on which patient rate their health state on a scale from 0-100, where 100 is the best possible health state.

The actual QOL scales are provided at the end of this Study 4 review. The protocol states, "For testing of treatment effects, the principal measures will be changes in the FSQ domain scores, the EuroQol utility score [= analog score], and time lost from work in the previous month."

The primary outcome variable was the change from baseline to end-of-maintenance of the sum of Parts I-III of the UPDRS.

The analysis plan stated that both linear and nonlinear regression models would be considered. "For analyzing efficacy and safety variables, there will be two analyses, one in which the independent variable will be the dose assigned by randomization, and a second analysis in which the actual dose received will be used rather than the dose level to which the subject was randomized."

Subset analyses were not specifically planned based on concomitant use of l-deprenyl, amantadine, and anticholinergic medications.

The sample size was computed using tolerability data from a previous pramipexole trial in which 30% of patients in the 4.5 mg/day group could not tolerate the target dose, while 4% of patients in the placebo group could not tolerate the target dose. With 50 patients per group in the current study, the study was powered to detect a similar difference.

The study was also powered at 0.97 to declare that a dose-response slope of 1.81 was different from zero. The smallest slope that could be detected with a power of at least

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B. Subject Disposition and Baseline Comparison

The planned enrollment was 250.

264 patients were randomized as below. The investigators and centers are listed at the end of this Study 4 review.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics as shown on the next page.

In addition the data on concomitant deprenyl use, amantidine use varied between for the different treatment groups. Anticholinergic use (benzotropine or trihexyphenidyl) varied

Patient Flow: The reasons for withdrawals are shown on the next page. Most of the discontinuations occurred during the ascending dose interval (19 of 26).

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SELECTED DEMOGRAPHIC AND BASELINE FACTORS

Parameter	Pramipexole - assigned dose				Placebo n=51	p value
	1.5 mg/day n=54	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55		
age (mean years)	60.2	62.2	62.7	62.8	60.4	0.67
sex (% male)	64.8	62.0	63.0	69.1	62.8	0.90
race (% caucasian)	96.3	98.0	96.3	98.2	96.1	0.58
duration of disease (mean years)	1.8	2.0	1.9	2.3	1.6	0.16
current selegiline use (% yes)	55.6	66.0	66.7	58.2	58.8	0.65
UPDRS total score (mean points)	29.0	28.3	27.3	32.9	28.7	0.08
Hoehn and Yahr score (mean points)	1.8	1.9	1.8	1.9	1.8	0.52

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REASONS FOR STUDY DRUG DISCONTINUATION - NUMBER PATIENTS

Reason	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
worsening PD	2	0	0	0	0
worsening other disease	1	0	0	0	0
other adverse event	7	0	4	8	0
administrative*	0	2	0	1	1
Total	10	2	4	9	1

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PATIENT DISPOSITION AND TOLERABILITY - NUMBER PATIENTS (%)

Endpoint	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
Number randomized	54	50	54	55	51
number (%) completing ascending dose	47 (87.0)	48 (96.0)	52 (96.3)	47 (85.5)	51 (100.0)
number (%) completing maintenance	44 (81.5)	48 (96.0)	50 (92.6)	46 (83.6)	50 (98.0)
number (%) completing at assigned dose - tolerability	44 (81.5)	46 (92.0)	43 (79.6)	37 (67.3)	49 (96.1)
number (%) completing with one or no dose reductions	44 (81.5)	48 (96.0)	50 (92.6)	44 (80.0)	50 (98.0)
number (%) dose limited during ascending dose interval due to clinical intolerance	2 (3.7)	3 (6.0)	7 (13.0)	10 (18.2)	1 (2.0)

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C. Efficacy Evaluation

Only one patient was not included in the ITT analysis. This patient did not have any post-baseline efficacy assessments.

1. UPDRS Total Score Change From Baseline

The first table on the next page shows the change from baseline in total score for each of the dose groups **as assigned by the randomization scheme**. All groups had significant improvements compared to placebo, but no dose response relationship was apparent.

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The second table on the next page shows the same change from baseline data for each of the dose groups, **but the dose groups are determined by actual dose received**. Again, all groups had significant improvements compared to placebo, but no dose response relationship was apparent.

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Regression analysis (the primary analysis plan stated in the protocol) showed that the coefficient of the linear term was statistically significantly different from zero and the coefficient of the quadratic term was marginally significant from zero for the "assigned group" analysis. Both coefficients were statistically significantly different from zero for the "actual dose received" analysis. The presence of the quadratic term indicates a lack of a linear dose response relationship for both "assigned group" and "actual dose group" analyses. The third table on the next page summarizes these results.

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UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	28.5	28.3	27.3	32.9	28.7
mean change*	-6.1	-5.8	-6.6	-7.1	-1.2
pairwise p value vs placebo	0.0027	0.0057	0.0008	0.0003	-
overall p value	0.0022	-	-	-	-

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UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Actual Dose				Placebo n=60
	1.5 mg/day n=57	3.0 mg/day n=53	4.5 mg/day n=50	6.0 mg/day n=43	
baseline	28.7	28.9	27.0	32.6	29.2
mean change*	-6.5	-5.7	-7.7	-7.5	-0.4
pairwise p value vs placebo	0.0001	0.0005	0.0001	0.0001	-
overall p value	0.0001	-	-	-	-

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UPDRS TOTAL SCORE REGRESSION ANALYSIS

Analysis	n	Linear Parameter Estimate	p value	Quadratic parameter estimate	p value
assigned dose group	263	-2.412	0.0296	0.252	0.0537
actual dose received	263	-2.974	0.0054	0.361	0.0056

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2. Subgroup Analyses

No qualitative interactions were present for pramipexole effects for subgroups of concomitant **selegiline** therapy. The sponsor's analysis of pramipexole effect by **anticholinergic** therapy is flawed because (as acknowledged by the sponsor on page 331 of the Integrated Summary of Efficacy) deprenyl was inadvertently classified as an anticholinergic agent. No analysis of pramipexole effect by **amantadine** use is presented.

Also, no qualitative interactions were present for pramipexole effects for subgroups based on age (<65 years vs. ≥65 years), sex, race (caucasian vs noncaucasian) , or baseline Hoehn-Yahr score. Since very few patients were noncaucasian, no meaningful comparison of responses by race can be made.

3. Secondary Efficacy Variables

UPDRS Part I scores were low at baseline and therefore did not contribute much to the change in total UPDRS.

UPDRS Parts II and III scores each showed a similar pattern of change as the total UPDRS scores (see next page). Cumulative distribution functions for Parts II and III, separately, are on the following pages.

The Hoehn and Yahr data is also shown on the next page, expressed as mean scores as well as percent change.

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UPDRS PART II - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	8.0	8.0	7.3	8.8	8.2
mean change*	-1.8	-1.9	-1.8	-1.8	-0.3
pairwise p value vs placebo**	N.D.	N.D.	N.D.	N.D.	N.D.
overall p value	0.0613	--	--	--	--

*Adjusted for center and treatment by center interaction
 **N.D. - not done since overall p value not significant
 Source - Appendix D, Table 11.2A

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UPDRS PART III - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	19.4	19.3	19.2	22.9	19.6
mean change*	-4.2	-3.8	-4.7	-5.1	-0.6
pairwise p value vs placebo	0.0052	0.0151	0.0016	0.0005	--
overall p value	0.0048	--	--	--	--

*Adjusted for center and treatment by center interaction
 Source - Appendix D, Table 12.2A

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MODIFIED HOEHN AND YAHR SCALE - MEAN SCORES

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
baseline	1.77	1.92	1.81	1.86	1.79
end maintenance	1.74	1.70	1.68	1.74	1.87

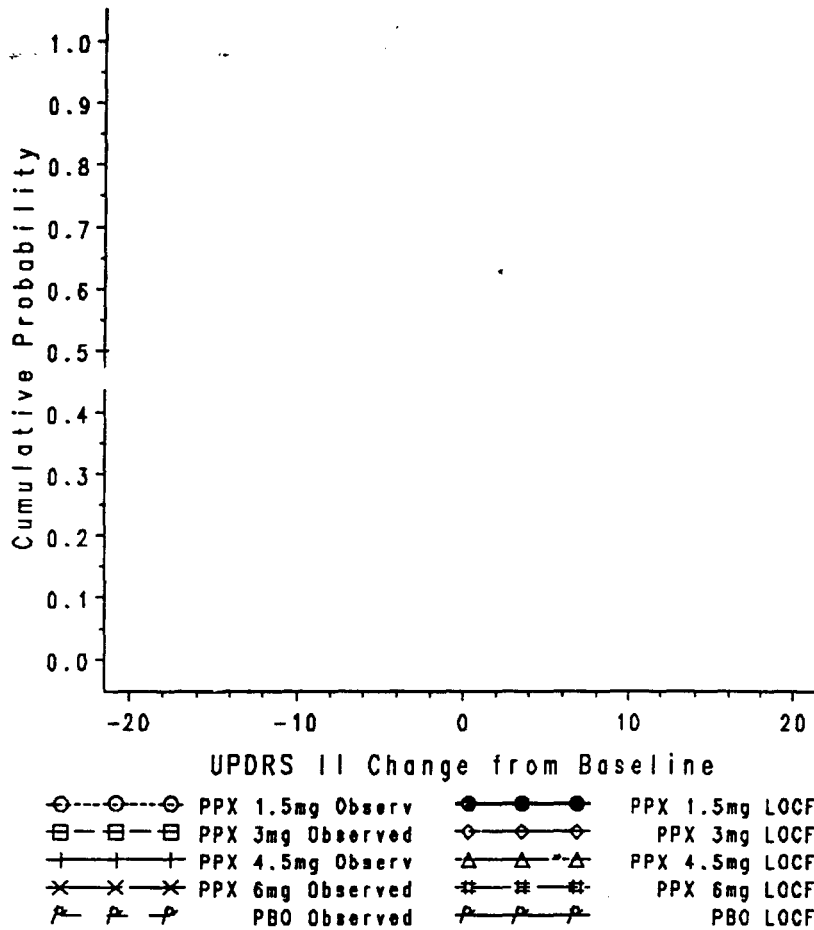
MODIFIED HOEHN AND YAHR SCALE - PERCENT CHANGE

Category	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
improved from baseline (%)	19.2	36.7	25.0	30.2	13.7
worsened from baseline (%)	17.3	6.1	5.8	9.4	25.5

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Figure 3
Ogive Curve of UPDRS II Change from Baseline -- M/2730/0004



PBO Observed overlapping PBO LOCF because there was no dropouts in PBO

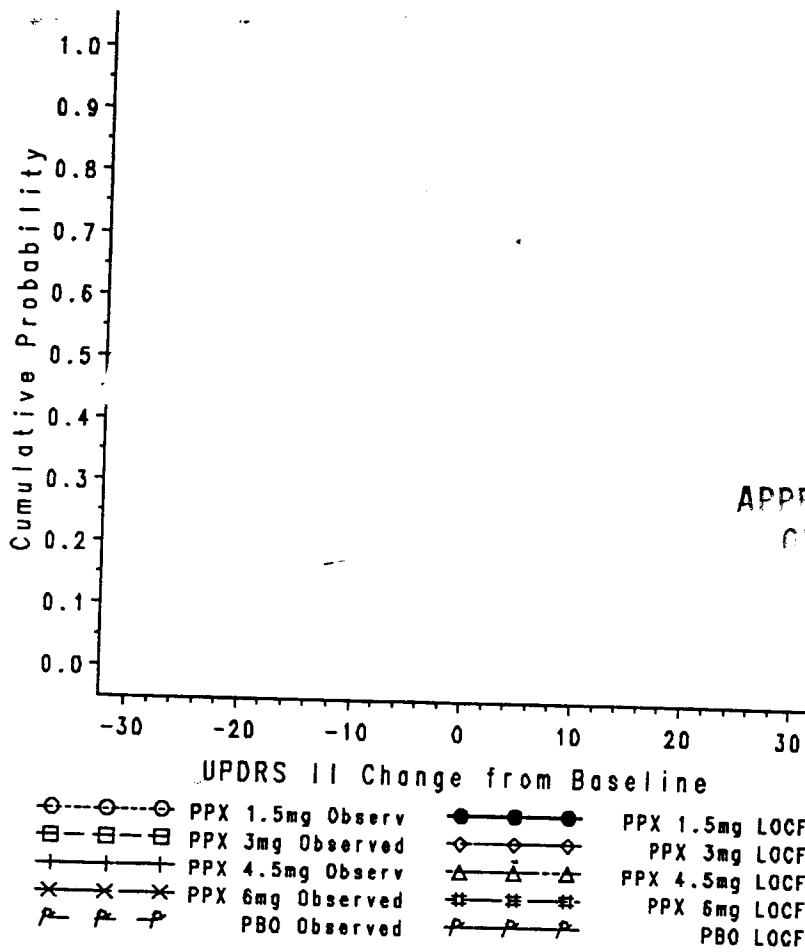
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Figure 4
Ogive Curve of UPDRS III Change from Baseline -- M/2730/0004



PBO Observed overlapping PBO LOCF because there was no dropouts in PBO

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4. Quality of Life Scales

The sponsor's table on the next page demonstrates mean change from baseline for different scales and components of scales. Responses are present for all but two patients (one in the 1.5 mg group and one in the 4.5 mg group). As a reminder, the scores are all converted to a 0-100 scale with 100 representing a best response. A positive change represents improvement, while a negative change represents worsening.

Note that the overall p-value is significant for only one domain, the FSQ basic ADL. Even for that domain, the magnitude of change is so small, except perhaps for the 1.5 mg/day group, as to be clinically insignificant. The overall p-value for the EuroQol analog scale approached significance ($p=0.065$), with the 3 mg/day and 4.5 mg/day groups demonstrating the largest differences compared to placebo.

Separately, the sponsor presents correlation coefficients for UPDRS change scores and QOL change scores. They all tended to be low.

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MEAN CHANGES FROM BASELINE FOR QOL SCORES

Domain / Item	Pramipexole - assigned dose				Placebo	Overall p-value
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day		
FSQ-Basic ADL	4.8**	1.6	2.0*	-0.7	-2.6	0.0255
FSQ-Interm. ADL	1.0	3.7	-1.5	-1.5	-0.1	0.1936
FSQ-Mental Health	1.0	2.0	0.1	0.9	1.5	0.9991
FSQ-Work Perf.	0.9	1.3	-1.9	-0.9	0.6	0.7353
FSQ-Social Activity	0.7	0.4	0.0	-1.3	-2.4	0.9836
FSQ-Quality of Interaction	0.1	-0.5	0.9	-0.1	-0.5	0.8629
FSQ-Days (not) in Bed	0.2	0.0	0.0	0.0	0.0	0.8032
FSQ-Days (not) cut down on activities	1.0	0.8	0.5	-0.1	-0.3	0.4150
FSQ-Satis. w/ sexual relations	-0.1	0.0	0.1	0.0	0.0	0.8175
FSQ-Feelings about own health	0.1	0.4	0.2	0.1	0.2	0.1650
FSQ-Freq. of social activity	-0.1	-0.1	0.0	0.2	-0.2	0.2974
EuroQol-Analog	1.4	4.8	4.0	0.7	-2.3	0.0654
No lost work	0.0	0.2	-0.3	-0.2	-0.4	0.4259

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**p-value vs. placebo=.0016

* p-value vs. placebo=.0686

Source: Appendix D, Table 18.1

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D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are not in the study report.
2. Plasma levels of concomitant deprenyl and anticholinergics were not measured during the conduct of this trial.

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E. Conclusions

A linear dose-response relationship was not demonstrated in this study. All doses performed equally.

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TR No.: 7217-95-037



**STEP-UP
EUROQOL QUESTIONNAIRE (Part 1 of 2)**

93-0286-28 3-88

DO NOT WRITE IN SHADED AREAS

PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE	DATE OF THIS REPORT	MO. / DAY / YR.	SITE NO.

INSTRUCTIONS: Please check the answer that best describes your (the patient's) health state today.

1. Mobility: ☐₀ I have no problems walking about ☐₁ I have some problems walking about ☐₂ I am confined to bed 2. Self-care: ☐₀ I have no problems with self-care ☐₁ I have some problems washing or dressing myself ☐₂ I am unable to wash or dress myself 3. Usual Activities: ☐₀ I have no problems with performing my usual activities (e.g., work, study, housework, family or leisure activities) ☐₁ I have some problems with performing my usual activities. ☐₂ I am unable to perform my usual activities.	4. Pain/Discomfort: ☐₀ I have no pain or discomfort ☐₁ I have moderate pain or discomfort ☐₂ I have extreme pain or discomfort 5. Anxiety/Depression: ☐₀ I am not anxious or depressed ☐₁ I am moderately anxious or depressed ☐₂ I am extremely anxious or depressed
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- 6. Compared with my general level of health over the past 12 months, my health state today is:**
- ₁ Better
- ₂ About the same
- ₃ Worse

COMMENTS:

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INITIALS or SIGNATURE:	SHEET NO.	24

TR No.: 7217-95-037



STEP-UP
EUROQOL QUESTIONNAIRE (Part 2 of 2)

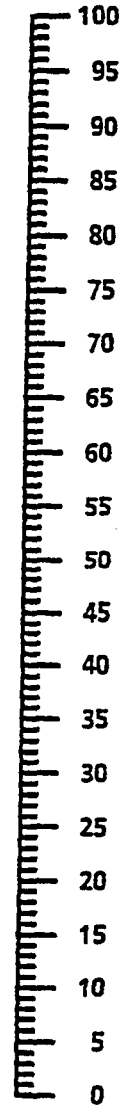
93-0284-29 3/94

PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100, and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Best imaginable
health state



Your Own Health State Today

Worst imaginable
health state

SCALE SCORE:

INITIALS or
SIGNATURE:

SHEET NO.

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TR No.: 7217-95-037

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STEP-UP

DAILY ACTIVITIES - FUNCTIONAL STATUS QUESTIONNAIRE² - Page 1 of 6

To be answered by the patient

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PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE	DATE OF THIS EVALUATION	MO. / DAY / YR.	SITE NO.

This group of questions refers to many types of physical and social activities. We would like to know how difficult it was for you to do each of these activities, on the average, during the past month. By difficult, we mean how hard it was or how much physical effort it took to do the activity because of your health.

Circle the number:

4	if you usually had no difficulty doing it;
3	if you usually had some difficulty doing it;
2	if you usually had much difficulty doing it;
1	if you usually did not do the activity because of your health; or
0	if you usually did not do the activity for other reasons.

DURING THE PAST MONTH, HOW MUCH PHYSICAL DIFFICULTY DID YOU HAVE . . .	USUALLY DID WITH NO DIFFICULTY	USUALLY DID WITH SOME DIFFICULTY	USUALLY DID WITH MUCH DIFFICULTY	USUALLY DID NOT DO BECAUSE OF HEALTH	USUALLY DID NOT DO FOR OTHER REASONS
1. Taking care of yourself, that is, eating, dressing, or bathing?	4	3	2	1	0
2. Moving in and out of a bed or chair?	4	3	2	1	0
3. Walking <u>several</u> blocks (a few hundred meters or yards)?	4	3	2	1	0
4. Walking <u>one</u> block or climbing <u>one</u> flight of stairs? (30-40 meters or yards)	4	3	2	1	0
5. Walking indoors, such as around your home?	4	3	2	1	0
6. Doing work around the house such as cleaning, light gardening, home maintenance?	4	3	2	1	0
7. Doing errands, such as grocery shopping?	4	3	2	1	0
8. Driving a car or using public transportation?	4	3	2	1	0
9. Visiting with relatives or friends?	4	3	2	1	0
10. Participating in community activities, such as religious services, social activities, or volunteer work?	4	3	2	1	0

Continued . . .

INITIALS or
SIGNATURE:

SHEET NO.

27

TR No.: 7217-95-037



**STEP-UP
DAILY ACTIVITIES - FUNCTIONAL STATUS QUESTIONNAIRE[®] - Page 2 of 6**

Answered by the Patient

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93-0286-31 1/76	PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.	

DURING THE PAST MONTH, HOW MUCH PHYSICAL DIFFICULTY DID YOU HAVE ...	USUALLY DID WITH NO DIFFICULTY	USUALLY DID WITH SOME DIFFICULTY	USUALLY DID WITH MUCH DIFFICULTY	USUALLY DID NOT DO BECAUSE OF HEALTH	USUALLY DID NOT DO FOR OTHER REASONS
11. Taking care of other people such as family members?	4	3	2	1	0
12. Doing vigorous activities such as running, lifting heavy objects or participating in strenuous sports?	4	3	2	1	0

13. During the past month, how many days did illness or injury keep you in bed all or most of the day? (If none, write "0")
 _____ DAYS IN BED during the past month

14. During the past month, how many days did you cut down on the things you usually did for one-half day or more because of your own illness or injury? (Do not count the day(s) spent in bed)
 _____ DAYS during the past month

15. Are you unable to do certain kinds or amounts of work, housework, or school or university work because of your health?
 (Circle one)
 YES, for less than 3 months 1
 YES, for 3 or more months 2
 NO, my health was not limited this way 0

16. Does your health keep you from working at a job, doing work around the house, or going to school or university?
 (Circle one)
 YES, for less than 3 months 1
 YES, for 3 or more months 2
 NO, my health was not limited this way 0

17. How do you feel about your own health?
 (Circle one)
 VERY SATISFIED 5
 SATISFIED 4
 NOT SURE 3
 DISSATISFIED 2
 VERY DISSATISFIED 1

Continued ...

INITIALS or SIGNATURE:	SHEET NO.	28

TR No.: 7217-95-037



STEP-UP WELL BEING - FUNCTIONAL STATUS QUESTIONNAIRE[®] - Page 3 of 6

Answered by the Patient

DO NOT WRITE IN SHADED AREAS

91-0286-24 3-94	PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.	

These next questions ask about how you feel and how things have been with you during the past month. For each question, please circle the number for the one answer that comes closest to the way you have been feeling.

DURING THE PAST MONTH HOW MUCH OF THE TIME:	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
18. Have you been a very nervous person?	1	2	3	4	5	6
19. Have you felt calm and peaceful?	1	2	3	4	5	6
20. Have you felt down-hearted and blue?	1	2	3	4	5	6
21. Were you a happy person?	1	2	3	4	5	6
22. Did you feel so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
23. Did you isolate yourself from people around you?	1	2	3	4	5	6
24. Were you affectionate toward others?	1	2	3	4	5	6
25. Did you act irritable toward those around you?	1	2	3	4	5	6
26. Did you make unreasonable demands on your family and friends?	1	2	3	4	5	6
27. Did you get along well with other people?	1	2	3	4	5	6

Continued ...

INITIALS or SIGNATURE:	SHEET NO.	29

TR No.: 7217-95-037



**STEP-UP
SOCIAL ACTIVITIES - FUNCTIONAL STATUS QUESTIONNAIRE[®] - Page 4 of 6**
Answered by the Patient

DO NOT WRITE IN SHADED AREAS

91-0286-15 3-94				
PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE		SITE NO.	

28. About how many close friends do you have - people you feel at ease with and can talk with about what is on your mind? (You may include relatives.)
 (Enter number on line:)

_____ CLOSE FRIENDS AND RELATIVES

29. During the past month, about how often did you get together with friends or relatives, like going out together, visiting in each other's homes, or talking on the telephone?

	(Circle one)
EVERY DAY	6
SEVERAL TIMES A WEEK	5
ABOUT ONCE A WEEK	4
2 OR 3 TIMES DURING THE MONTH	3
ABOUT ONCE A MONTH	2
NOT AT ALL	1

30. During the past month, how satisfied were you with your sexual relationships?

	(Circle one)
VERY SATISFIED	5
SATISFIED	4
NOT SURE	3
DISSATISFIED	2
VERY DISSATISFIED	1
DID NOT HAVE ANY SEXUAL RELATIONSHIPS	0

Continued...

INITIALS or SIGNATURE:	SHEET NO.	30

TR No.: 7217-95-037



**STEP-UP
EMPLOYMENT - FUNCTIONAL STATUS QUESTIONNAIRE® - Page 5 of 6**

Answered by the Patient

DO NOT WRITE IN SHADED AREAS

91-0784-36 3/84	PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.	

The next question concerns your present working situation other than managing your home.

31. Which of the following statements best describes your work situation during the past month?

- WORKING FULL-TIME
- WORKING PART-TIME
- UNEMPLOYED, LOOKING FOR WORK
- UNEMPLOYED BECAUSE OF MY HEALTH
- RETIRED BECAUSE OF MY HEALTH
- RETIRED FOR SOME OTHER REASON
- OTHER

(Circle one)

1	} Go to #32
2	
3	} Go to Next Page
4	
5	
6	
7	

DURING THE PAST MONTH, HOW MUCH OF THE TIME DID YOU:	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	NONE OF THE TIME
32. Do as much work as others in similar jobs?	1	2	3	4
33. Work for short periods of time or take frequent rests because of your health?	1	2	3	4
34. Work your regular number of hours?	1	2	3	4
35. Do your job as carefully and accurately as others with similar jobs?	1	2	3	4
36. Work at your usual job, but with some changes because of your health (for example, use special equipment, trade tasks with other workers)?	1	2	3	4
37. Fear losing your job because of your health?	1	2	3	4

Continued ...

INITIALS or SIGNATURE:	SHEET NO.	31

TR No.: 7217-95-037

Upjohn**STEP-UP
EMPLOYMENT - SUPPLEMENTAL - Page 6 of 6***Answered by the Patient***DO NOT WRITE IN SHADED AREAS**

93-0786-17 1'94				
PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.

INSTRUCTIONS: If, based on question 31 on the previous page, you are:

- working full or part time, go to part A below.
- retired for any reason or unemployed for health reasons, go to Part B below (skip part A).
Otherwise, skip parts A, B, and C. You have completed this questionnaire.

PART A. For those working full or part-time according to question 31:

- A1. How many hours do you normally work per week? ___ hours
- A2. In the last month, approximately how much work time have you missed due to problems resulting from your Parkinson's Disease?
___ Days (enter 0 if you did not miss any work time)

GO TO PART C BELOW (skip part B).**PART B.** For those retired for any reason or unemployed for health reasons based on question 31:

- B1. Are you currently unemployed, or did you retire early, because of your Parkinson's Disease?
- ₁ Yes (go to next question)
₀ No (go to Part C below)
- B2. How long have you been retired or unemployed solely because of your Parkinson's Disease? (Do not count time since your normal retirement age):
___ years, ___ months

GO TO PART C BELOW.**PART C.**

Please check the category below which best describes the kind of work you do (or did) on your current (or most recent) job:

- ₁ Professional, technical or related
- ₂ Administrative or managerial
- ₃ Clerical or related
- ₄ Sales
- ₅ Service (including all food and lodging services)
- ₆ Agriculture, animal husbandry, forestry, fishing
- ₇ Production or related work, transport equipment operators or laborers
- ₈ Armed forces
- ₉ None of the above

(If you have trouble picking the best category please ask the study nurse or doctor for assistance. A detailed list of occupations by category is provided in the operations manual.)

INITIALS or SIGNATURE:	SHEET NO.	32

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Brin, Mitchell, M.D. Bressman, Susan, M.D. Columbia University 710 W. 168th, Rm. 309 New York, NY 10032	15
Gauthier, Serge, M.D. McGill Ctr. for Studies in Aging St. Mary's Hospital 3830 Lacombe Avenue Montreal, Quebec H3T 1M5 Canada	6
Grimes, J. David, M.D. Ottawa Civic Hospital Ottawa, Ontario K1Y 4E9 Canada	15
Harrison, Madaline B., M.D. Dept. of Neurology, Box 394 Univ. of Virginia Health Sciences Ctr. Charlottesville, VA 22908	10
Hauser, Robert, M.D. (6/13/94 - present) Olanow, C. Warren, M.D. (1/19/93 - 6/12/94) University of South Florida 4 Columbia Dr., Suite 410 Tampa, FL 33606	15
Hubble, Jean, M.D. Univ. of Kansas Medical Center Department of Neurology 3901 Rainbow Blvd. Kansas City, KS 66160-7314	10
Hurtig, Howard I, M.D. The Graduate Hospital University of Pennsylvania Department of Neurology 1 Graduate Plaza Philadelphia, PA 19146	18

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Kurlan, Roger, M.D. University of Rochester Department of Neurology 601 Elmwood Avenue, Box 673 Rochester, NY 14642	15
Lew, Mark F, M.D. Univ. of Southern California Department of Neurology USC School of Medicine 1510 San Pablo, Suite 615 Los Angeles, CA 90033	20
Marek, Kenneth I, M.D. Yale Univ. School of Medicine Department of Neurology 333 Cedar Street New Haven, CT 06510	11
Perlmutter, Joel, M.D. Washington Univ. School of Medicine Neurology, Campus Box 8225 510 S. Kings Highway St. Louis, MO 63110	7
Rajput, Ali H, M.D. University of Saskatchewan Clinical Neurology, Rm 1663 Royal University Hospital Saskatoon, SK S7N 0X0 Canada	10
Rao, Jayaraman, M.D. LSU Medical Center 1542 Tulane Avenue New Orleans, LA 70112	15
Rodnitzky, Robert, M.D. University of Iowa Department of Neurology University Hospitals Iowa City, IA 52242	12
Sethi, Kapil D, M.D. Medical College of Georgia B1W-340 Dept. of Neurology 1120 15th Street Augusta, GA 30912	15

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Shannon, Kathleen M, M.D. Rush-Presbyterian/St. Luke's Medical Center Dept. of Neurological Sciences 1725 W. Harrison, Suite 1106 Chicago, IL 60612	14
Suchowersky, Oksana, M.D. Univ. of Calgary/Foothills Hospital 3350 Hospital Drive, NW Calgary, Alberta T2N 4N1 Canada	10
Tanner, Caroline M, M.D. The Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089	14
Trosch, Richard, M.D. Sinai Hospital of Detroit Clinical Neuroscience Program Blumberg Professional Offices 14800 W. McNichols Rd., Suite 100 Detroit, MI 48235	19
Weiner, William, M.D. Univ. of Miami School of Medicine Department of Neurology National Parkinson Foundation 1501 NW 9th Avenue Miami, FL 33136	13

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Study 17

This was designed to be a **single-blind**, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 48 patients were to be enrolled.

Patients were early-onset PD patients who had not received more than 3 months of L-dopa in the past. Concomitant anticholinergics were allowed. Concomitant amantadine was prohibited. All patients were on deprenyl.

There was a 7-week dose-escalation phase, with a maximal daily dose of 4.5-mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced to a prior tolerated dose and that patient would begin the maintenance phase. Following dose-escalation, there was a 3 week maintenance period and then a 1 week dose reduction period.

Replacement of dropouts was allowed (p 5 of the protocol).

"Patients who drop from the study prior to completing at least two weeks of the maintenance dose interval...or are less than 75% compliant with the study drug...will be replaced."

Assessments included Parts II and III of the UPDRS. The primary outcome was mean change from baseline on Parts II and III of the UPDRS at the end of maintenance.

Results:

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Fifty-six patients were randomized; only 55 ever received a first dose, so that the ITT population includes 55 patients. The sponsor has provided an analysis of an evaluable data set, which excludes 2 patients that the sponsor believes were shown after randomization to not have idiopathic PD. One of the 2 pts was replaced, but the second patient was reclassified after the trial was over and, thus, could not be replaced.

The results for the evaluable, observed case analysis is shown below: ["Observed case" seems to be a misnomer here since, by protocol, if a patient had not been in the maintenance phase for 2 weeks, that pt was to be replaced.]

Adjusted Change From Baseline, UPDRS II

Pramipexole	5.19 (n=28)	
Placebo	2.16 (n=24)	p=0.002

Adjusted Change From Baseline, UPDRS III

Pramipexole	11.97 (n=27)	
Placebo	8.31 (n=24)	p=0.10

There were no deaths or serious AEs. There was only one discontinuation for AE, a placebo patient with worsening of PD. Ten patients (1 placebo; 9 pramipexole) had dose-limiting toxicity from AEs, to include hallucinations, violent dreams, insomnia, and drowsiness.

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Conclusions:

Hallucinations resulted in dose-limiting toxicity in 3 pramipexole patients. Note that the primary outcome encompassed Parts II and III of the UPDRS, so that a favorable score on those subscales could be recorded in the face of serious AEs that required dose adjustments.

The maintenance period here was only 3 weeks long, making any extrapolation from these results difficult.

While more patients may have improved on the ADL scale while on pramipexole as opposed to placebo, some pramipexole patients had serious AEs (hallucinations) requiring dose adjustments. Given the brief maintenance period, it is unknown how long the risk-benefit ratio would have continued in favor of pramipexole.

It is reassuring that the estimates of change from baseline on the ADL scale here are so similar to those seen in Study 21 (a study very comparable in design to Study 17). The difference on the ADL scale is statistically significant here, but not in Study 21.

On the other hand, the estimates of change from baseline on the Motor Exam scale here are different from those in Study 21. The directionality favors pramipexole in both studies, but is statistically significant only in Study 21.

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Study 21

This was designed to be a double-blind, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 52 patients were required to complete the maintenance dose schedule; in order to achieve this, the protocol called for 72 patients to be randomized.

Patients were early-onset PD patients who had not received more than one week of L-dopa in the past. Concomitant anticholinergics and deprenyl were allowed. Concomitant amantadine was prohibited. Domperidone was allowed.

There was a 9-week dose-escalation phase, with a maximal daily dose of 4.5 mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced 1 or 2 levels. Following dose-escalation, there was a 2 week maintenance period and then a 1 week dose reduction period.

Assessment included Parts II and III of the UPDRS. The primary outcome was mean change from baseline on Part III of the UPDRS at the end of maintenance.

Results:

Only 24 patients were recruited out of the planned 72 before the sponsor stopped the study. The sponsor has provided an analysis of an **explanatory data set**, which excludes a pramipexole patient with a prior history of hallucinations and a placebo patient previously treated for 5 months with L-dopa. The sponsor maintains that these patients did not meet the inclusion/exclusion criteria.

The results for this explanatory data set are shown below:

	Change From Baseline	
Pramipexole	7.2 (n=10)	
Placebo	1.6 (n=12)	p=0.02

The sponsor also examined the results for Part II of the UPDRS (ADL). There was a trend toward improvement following treatment with

pramipexole, but no statistically significant difference. The mean change from baseline for pramipexole was 5 points, while the mean change from baseline for placebo was 2 points.

The sponsor maintains that an improvement of 30% on the motor exam is significant in terms of patient benefit (p 75 of the Technical Report). Using the entire cohort of 24 patients, I categorized patients as 30% improved or not. The results follow:

30% Improved on Motor Exam

- Pramipexole	6/11
- Placebo	2/13

However, note that 2 placebo patients were withdrawn early (pts 29,76) because of "lack of efficacy" or protocol violation (late recognition that pt had 5 months prior treatment with L-dopa). These represent 2 potential "winners" on placebo who were prematurely taken out of the running. One would assume that "lack of efficacy" would at least have led to further dose escalation, rather than withdrawal. Meanwhile, the 6 pramipexole patients with 30% improvement are balanced by 2 pramipexole patients who discontinued with serious AEs.

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Conclusions:

The study was stopped early because of low enrollment. The sponsor states that the protocol required weekly visits and that the early PD patients (who were often working) had a hard time making that sort of time commitment.

Two (out of 11) pramipexole patients discontinued because of hallucinations. Note that the primary outcome was the motor exam of the UPDRS, so that a favorable score on that scale could be recorded in the face of serious AEs that required discontinuation.

The maintenance period here was only 2 weeks long, making any extrapolation from these results difficult. (Note also that one pramipexole patient, pt 65, inadvertently skipped the 2-week maintenance phase so that the score at end of dose-escalation was used for outcome assessment.)

While more patients may have improved on the motor exam while on pramipexole as opposed to placebo, 2 pramipexole patients had serious AEs (hallucinations) requiring discontinuation. Given the brief maintenance period, it is unknown how long the risk-benefit ratio would have continued in favor of pramipexole.

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Study 10

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of pramipexole vs. placebo, added on to maintenance L-dopa (with a decarboxylase inhibitor) therapy. The treatment periods were designed to be at least 6 months in duration.

The target population were patients with a less than optimal response to L-dopa, characterized by the presence of motor fluctuations. 300 patients were to be entered, 150 per treatment group. A total of 24 centers in the U.S. and Canada were planned with up to 24 patients per center.

Inclusion criteria were:

1. Patients with idiopathic Parkinson's disease, Hoehn and Yahr Scale scores of II-IV during an on period, age 30 years and older. Scores of II-IV encompass patients with bilateral disease with minimal-severe disability and balance problems. A score of V would be given to a bedbound or wheelchair-bound patient. A score of I would be given to a patient with only unilateral disease.

2. Given a stable dose of L-dopa for 30 days prior to randomization, patients had to demonstrate continued motor fluctuations, specifically the so-called "wearing-off" effect, where the duration of effect from a single dose of L-dopa becomes progressively shorter over time.

Page 11 of the protocol added that, if the patient was taking deprenyl, amantadine, or and anticholinergic medication, the dose of that medication should be stable for 30 days prior to randomization.

3. Patients had to be able to keep an accurate daily diary of "on" and "off" periods during waking hours, with the help of caregivers.

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Exclusion criteria were:

1. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.
2. Dementia or active psychosis.
3. Second or third degree AV block or sick sinus syndrome; resting heart rate below 50; CHF Class III or IV; MI within 6 months; other clinically significant heart conditions.
4. Occurrence of a seizure within 2 years.
5. Renal or hepatic impairment. Neoplastic disease.
6. Surgery within 6 months which the investigator believes could impact patient's participation.
7. History of stereotactic brain surgery.
8. SBP less than 100 or a symptomatic drop in SBP or 20 or greater upon standing.
9. Neuroleptics within 60 days; alpha-methyl dopa within 60 days; metoclopramide within 60 days; flunarizine, cinnarizine, parenteral ergots, bromocriptine, pergolide, lisuride, MAO inhibitors other than deprenyl, methylphenidate, amphetamine, beta blockers if used to treat tremor, or reserpine within 30 days.
10. Adequate contraception and a negative pregnancy test for all women of childbearing potential.
11. Electroconvulsive therapy within 90 days.

The schedule of time and events is on the next page. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria and if they demonstrated the ability to keep the daily diary, patients were **randomized** to receive the first dose of study medication. An

PRAMIPEXOLE PHASE III TRIAL IN ADVANCED PARKINSON'S DISEASE
 PROTOCOL SUMMARY - 00679A (Double-Blind, Placebo-Controlled)

	Screening	Ascending-Dose Interval ^a								Maintenance-Dose Interval ^b								
Visit Number	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 ^c
Days since the last visit		1-14	5-9	5-9	5-9	5-9	5-9	5-9	5-9	10-16	10-16	10-16	10-16	10-16	10-16	25-35	25-35	26-35
Dose Level		1	2	3	4	5	6	7	M ^d	M	M	M	M	M	M	M	M	M
History	X																	
Physical Examination ^e	X																	
Laboratory Tests ^e	X				X				X				X ^f			X ^f		X ^f
Chest X-Ray	X																	
12-Lead ECG ^e	X				X				X				X			X		X
Disability Ratings ^g	X	X	X	X	X	X	X	X	X		X		X		X	X		X
Dispense Daily Patient Records (on/off diaries)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluate Daily Patient Records (on/off diaries)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events ^h and Concomitant Meds ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization to Treatment		X																
Dispense Trial Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs ⁱ	X	X	X	X	X	X	X	X	X		X		X		X	X		X
Medication Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Motor Examination ^j		X	X	X	X	X	X	X	X		X		X		X	X		X
Dyskinesia Scales ^k		X	X	X	X	X	X	X	X		X		X		X	X		X

1. The levodopa/decarboxylase inhibitor daily dose and timing of dosing must be stable for 30 days prior to Visit 2.
 2. Duration of the ascending-dose interval varies depending upon the optimal daily dose of study medication that is achieved. The optimal daily dose is defined as either the maximally tolerated dose of study medication or the dose associated with stable improvement (i.e., lack of further improvement despite up to two additional dose increases). The degree of improvement is based upon the clinical judgement of the investigator without examination of previous scores on various rating scales used in the trial.
 3. Maintenance dose (M) is either the maximally tolerated dose or the optimal dose if adverse events do not prevent dose escalation during the ascending-dose interval.
 4. Parts I, II, and IV of the UPDRS, Modified Schwab-England Disability Scale, and the timed-walking test (start at Visit 2). Modified Hoehn and Yahr Scale (start at Visit 1).
 5. Vital signs (supine and 1 minute standing blood pressure and pulse rate) are taken at Visit 1 in triplicate per protocol, prior to study medication at Visit 2 only and at 2 hours post-dose of study medication at all visits beyond visit 1 as noted above.
 6. UPDRS Part III (motor examination) is done two to three hours following a levodopa dose taken either before the clinic visit or at the start of a clinic visit.
 7. Parkinson's Dyskinesia Scale done two to three hours following a levodopa dose.
 8. Dose-Reduction Interval starts with Visit 18 and ends at Visit 19, the final visit in Part I. See Protocol Summary Part II for specific procedures to be completed for Visit 19.
- ^a Required for patients who drop from the trial.
^e Blood samples for determination of pramipexole serum concentrations to be obtained.

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ascending-dose phase followed and could last as long as 7 weeks. If patients experienced dose-limiting toxicity prior to reaching the maximal dose, they entered the **maintenance phase** at that point (prior to 7 weeks). A patient who moved into the maintenance phase after only 1 or 2 weeks of the ascending-dose phase was considered to have missing data for the additional 5-6 weeks of the ascending-dose phase, resuming entries with visit 9. The maintenance phase was 6 months in duration and was followed by a **1 week dose reduction phase**.

The ascending dose schedule is on the next page. Study medication was to be taken 1 hour before or 2 hours after meals. There were 7 possible fixed dose regimens, ranging from a total daily dose of The dose was to be raised until dose-limiting toxicity was reached, the maximum dose was reached, or there was a lack of further clinical improvement in the judgment of the investigator despite up to two additional increases in the dose of study medication.

The protocol does not have instructions for dose adjustments of study medications if patients developed AEs during the maintenance phase. That is, if a patient developed nausea during the maintenance phase, it is not clear if the dose of study drug could be lowered.

During the maintenance phase, the dose of L-dopa could be adjusted downward if dyskinesias, hallucinations, or psychiatric side effects developed. The dose could subsequently be increased, but not to a level in excess of the original daily dose. Doses of concomitant anticholinergics, deprenyl, and amantadine were to remain constant during the study.

Patient visits occurred every week during the ascending dose phase. Patient visits occurred every 2 weeks for the first 3 months of the maintenance phase and every month for the last 3 months of the maintenance phase.

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Pramipexole Ascending-Dose Schedule

	<u>Dose Level</u>	<u>Dosage</u>	<u>Total Daily Dose</u>
Week 1	1	3 x 0.125 mg	0.375 mg
Week 2	2	3 x 0.25 mg	0.75 mg
Week 3	3	3 x 0.5 mg	1.50 mg
Week 4	4	3 x 0.75 mg	2.25 mg
Week 5	5	3 x 1.0 mg	3.00 mg
Week 6	6	3 x 1.25 mg	3.75 mg
Week 7	7	3 x 1.5 mg	4.50 mg

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Monthly, during the maintenance phase, the investigator completed the following scales:

1. Parts I, II, and IV of the UPDRS. Part I rates mentation, mood, and behavior. Part II rates ADLs during the past week. Part IV rates complications of therapy, including dyskinesias.
2. Modified Schwab-England Disability Scale
3. Timed Walking Test
4. Modified Hoehn and Yahr Scale

At the same time intervals, the investigator completed the following 2 exams:

1. Part III of the UPDRS (the motor exam). Protocol Amendment #4 clarified that this was to be completed during an "on" period.
2. Parkinson's Dyskinesia Scale

These last 2 exams were to be performed 2-3 hours after the last dose of L-dopa, taken either at home or at the beginning of the clinic visit, and 1-4 hours after the last dose of test drug.

At the same monthly intervals, the investigator evaluated the **daily diaries** for the previous time interval. Patients were instructed to complete the diaries for at least 2 full days prior to their scheduled clinic visits. This was recorded in the CRF as the total waking hours for each day, the number of "off" hours for each day, and the average severity level for the "off" hours in a given day (1-4 scale).

Copies of all scales from the CRF are attached at the end of this Study 10 review. Note that several of the above scales yielded 2 scores, one representing best performance during an "on" period and one representing best performance during an "off" period. This applies to:

1. Part II of the UPDRS
2. Modified Schwab-England Disability Scale
3. Modified Hoehn and Yahr Scale

An operational definition of "on" and "off" was never provided in the protocol. Generally these terms are used to differentiate times when patients are responding well to medicines and periods when they are not

responding well. Off times could occur at predictable times, especially in the time preceding the next dose of medicine. Off times could also occur at unpredictable times, unrelated to time of medicine. The latter unpredictable off times could be brief, referred to as "freezing," or they could be more prolonged. Off time may not represent as low a level of functioning as might be seen in the total absence of medicine, but is generally referenced to a better level of functioning that occurs on the same daily dose of medication.

Replacement of patients was allowed by protocol if those patients discontinued the study for any reason other than AEs (to include worsening of underlying Parkinson's Disease) prior to completing half of the maintenance phase. **Protocol Amendment #1** added that patients who dropped out of the study prior to completing the maintenance phase were to return for a final visit at the time their final visit would have occurred.

Note that during the ascending-dose phase, patients assigned to the pramipexole group received both pramipexole and placebo tablets; patients assigned to the placebo group were not exposed to pramipexole.

Two primary outcome variables were stated in the protocol: Part II of the UPDRS (ADL) and Part III of the UPDRS (motor exam).

The analysis plan stated that "the primary efficacy endpoint for each of these parts of the UPDRS is the change in the score between baseline and maintenance where the maintenance score is the last available score prior to the dose-reduction interval." The primary analysis plan was not clearly specified in the protocol. **Protocol Amendment #4** clarified this situation. It stated that "In order for this study to be declared positive, both primary endpoints must achieve statistical significance." The ITT population was to be the primary analysis population with an LOCF technique employed for missing data.

The sample size was computed using results in the DATATOP study and making assumptions about how the early Parkinson's Disease population in DATATOP might differ from the target population in the current study. It was estimated that with 150 patients per treatment group, the study would have 90% power to detect small differences on the order of 2-4 points in change from baseline in Part III of the UPDRS (motor exam).

B. Subject Disposition and Baseline Comparison

The planned enrollment was 300, with plans to replace patients who did not complete half the maintenance phase for reasons other than AEs. On page 37 of the study report, the sponsor states that enrollment exceeded the planned enrollment because, by the time it became apparent that enough patients would complete the trial, other patients were already enrolled in earlier stages of the trial.

360 patients were randomized: 181 pramipexole and 179 placebo. The investigators and centers (22 U.S. and 4 Canadian) are listed at the end of this Study 10 review.

Protocol Deviations: 3% of patients entered without meeting all inclusion/exclusion criteria. These included systolic blood pressure < 100, concomitant use of bromocriptine, lack of advanced Parkinson's Disease symptoms, abnormal baseline labs, and prior pramipexole use.

4% of patients had their baseline Sinemet dose exceeded during the trial.

4% of patients took excluded meds during the study to include pergolide, bromocriptine, haloperidol, timolol, and metaclopramide.

37/69 patients who withdrew from the study did not return for the follow-up visit at what would have been Visit 18, as outlined in a protocol amendment.

15% of patients had some baseline testing done after the first dose of study medication. The sponsor states that the first dose was placebo for all patients so that the results should not have been affected.

At least 28% of patients had at least one evaluation performed outside the protocol-specified time interval.

Likewise, at select visits, 10% of patients demonstrated medication compliance less than 75% or greater than 125%.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics.

	Placebo N=179	Pramipexole N=181
Age	63 (39-89)	63 (31-84)
Sex	116M/63F	119M/62F
Race	96% White	95% White
Parkinson's Duration	9 yrs	9 yrs
Deprenyl Use	53%	56%
Anticholinergic Use	12%	14%
Part II "On" Score	8	7
Part II "Off" Score	17	17
Part III Score	23	23
Hoehn & Yahr "On"	2.3	2.3
Hoehn & Yahr "Off"	2.9	3.0

Patient Flow: One patient (placebo) withdrew before receiving drug, so that only 359 patients were treated. Altogether, 9 patients (including the one just mentioned) did not meet the ITT definition, i.e. they did not have at least one efficacy assessment. Therefore, 351 patients are included in the efficacy analysis: 179 pramipexole and 172 placebo.

The following table outlines the withdrawals during the study. In addition to the 68 withdrawals in the table, there was the 1 placebo patient already mentioned who withdrew prior to receiving the first dose. Therefore, there were 69 withdrawals altogether.

Withdrawals (Withdrawals Due to AEs)

	Pramipexole	Placebo
Ascending Dose Phase	12 (9)	22 (16)
Maintenance Phase	18 (15)	16 (14)
TOTAL	30 (24)	38 (30)
	68 (54)	

The timing of the withdrawals had the potential to be important as the protocol allowed for replacement of patients who withdrew prior to visit 15 for reasons other than AEs. However, since only 14 patients withdrew for reasons other than AEs, the latter point took on less importance. As far as I know, there were no replacements during the conduct of the trial. Sponsor's Table 7.3.3:1 on the next page outlines the number of withdrawals by visit for the two treatment groups.

The reasons for withdrawals are shown in the next table.

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Patient Disposition

	Pramipexole	Placebo
Disease Worsening	3	9
Worsening of Pre-existing Disease	0	3
Other AEs	21	18
Protocol Violation	1	0
Lost to Follow-Up	0	2
Withdrew Consent	4	3
Other	1	4

151/181 pramipexole patients completed the trial. 140/179 placebo patients completed the trial.

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Of the 360 patients who were randomized into the trial, 291 patients completed the protocol planned, and 69 patients withdrew. The visits after which these 69 patients withdrew are displayed in TABLE 7.3.3:1.

TABLE 7.3.3:1 Number of Patients Withdrawing from the Trial by Last Visit

Visit	Pramipexole	Cumulative Number (Percentage) of Pramipexole Patients Withdrawing by Visit	Placebo	Cumulative Number (Percentage) of Placebo Patients Withdrawing by Visit
2	0	0 (0%)	3	3 (8%)
3	2	2 (7%)	6	9 (23%)
4	2	4 (13%)	1	10 (26%)
5	1	5 (17%)	5	15 (38%)
6	0	5 (17%)	1	16 (41%)
7	3	8 (27%)	3	19 (49%)
8	1	9 (30%)	3	22 (56%) ¹
9	3	12 (40%)	0	22 (56%)
10	4	16 (53%)	3	25 (64%)
11	6	22 (73%)	5	30 (77%)
12	1	23 (77%)	1	31 (79%)
13	1	24 (80%)	2	33 (85%)
14	1	25 (83%)	1	34 (87%)
15	2	27 (90%)	2	36 (92%)
16	3	30 (100%)	1	37 (95%)
17	0	30 (100%)	1	38 (97%)
18	0	30 (100%)	1	39 (100%)
Total	30		39	

Source Data: Appendix 15.12 LISTINGS 7.1 and 7.2

¹ Patient 1054 discontinued prior to receiving study medication.

Thirty (43%) of the withdrawing patients were from the pramipexole group, while 39 (57%) were from the placebo group. The placebo group had both more withdrawing patients, and also faster withdrawal than the pramipexole group. By Visit 8 over half of the placebo dropouts had occurred, while only 30% of the pramipexole group dropouts had occurred. TABLE 7.3.3:1 also gives the cumulative percentage of dropouts by group for each visit, and it is apparent that dropouts occurred more quickly in the placebo group.

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C. Efficacy Evaluation

All the analyses in 1-10 below are LOCF analyses, unless specifically described otherwise.

In addition to the 9 patients excluded from all analyses because of lack of any efficacy measurements, some patients had to be excluded from the efficacy analysis for individual efficacy endpoints because of missing data. The sponsor lists all these cases, but they are rare enough that they are not reproduced here. For example, the largest number of patients excluded for a specific endpoint was 12 (3%), which was for the Average Severity of "Off" Time..

On page 62 of the study report, the sponsor addresses the issue of missing data. The sponsor notes the special case where a patient was to be rated for both the on and off periods. This applies to the UPDRS Part II, the Schwab-England Scale, and the Hoehn and Yahr Scale. The sponsor states that "on a few occasions" there was no off score recorded because the patient had no off periods during that particular reporting period. In that situation, the sponsor states that the on score was used to estimate the off score. My review of the data listings suggests otherwise. As shown in the table on the next page, an LOCF approach was used. The number of times that this situation arose is so small that it would not affect the overall results, however.

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**Patients With No Reported OFF Time (by diary) at Visit 18
and No Recorded OFF Score on UPDRS Part II**

Patient Number	Observed OFF Score (Imputed OFF Score)	Observed ON Score
Placebo Patients		
1035	* (12)	10
1041	* (14)	12
1154	* (13)	7
1294	* (4)	2

Pramipexole Patients		
1072	* (1)	0
1177	* (12)	4
1195	* (0)	2
1200	* (0)	9
1213	* (12)	5
1238	* (12)	1
1264	* (18)	10
1277	* (15)	17
1323	* (1)	0

* no valued recorded because of lack of "off" periods during that treatment period

[Data taken from Listings 4.5.2, 4.3.2, 4.4.2, and 4.3.1]

1. Percentage of On Time, On Time With Dyskinesia, and Off Time:

The percentage of awake time spent in the "off" state was not a primary outcome, but was a secondary outcome. I present this first because it seems to be integral to the whole study. First, the inclusion criteria mandated that patients have on-off phenomenon, especially end-of-dose failure. Second, the two primary outcome variables were defined in terms of on and off time (see below).

Note that, despite the prominent role of the "on-off" phenomenon in this trial, an operational definition is never clearly laid out in the protocol. The instructions for the patient daily diaries define "on" simply as a period of "good motor function." "Off" is defined as "able to move slowly or not at all." In the diaries, off periods were to be graded on a 1-4 scale with the mildest 1 rating defined as "mild slowness, stiffness, or resting tremor." Given this last qualification, one might infer that any emergence of underlying symptoms of Parkinson's Disease in a given patient would meet the definition of "off."

The UPDRS Part II score is an average of an on score and an off score. However, it does not weight the on score and off score with respect to changing amounts of time in the on period and the off period. Theoretically, a patient's on score and off score could both improve, but if more time was spent as off time, the patient would be worse on average, despite a better UPDRS Part II score.

The UPDRS Part III score was collected during an on period. It is called the motor exam portion of the UPDRS, but in fact, an important part of a patient's motor performance, dyskinesia, is not captured in Part III, but is displaced to Part IV.

The protocol defined a positive outcome as a joint outcome, a positive result on Part II and a positive result on Part III. Sponsor's Figures 9.3.1.1.3:1 and 2 on the next page demonstrate quite clearly for both the pramipexole and placebo groups that Parts II and III of the UPDRS are not correlated in Study 10. A patient with improvement on one scale has a fifty-fifty chance of improving on the other. That being the case, a more global assessment of patient function such as percentage off time is informative.

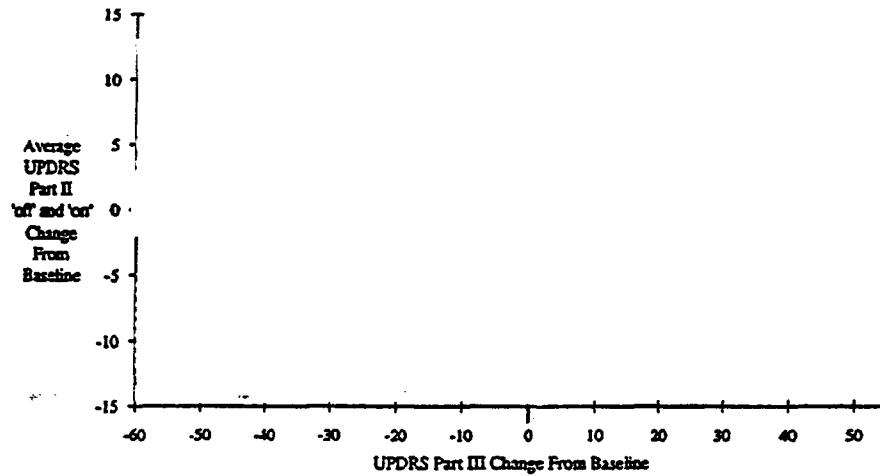


FIGURE 9.3.1.1.3:1 Pramipexole Group Change from Baseline for UPDRS Part II (Averaged) and Part III. Each Point Represents One Patient.
Last Observation Carried Forward Analysis

Source Data: Appendix 15.12.4

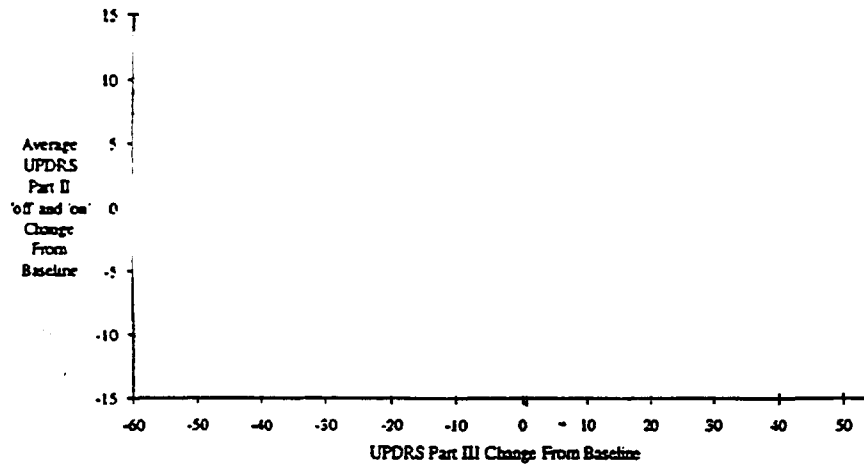


FIGURE 9.3.1.1.3:2 Placebo Group Change from Baseline for UPDRS Part II (Averaged) and Part III. Each Point Represents One Patient.
Last Observation Carried Forward Analysis

Source Data: Appendix 15.12.4

Sponsor's Figure 9.3.1.2.3:1 on the next page shows the average percentage of waking hours spent in an "off" state by visit for the two treatment groups. The information used for this evaluation was collected on the patient daily diary and then summarized by the investigator in the CRF at the time of patient visits. On the patient diary, patients were asked to choose between 4 options: on, off, on with dyskinesia, or asleep. When the investigator summarized this data on the CRF, only the amounts of "off" time and asleep time were transcribed. The sponsor presents the data in terms of percentage of awake time in an "off" state.

The observed case results for the same comparison are not presented by the sponsor.

The sponsor presents an analysis of change from baseline to final results on maintenance. The pramipexole group reduced their percentage of off time by 35% while the placebo group reduced their percentage of off time by 8% ($p=0.0006$).

Note that movement from "off" time could be in the direction of "on" time or "on with dyskinesia" or even "asleep." The sponsor has not provided data on these latter three options separately in the NDA. In fact, data on two of the latter three categories were not transferred from patient diaries to the CRFs. The sponsor addressed this in a September 27 submission.

In that submission the sponsor reports that, at the final maintenance visit, average off hours drop from 6 hrs at baseline to 3.9 hrs in the pramipexole group compared to from 6.2 hrs at baseline to 5.7 hrs in the placebo group. The average awake hrs changed very little throughout the study for both groups.

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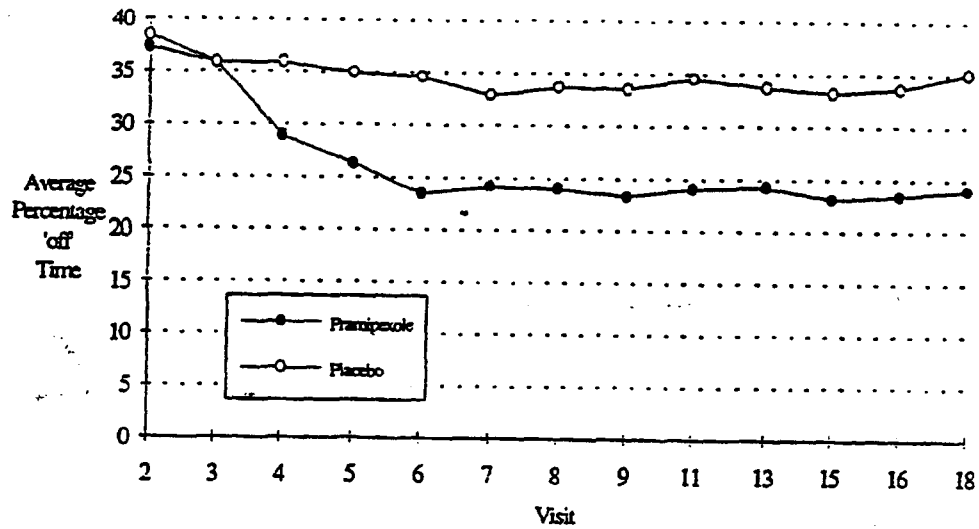


FIGURE 9.3.1.2.3:1 Average Percentage 'off' Time by Visit.

Last Observation Carried Forward Analysis

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TABLE 9.3.1.2.3:2 Mean (S.D.) Average Percentage of 'off' Period Time Change from Baseline.

Last Observation Carried Forward Analysis

	Baseline	Final Maintenance Visit	Unadjusted Change from Baseline to Final Visit on Maintenance	Adjusted ¹ Change from Baseline to Final Visit on Maintenance
Pramipexole n = 173	37.20 (19.91)	24.01 (22.45)	-13.18 (22.15)	-11.70
Placebo n = 172	38.28 (20.35)	35.13 (24.24)	-3.15 (23.20)	-2.82
p-value				0.0006

Source Data: Appendix 15.9.2 STATDOC 4.5.3

¹ Adjusted by center and center-by-treatment interaction (as per protocol).

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But there is an even more confusing issue raised by the data. In the table on the next page is a listing of patients who rated themselves as having no "off" time at visit 18, yet who were given "off" ratings on UPDRS Part II. This is incongruous. How could a patient have a score for a physiologic state that did not occur? The answer is that off periods did occur for these patients, but were not captured in the diary data.

In the September 27 submission, the sponsor reports frequency tables of number of days in the CRF diary at each visit for the two treatment groups. Patients were told to record diaries for at least 2 days prior to the next clinic visit; the CRF provided space to transcribe diary data for up to 10 days. Obviously, this presents a problem when looking at the last 3 months of maintenance, when pts were seen only once monthly. Two days may not capture the true experience of the month.

In fact the instructions for the diaries state, "The number of hours off per day divided by the total number of waking hours will be averaged over each week of assessment and recorded on case report forms." This implies an intent to analyze diary data weekly, an intent that could not be realized because of the study design which collected only snapshots of diary information every 30 days.

Reassuring is the fact that the snapshots were collected every 30 days and show a consistent trend in favor of the pramipexole group.

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Patients With No Reported OFF Time (by diary) at Visit 18

Patient Number	Observed OFF Score	Observed ON Score
Placebo Patients		
1168		
1169		
1222		
1311		
1358		

Pramipexole Patients		
1030		
1093		
1156		
1157		
1171		
1228		
1230		
1232		
1234		
1250		
1255		
1295		
1306		
1316		
1321		
1368		
1385		
1413		

Table D1
Frequency Tables of the Number of Days in the Diary at Each Visit
M/2730/0010

Visit	MC	Number of Days in the Diary										total N	p-value
		1	2	3	4	5	6	7	8	9	10		
Visit 2 (baseline)	PPX	6	47	29	32	13	18	11	5	3	11	175	0.896
	PBO	2	56	25	32	9	19	13	6	3	13	178	
Visit 3 (week 1)	PPX	0	53	24	27	12	20	28	9	2	3	178	0.829
	PBO	0	50	31	26	14	21	18	5	2	3	170	
Visit 4	PPX	0	50	28	27	7	30	26	4	2	3	177	0.911
	PBO	0	53	32	21	4	24	23	2	2	2	164	
Visit 5	PPX	0	53	17	25	9	20	23	9	3	1	160	0.459
	PBO	0	46	28	21	10	17	25	6	0	2	155	
Visit 6	PPX	0	50	19	22	12	20	18	7	1	2	151	0.643
	PBO	0	48	22	21	10	22	22	2	2	0	149	
Visit 7	PPX	0	44	17	21	8	15	22	0	4	1	132	0.592
	PBO	1	45	19	19	8	19	15	4	3	2	135	
Visit 8	PPX	0	38	11	16	5	13	17	3	2	0	105	0.922
	PBO	2	43	14	19	6	14	17	3	3	2	123	
Visit 9@	PPX	0	58	20	31	7	21	21	5	1	1	165	0.687
	PBO	0	53	26	23	7	18	24	2	3	0	156	
Visit 10	PPX	0	48	15	30	3	5	6	6	5	42	160	0.620
	PBO	1	46	23	32	0	4	6	4	6	34	156	
Visit 11	PPX	0	46	15	36	8	3	6	4	9	36	163	0.096
	PBO	1	39	26	32	1	2	5	3	2	40	151	
Visit 12	PPX	3	42	17	31	3	4	6	4	4	40	154	0.907
	PBO	3	35	22	32	1	1	5	4	3	39	145	
Visit 13	PPX	0	42	16	32	6	7	10	5	4	32	154	0.084
	PBO	2	39	22	27	2	1	9	0	2	36	140	

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End of Maintenance week 24

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Table D1
Frequency Tables of the Number of Days in the Diary at Each Visit
M/2730/0010

Visit	MC	Number of Days in the Diary										total N	p-value
		1	2	3	4	5	6	7	8	9	10		
Visit 14	PPX	2	44	15	33	1	6	8	7	2	35	153	0.552
	PBO	2	39	20	27	1	3	6	1	5	32	136	
Visit 15	PPX	1	45	12	34	3	5	7	4	6	31	148	0.747
	PBO	1	41	21	30	2	4	2	3	50	30	139	
Visit 16	PPX	1	42	15	24	5	4	8	8	4	39	150	0.987
	PBO	1	39	17	28	4	3	8	4	3	35	142	
Visit 17	PPX	2	42	14	24	6	3	7	10	7	32	147	0.884
	PBO	3	40	19	24	2	4	6	6	5	31	140	
Visit 18 #	PPX	2	37	17	24	4	2	3	10	6	40	145	0.902
	PBO	3	42	19	23	3	3	4	6	7	28	138	

@ Maintenance Week 0

End of Maintenance week 24

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2. UPDRS Part II

Sponsor's Figure 9.3.1.1.1:1 (next page) shows the average Part II scores (off and on means) by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

Sponsor's Figure 13.2.1 (next page) shows the observed case results for the same comparison. Page 68 of the study report states that 37 of 69 patients who dropped out did not return for evaluation at what would have been their visit 18. These 37 patients are not part of the OC analysis.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant. Consistency across other analyses of the same outcome variable can be seen below:

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)	OC Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-2.7	-2.8	-57	-54
Placebo	-0.5	-0.5	-18	-17
p-value	≤ 0.0001	≤ 0.0001	≤ 0.0001	≤ 0.0001

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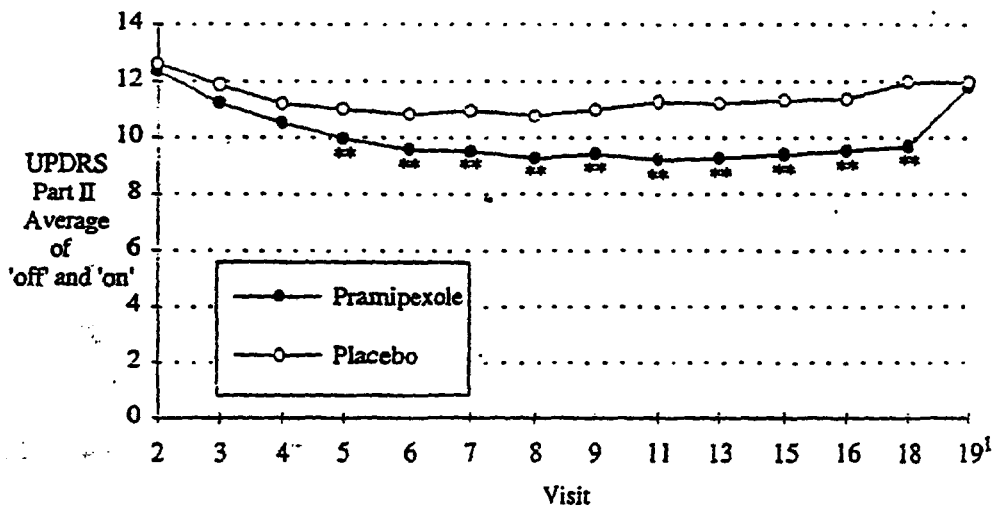


FIGURE 9.3.1.1.1:1 Average UPDRS Part II 'off' and 'on' Means by Visit.
Last Observation Carried Forward Analysis

Source Data: TABLE 9.3.1.1.1:1
* p ≤ 0.05 ** p ≤ 0.01 ¹ Observed Cases Analysis Only

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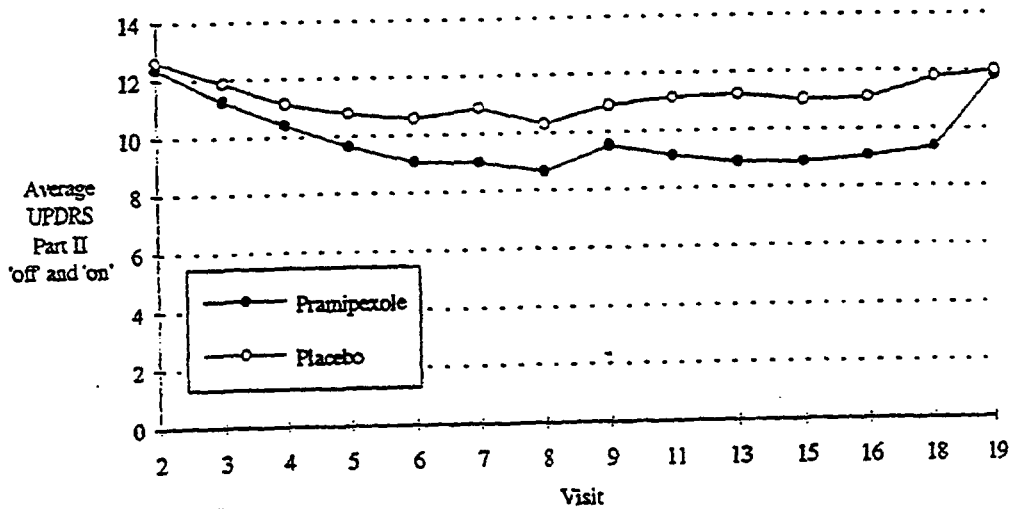
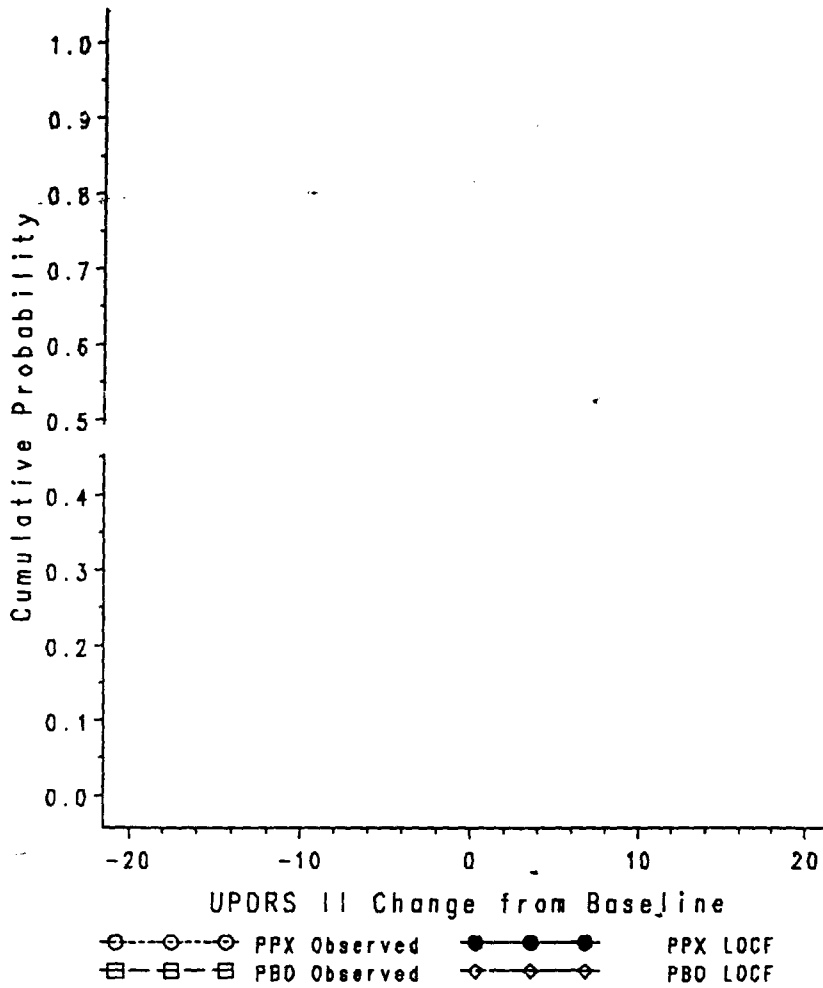


FIGURE 13.2.1 Average UPDRS Part II 'off' and 'on' Means by Visit.

Observed Cases Analysis

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Ogive Curve of UPDRS II Change from Baseline -- M/2730/0010



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Sponsor's Figure 9.3.1.2.2:1 (next page) shows the average Part II scores (on only) by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.1:1 (next page) shows the average Part II scores (off only) by visit for the two treatment groups.

For Part II, on, the difference in the treatment groups came from a number of components, with the largest components being: Turning in Bed, Cutting Food, and Hygiene.

For Part II, off, the difference in the treatment groups came from a number of components, with the largest components being: Freezing When Walking, Cutting Food, Walking, Hygiene, Turning in Bed, and Tremor.

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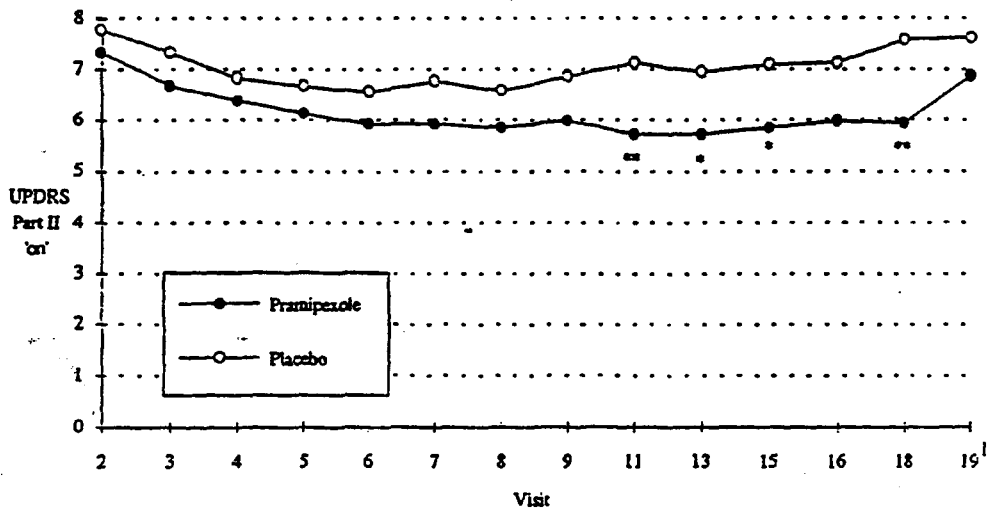


FIGURE 9.3.1.2.2:1 UPDRS Part II 'on' Means by Visit.

Last Observation Carried Forward Analysis

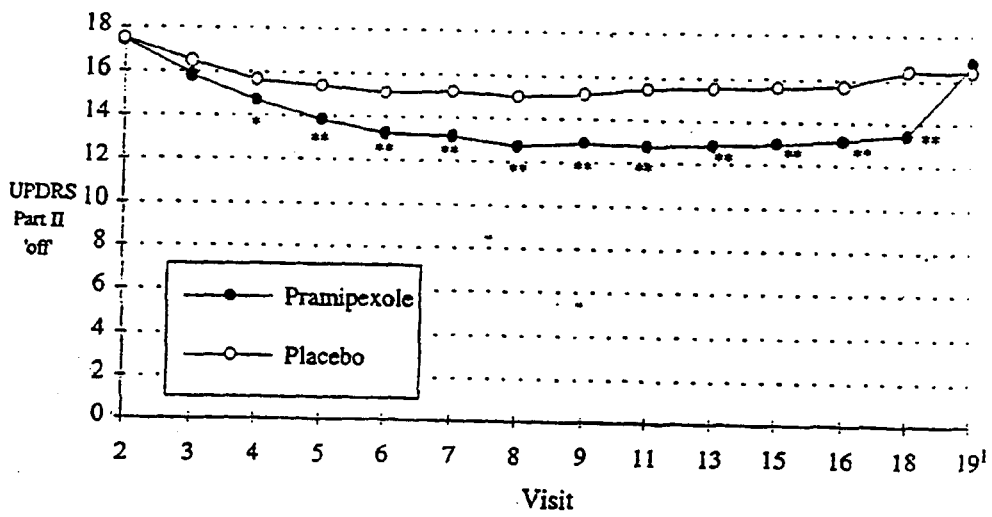


FIGURE 9.3.1.2.1:1 UPDRS Part II 'off' Means by Visit.

Last Observation Carried Forward Analysis

3. UPDRS Part III

Sponsor's Figure 9.3.1.1.2:1 (next page) shows the average Part III scores by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

Sponsor's Figure 13.2.2 (next page) shows the observed case results for the same comparison.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant. Consistency across other analyses of the same outcome variable can be seen below:

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)	OC Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-5.6	-5.7	-114	-126
Placebo	-2.8	-3.7	-64	-75
p-value	0.01	0.08	0.01	0.02

For Part III, the difference in the treatment groups came from a number of components, with the largest components being: Leg Agility, Finger Taps, Rigidity, and Hand Movements.

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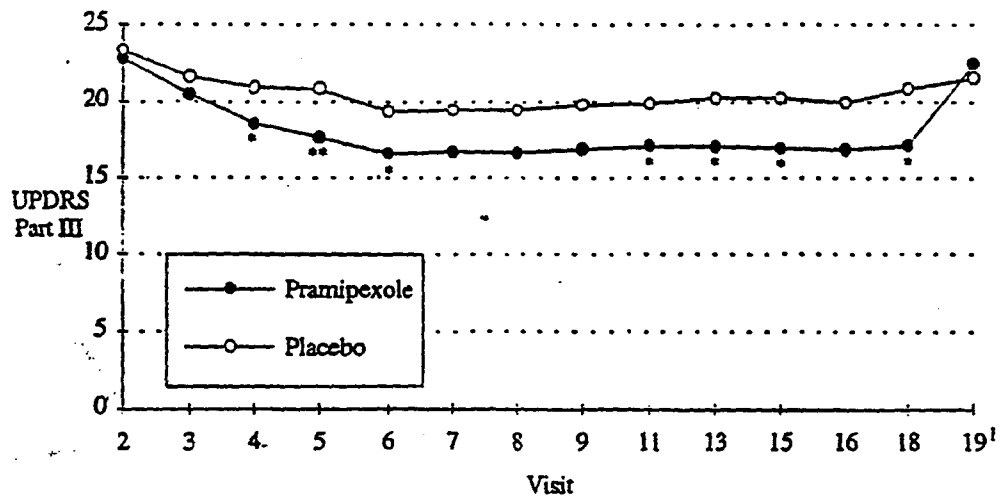


FIGURE 9.3.1.1.2:1 UPDRS Part III Means by Visit.

Last Observation Carried Forward Analysis

Source Data: TABLE 9.3.1.1.2:1
 † Observed Cases Analysis Only
 * $p \leq 0.05$ ** $p \leq 0.01$

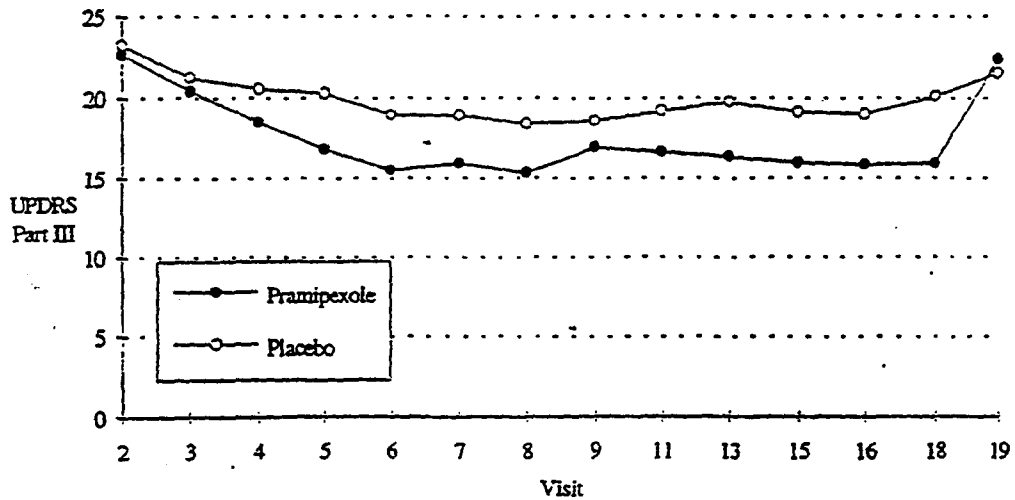
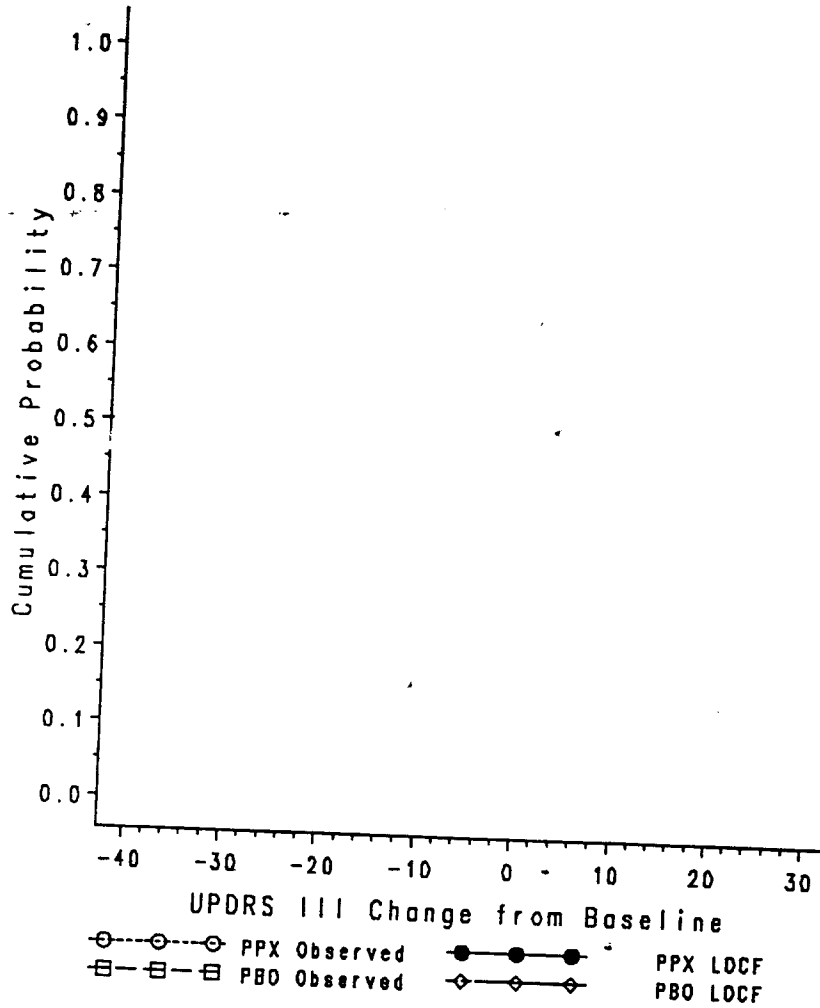


FIGURE 13.2.2 UPDRS Part III Means by Visit.

Observed Cases Analysis

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4. UPDRS Part I

Sponsor's Figure 9.3.1.2.10:1 (next page) shows the average Part I scores by visit for the two treatment groups. No real difference between groups is seen.

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5. UPDRS Part IV

Sponsor's Figure 9.3.1.2.11:1 (next page) shows the average Part IV scores by visit for the two treatment groups.

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6. Parkinson Dyskinesia Scale

Sponsor's Figure 9.3.1.2.12:1 (next page) shows the average PDS scores by visit for the two treatment groups. There is an interesting peak in scores for pramipexole patients at visit 9. Note that the scores that contribute to this visit average score represent a mix of experience on a new higher dose for patients who were increased to the maximum allowed dose at visit 8 as well as experience on a stable dose for patients who did not reach the highest dose and were moved to visit 9 after skipping intermediate visits. This might tell us that the highest dose caused a significant increase in dyskinesia in those patients that achieved that dose, an increase that was diluted out by the scores of patients that did not go to that level. Presumably, patients could have the dose lowered at visit 9 back down to the next highest dose.

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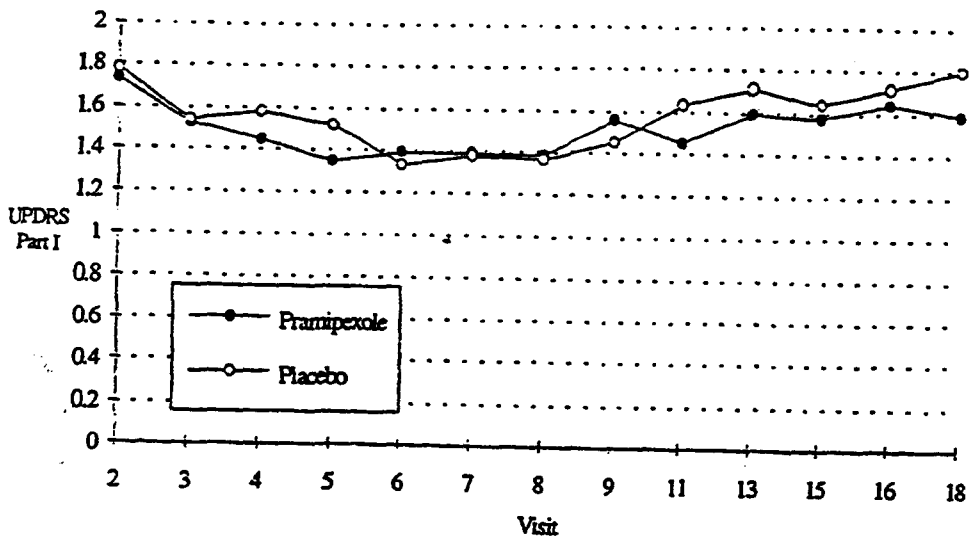


FIGURE 9.3.1.2.10:1 UPDRS Part I Means by Visit.
Last Observation Carried Forward Analysis

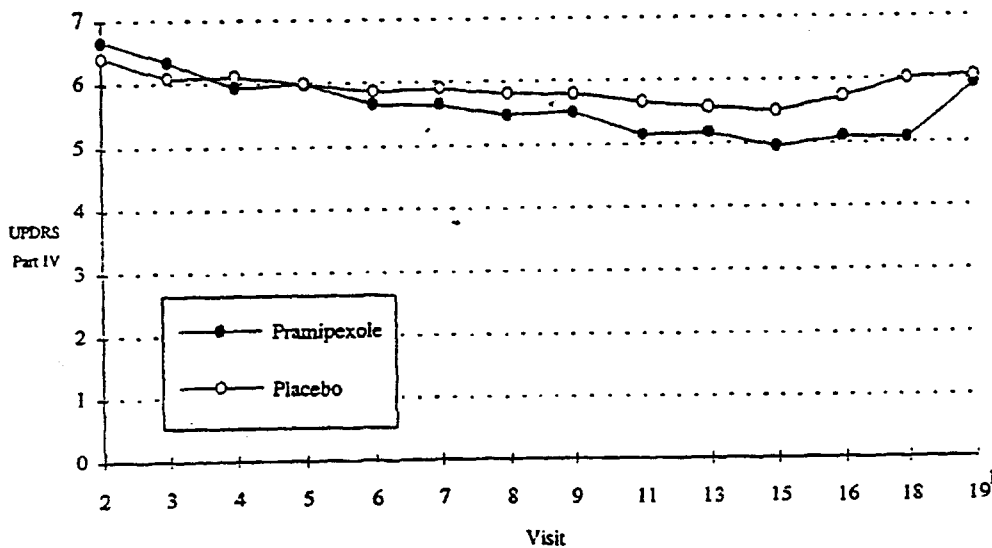


FIGURE 9.3.1.2.11:1 UPDRS Part IV Means by Visit.
Last Observation Carried Forward Analysis

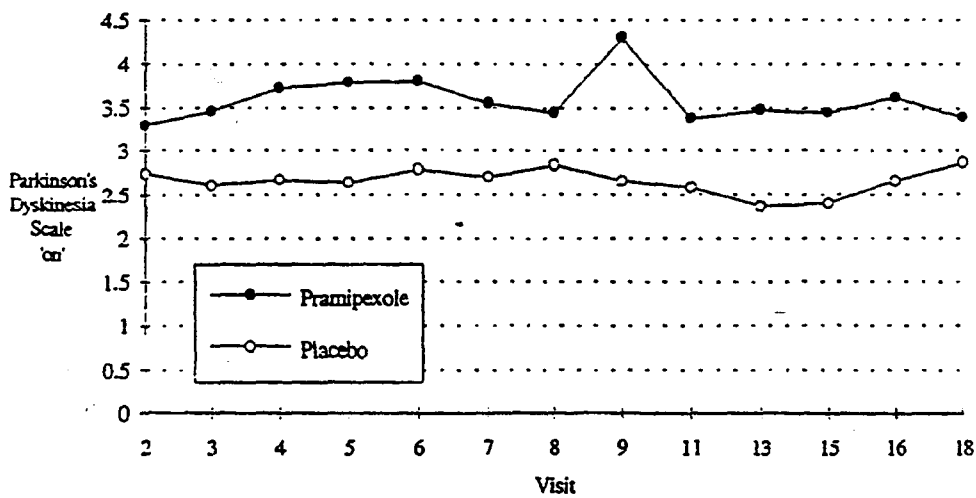


FIGURE 9.3.1.2.12:1 Parkinson Dyskinesia Scale 'on' Means by Visit.
Last Observation Carried Forward Analysis

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7. Modified Schwab-England Disability Scale

This scale was completed for both the on and off periods.

Sponsor's Figure 9.3.1.2.6:1 (next page) shows the average "off" scores by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.7:1 (next page) shows the average "on" scores by visit for the two treatment groups.

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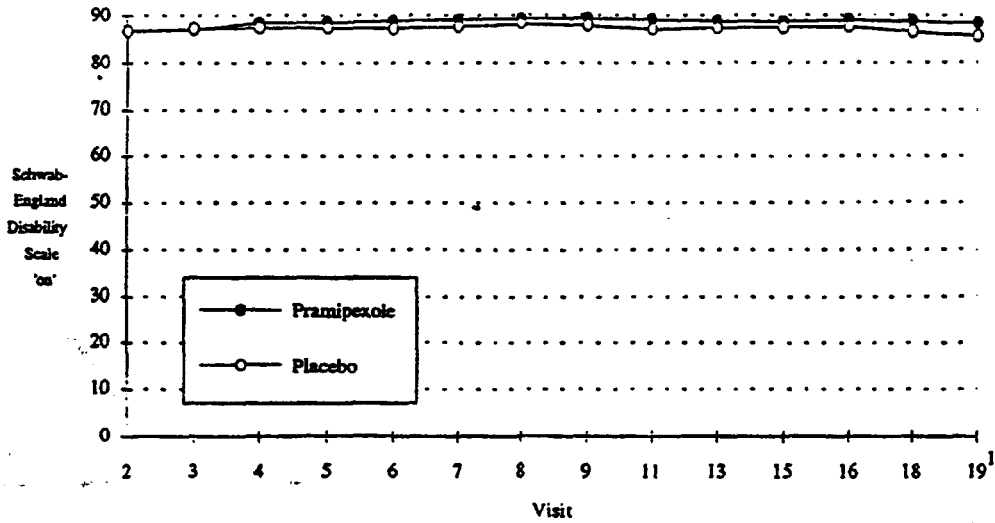


FIGURE 9.3.1.2.7:1 Schwab-England Disability Scale 'on' Means by Visit.
Last Observation Carried Forward Analysis

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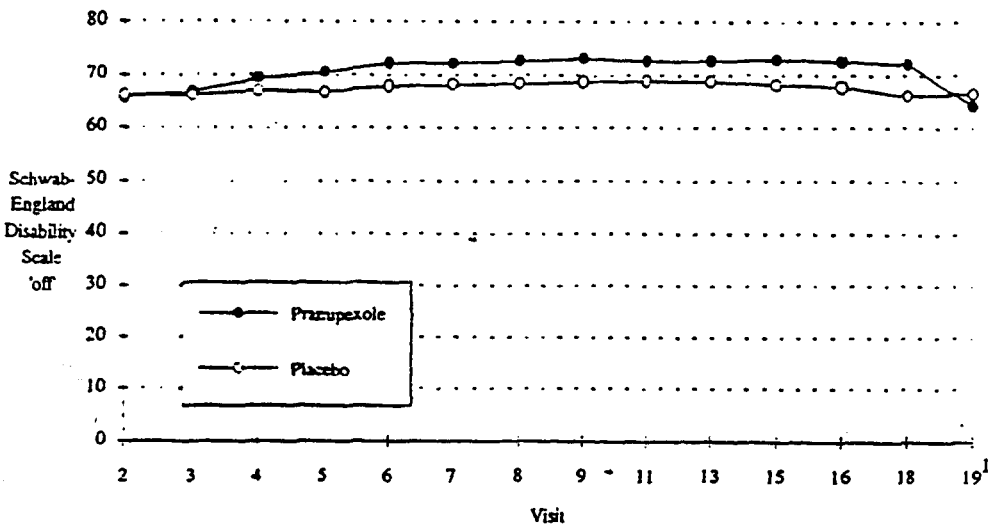


FIGURE 9.3.1.2.6:1 Schwab-England Disability Scale 'off' Means by Visit.
Last Observation Carried Forward Analysis

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8. Modified Hoehn and Yahr Scale

This scale was completed for both the on and off periods.

Sponsor's Figure 9.3.1.2.8:1 (next page) shows the average "off" scores by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.9:1 (next page) shows the average "on" scores by visit for the two treatment groups.

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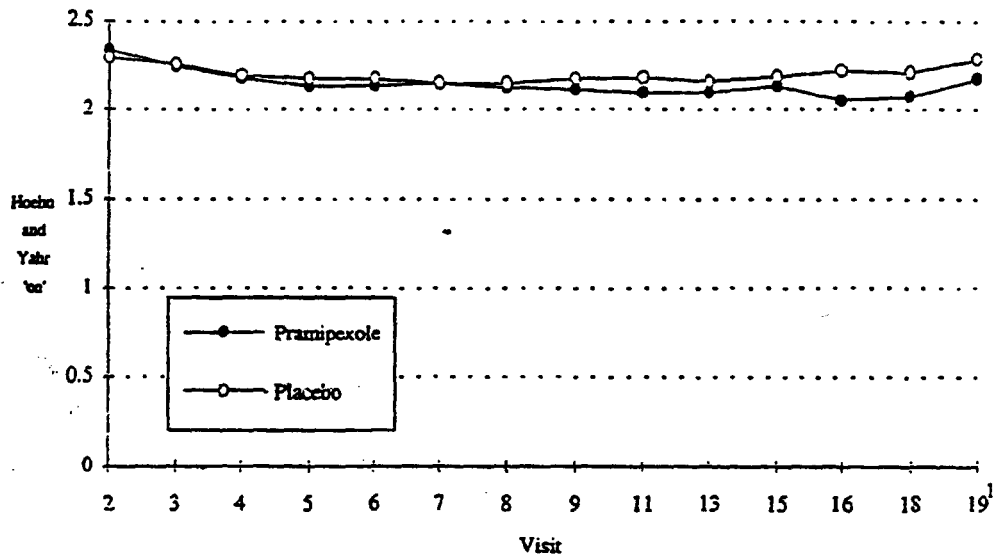


FIGURE 9.3.1.2.9:1 Modified Hoehn and Yahr Scale 'on' Means by Visit.
Last Observation Carried Forward Analysis

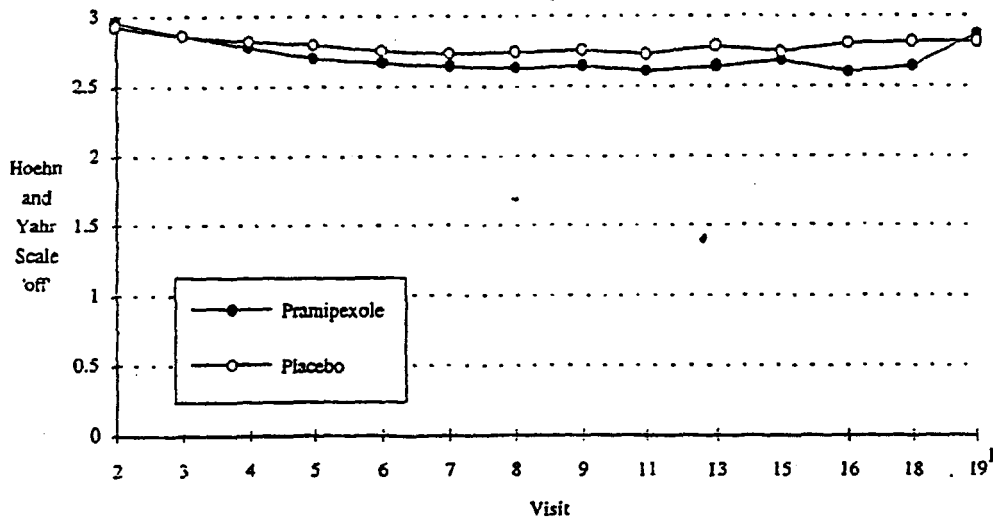


FIGURE 9.3.1.2.8:1 Modified Hoehn and Yahr Scale 'off' Means by Visit.
Last Observation Carried Forward Analysis

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9. Timed Walking Test

Sponsor's Figure 9.3.1.2.13:1 (next page) shows the average times by visit for the two treatment groups. The curves cross several times, with no overall differences emerging.

10. Average Severity Level of Off Periods From Patient Diaries

Sponsor's Figure 9.3.1.2.4:1 (next page) shows the average severity score by visit for the two treatment groups.

Dosage of L-Dopa, Other Concomitant Anti-Parkinson's Drugs

By protocol, during the maintenance phase, the dose of L-dopa could be adjusted downward if dyskinesias, hallucinations, or psychiatric side effects developed.

Dosage data on L-dopa was collected at each visit, but the sponsor states (without further explanation on p95 of the study report) that problems arose with interpreting CRF data on dosage. "Ultimately it was decided that the CRFs for baseline and final maintenance visit had to be individually reviewed by a sponsor's medical monitor. This review was conducted while the treatment code was still blinded. Because this review was very time consuming, only data from these two visits were collected."

Sponsor's Table 9.3.1.2.5:1 (next page) gives the baseline visit mean dosage, the final maintenance visit mean dosage, and the unadjusted and adjusted change from baseline to final maintenance visit. The pramipexole group reduced L-dopa dosage by 25% while the placebo group reduced dosage by 6% ($p \leq 0.0001$).

For each visit during the study, the CRF contained a box that the investigator could check if there had been no change in L-dopa dosage since the previous visit. It is informative to know the proportion of patients in each treatment group that had no change in L-dopa dosage throughout the study: 24% pramipexole, 46% placebo. Given the protocol-specified rules for changing L-dopa dose, the different proportions of patients requiring L-dopa dosage changes would be consistent with the 19% higher frequency of dyskinesias and the 15% higher frequency of

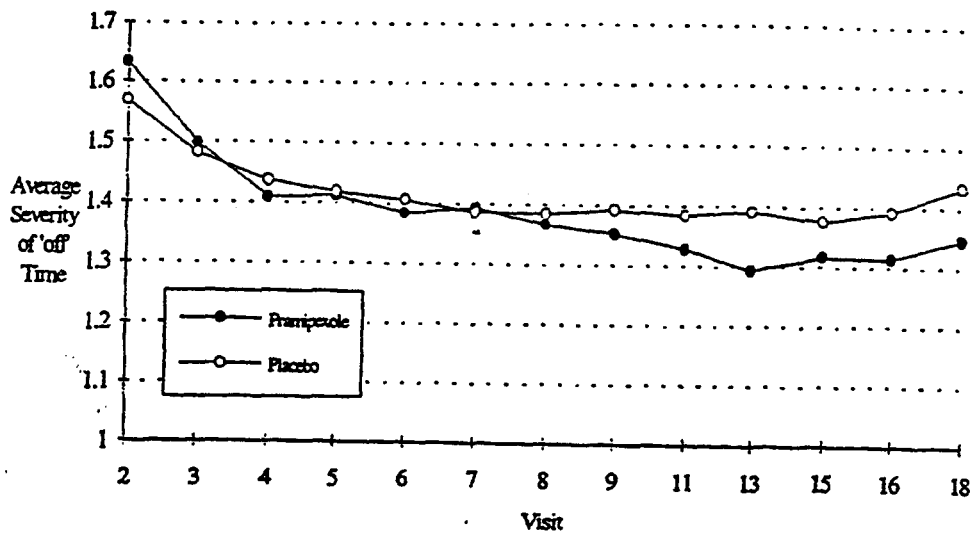


FIGURE 9.3.1.2.4:1 Average Severity of 'off' Time by Visit.
Last Observation Carried Forward Analysis

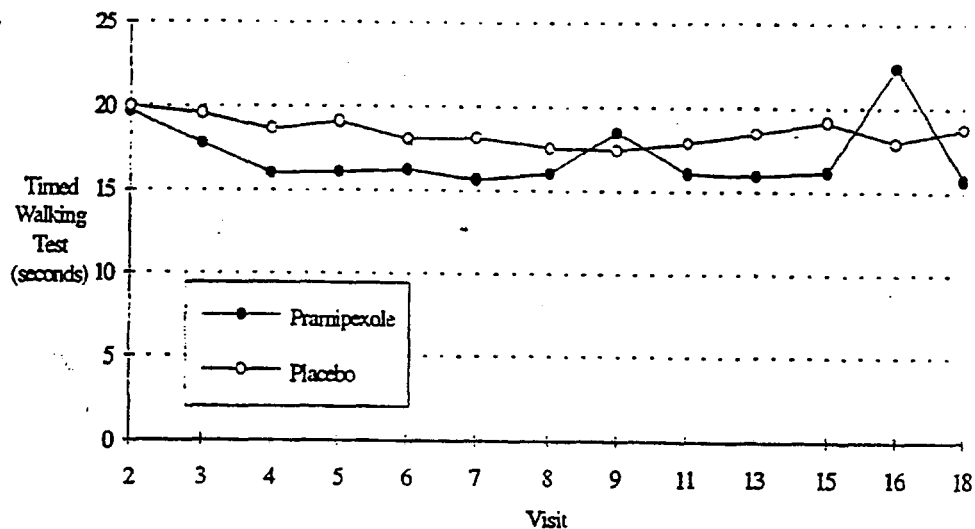


FIGURE 9.3.1.2.13:1 Timed Walking Test Means by Visit.
Last Observation Carried Forward Analysis

TABLE 9.3.1.2.5:1 Levodopa Dose (mg) Mean (S.D.) Change from Baseline.
Last Observation Carried Forward Analysis

	Baseline	Final Maintenance Visit	Unadjusted Change from Baseline to Final Visit on Maintenance	Adjusted ¹ Change from Baseline to Final Visit on Maintenance
Pramipexole n = 179	843.37 (578.86)	633.89 (540.91)	-209.48 (272.55)	-229.68
Placebo n = 172	819.19 (466.08)	773.98 (453.72)	-45.20 (115.86)	-43.20
p-value				≤ 0.0001

Source Data: Appendix 15.9.2 STATDOC 4.7.1 & 4.7.2

¹ Adjusted by center and center-by-treatment interaction (as per protocol).

hallucinations in the pramipexole group.

Changes in deprenyl, anticholinergic, and amantadine dosing during the trial were not allowed by protocol. Any changes should have been reported as protocol violations. No protocol violations on this issue are recorded in the study report.

In the September 27 submission, the sponsor reported that small numbers of patients did have their dosages of these drugs changed during the trial. However, the numbers are so small as to be insignificant.

The importance of the above questions should be obvious. All alternative explanations for a favorable effect in the pramipexole group must be ruled out.

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Table A4
Number of patients received Amantadine, Deprenyl, and Anti-Cholinergics
M/2730/0010

		Pramipexole	Placebo
	Total N randomized	181	178
Amantadine	Took Drug During Study*	33	25
	Stopped Drug During Study	1	0
	Increased Dosage	0	2
	Decreased Dosage	4	1
	Stopped/Restarted Drug	1	0
	No Change	27	22
Deprenyl	Took Drug During Study*	103	93
	Stopped Drug During Study	4	0
	Increased Dosage	1	0
	Decreased Dosage	5	2
	Stopped/Restarted Drug	1	1
	No Change	92	90
Anti-Cholinergics	Took Drug During Study*	25	26
	Stopped Drug During Study	0	0
	Increased Dosage	1	4
	Decreased Dosage	5	6
	Stopped/Restarted Drug	1	0
	No Change	18	16

* Not include patients who were on such drugs but stopped them prior to enrollment in the study, also does not include patients who started the drugs after the end of the maintenance dose phase.

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D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are to be summarized in a separate report.
2. Plasma levels of concomitant L-dopa, deprenyl, and anticholinergics were not measured during the conduct of this trial.

Only 26 patients in the pramipexole group were using anticholinergic medications. 97 patients in the pramipexole group were using deprenyl. By design, all patients were using L-dopa.

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E. Adverse Events

Sponsor's Table 11:1 shows the AEs with an incidence of 10% or greater in the pramipexole group. Only dyskinesia and hallucinations were statistically significantly different between the two treatment groups. Dose reductions of study medication controlled most cases of dyskinesia and hallucination.

Most AEs were typical of dopamine agonists and were mild to moderate in severity.

One pramipexole patient experienced repeated elevations of LFTs and was discontinued. Later rechallenge was tolerated. When comparing pramipexole and placebo patients with respect to lab change-from-baseline, statistically significant differences between the treatment groups were noted for: SGOT, SGPT, CPK, and LDH. The sponsor believes all these lab changes could be explained by pramipexole induced dyskinesias.

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TABLE 11:1 Summary of the Most Common Adverse Events for the Pramipexole and Placebo Treatment Groups

	Pramipexole N=181		Placebo N=179		P Value
	Number	Percent	Number	Percent	
Dyskinesia	113	62	77	43	0.0003
Asymptomatic orthostatic hypotension	102	56	108	60	NS
Dizziness	75	41	67	37	NS
Parkinsonism aggravated	64	35	61	34	NS
Pain	62	34	60	34	NS
Insomnia	51	28	49	27	NS
Nausea	44	24	50	28	NS
Hallucinations	38	21	10	6	<0.0001
Symptomatic orthostatic hypotension	30	17	23	13	NS
Confusion	23	13	18	10	NS
Constipation	23	13	22	12	NS
Upper respiratory tract infection	21	12	29	16	NS
Somnolence	19	11	16	9	NS

Source Data: TABLE 13.1.16

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F. Conclusions

Pramipexole-treated patients, on average, saw a larger change-from-baseline on Part II of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was small, but highly statistically significant.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline on Part III of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was again small, but highly statistically significant.

The protocol called for a statistically significant result on each of these outcome measures (a dual outcome) in order for a positive result to be declared for the trial as a whole.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline in percentage of waking hours spent in the "off" state compared to their counterparts treated with placebo. The shift from "off" could have been to "on with dyskinesia" and not simply to "on." This issue could be resolved by patient diaries, but not by CRFs. The sponsor has not shown an interest in pursuing this further.

The 3 improvements above came at a cost of more hallucinations and more dyskinesias as demonstrated in AE listings. In the UPDRS scale, hallucinations are only a component of Part I and dyskinesias are only a component of Part IV. The pertinent items from Parts I and IV for hallucinations and dyskinesias are not analyzed separately.

In short, Part III of the UPDRS may be a good scale for measuring Parkinson's Disease, but it may not be a good scale for measuring the patient population under study here: patients with motor fluctuations after 2-3 years of L-dopa therapy. Dyskinesias are a part of the motor fluctuations and are not included in Part III. The optimal state for these patients probably represents a fine balance in their dopaminergic states. Each patient will have a preference toward one end of the spectrum: too much dopaminergic stimulation with hallucinations, dyskinesias, but better mobility versus too little dopaminergic stimulation with decreased mobility. The labeling should clarify the trade off between the two states.

There is one last comment, more for the record than anything else. That is, the evidence accrued in this study, viewed in isolation, provides an alternate explanation for better performance in the pramipexole group than the use of pramipexole. To assume that pramipexole explains the better performance, one has to assume (reasonably I think) that chronic L-dopa in this patient population does not **cause** the "off" state and does not **worsen** performance on Parts II and III of the UPDRS. If L-dopa did these things, then the mere fact that dosage of L-dopa was reduced more in one group than the other could explain the better performance in one group. The prevalent theory, however, holds that the "on-off" phenomena and the decreased performance that occur after chronic use of L-dopa are all due to **decreased responsiveness to L-dopa**. It would then follow logically that the decreased average dose of L-dopa seen in one treatment group would serve to worsen, not improve that group's outcomes; improvement in that group could then be attributed to the addition of pramipexole (c.f. drug holidays in Parkinson's disease).

In short, pramipexole **substituted for L-dopa** resulted in less off time, better scores on UPDRS Parts II and III, more hallucinations, and more dyskinesias than when placebo was added to L-dopa.

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RATING SCALES					Pramipexole 00679A - M2730/0010	
PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
[] [] []	[] [] [] [] []	2			1001	19

The same person should conduct each part of this evaluation throughout the trial.

PARKINSON DYSKINESIA SCALE (This exam MUST be completed when the patient is in an 'on' period)
 This examination should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

TIME OF EXAMINATION: _____ : _____ (24-hour clocktime) RATER'S INITIALS (3): _____

INTENSITY OF DYSKINESIA DURING 'ON' PERIOD:
 Rate the patient's present intensity of dyskinesia during an 'on' period by using the following scale. If the patient is in an 'off' period, wait until the patient enters an 'on' period.

0 = Normal
 1 = Intermittent
 2 = Generalized, mild but continuous, may not be obvious to untrained observer
 3 = Moderate, generalized, definitely noticeable to untrained observer
 4 = Incapacitating

	0	1	2	3	4
Head	☐	☐	☐	☐	☐
RUE	☐	☐	☐	☐	☐
LUE	☐	☐	☐	☐	☐
RLE	☐	☐	☐	☐	☐
LLE	☐	☐	☐	☐	☐
Trunk	☐	☐	☐	☐	☐

MODIFIED SCHWAB-ENGLAND DISABILITY SCALE RATER'S INITIALS (3): _____

Rate the patient's best 'on' period and worst 'off' period during the past week by checking one box under each column.

ON	OFF	Description
☐	☐	100% - Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
☐	☐	90% - Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty.
☐	☐	80% - Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
☐	☐	70% - Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
☐	☐	60% - Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
☐	☐	50% - More dependent. Help with half, slower, etc. Difficulty with everything.
☐	☐	40% - Very dependent. Can assist with all chores, but few alone.
☐	☐	30% - With effort, now and then does a few chores alone or begins alone. Much help needed.
☐	☐	20% - Nothing alone. Can be a slight help with some chores. Severe invalid.
☐	☐	10% - Totally dependent, helpless, complete invalid.
☐	☐	0% - Vegetative functions such as swallowing, bladder, and bowel functions are not functioning. Bedridden.

MODIFIED HOEHN AND YAHR SCALE RATER'S INITIALS (3): _____

Indicate the patient's Parkinson stage for both 'on' and 'off' periods by checking one box for 'on' and one box for 'off' below.

STAGE	ON	OFF	Description
0	☐	☐	No signs of disease
1	☐	☐	Unilateral disease
1.5	☐	☐	Unilateral plus axial involvement
2	☐	☐	Bilateral disease, without impairment of balance
2.5	☐	☐	Mild bilateral disease, with recovery on pull test
3	☐	☐	Mild to moderate bilateral disease; some postural instability; physically independent
4	☐	☐	Severe disability; still able to walk or stand unassisted
5	☐	☐	Wheelchair bound or bedridden unless aided

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TREATMENT EVALUATION					Pramipexole 00679A - M2730/0010		
PATIENT INITIALS (I)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE	
		2			1001	20	

Last Dose	Date (month/day/year)	Time (24-hour clocktime)	Dose (e.g. 25 / 100)	Number of Tabs / Caps
Decarboxylase inhibitor / Levodopa				

TIMED WALKING TEST	TIME OF EXAMINATION: : (24-hour clocktime)
(This exam MUST be completed when the patient is in an 'on' period)	
The Timed Walking Test should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.	
Record the time needed to complete the test to the nearest whole second.	
Time to complete: ____ min. ____ sec.	Was the use of a walker required? ☐ No ☐ Yes
	Completed test within 10 minutes? ☐ No ☐ Yes

Time Interval	24-hour Clocktime	SUPINE VITAL SIGNS (after 5 minutes of quiet rest)		STANDING VITAL SIGNS (after 1 minute standing)		ORTHOSTATIC HYPOTENSION*
		Systolic/Diastolic BP (mm Hg)	Pulse (bpm)	Systolic/Diastolic BP (mm Hg)	Pulse (bpm)	(refer to protocol for definition)
Pre-Dose	__ : __	/		/		☐ None ☐ Symptomatic* ☐ Asymptomatic*
Administer Trial Medication	__ : __	Administer the contents of the first blister for Dose 1.				
2 Hours after Administration	__ : __	/		/		☐ None ☐ Symptomatic* ☐ Asymptomatic*

* If orthostatic hypotension is present, record on the "Adverse Event Report" form. Indicate symptomatic or asymptomatic. If symptomatic, record specific symptoms.

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Appendix D

Daily Patient Records

The patient will record when "on-off" disabilities occur during waking hours. "On" periods are periods with good motor function, while "off" periods are periods when patients move slowly or not at all. In addition to recording the specific times of on and off periods during the day, patients should also score the degree of disability during "off" periods using the following 4-point scale:

1. (mild slowness, stiffness, or resting tremor)
2. (moderate slowness, stiffness, or resting tremor, but remaining functionally independent)
3. (severe disability, the patient requiring some help in several activities)
4. (immobile, severely incapacitated and totally dependent on others)

"On" periods with dyskinesia (i.e., when patients are able to move, but are troubled by involuntary or unintentional movements) will also be recorded.

The patient will be asked to record activity for one-hour periods during waking hours. If more than one activity applies (e.g., "on" and "on" with dyskinesia), record the activity which predominated during the one hour period.

The number of hours off per day divided by the total number of waking hours will be averaged over each week of assessment and recorded on case report forms. In addition, the disability score during "off" periods per day will also be averaged over each week of assessment. "On-off" periods for at least 2 full days prior to the next clinic visit should be recorded by the patient within the diary.

Guardians, family members, or nursing personnel, etc., may assist the patient in completing the daily patient record. If there are errors, inconsistencies, discrepancies, or missing information, these should be resolved at the time of the clinic visit.

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DAILY PATIENT RECORD			SND 919 00655
PATIENT INITIALS (3)	DATE RECORD COMPLETED (month/day/year)	VISIT (disperseed)	PATIENT NUMBER
		2	

INSTRUCTIONS:

Circle the appropriate description for each one-hour period during the day. If more than one applies, circle the clinical status description which predominated (lasted 30 minutes or more) during each period.

- ON = Good motor function
- ON WITH DYSKINESIAS = Able to move, but troubled by involuntary or unintentional movements
- OFF = Able to move slowly or not at all.

For each 'OFF' period, check the highest degree of severity experienced. Four degrees of severity are defined below:

- 1 = mild slowness, stiffness, or resting tremor
- 2 = moderate slowness, stiffness, or resting tremor, but remaining functionally independent
- 3 = severe disability, requiring assistance in several activities
- 4 = immobile, severely incapacitated, and totally dependent on others

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TIME INTERVAL	CLINICAL STATUS				Severity of "OFF" period				
					1	2	3	4	
MIDNIGHT - 1 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
1 AM - 2 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
2 AM - 3 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
3 AM - 4 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
4 AM - 5 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
5 AM - 6 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
6 AM - 7 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
7 AM - 8 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
8 AM - 9 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
9 AM - 10 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
10 AM - 11 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
11 AM - 12 NOON	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
12 NOON - 1 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
1 PM - 2 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
2 PM - 3 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
3 PM - 4 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
4 PM - 5 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
5 PM - 6 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
6 PM - 7 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
7 PM - 8 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
8 PM - 9 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
9 PM - 10 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
10 PM - 11 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
11 PM - 12 MIDNIGHT	ASLEEP	ON	ON WITH DYSKINESIAS	OFF					
FOR OFFICE USE ONLY									
TOTAL NUMBER OF HOURS					24 -	asleep =	waking hrs. -		

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Name and Address of Investigator	Number of Patients Randomized at Site
Adler, Charles H, M.D., Ph.D. Assistant Professor Mayo Clinic Scottsdale 13400 East Shea Boulevard Scottsdale, AZ 85259	13
Comella, Cynthia, M.D. Dept. of Neurological Sciences Rush Medical College Rush-Presbyterian St. Luke's Medical Center 1725 West Harrison Chicago, IL 60612	12
Curran, Terry, M.D. (6/24/93-12/12/93) Goodridge, Alan, M.D. (12/13/93- present) Division of Neurology The General Hospital Health Sciences Centre 300 Prince Philip Drive St. John's Newfoundland A1B 3V6	12
Eidelman, Benjamin, M.D. Acting Chairman, Dept. of Neurology University of Pittsburgh 337 East Scaife Hall Pittsburgh, PA 15261	11
Factor, Stewart A, D.O. Assistant Professor of Neurology Dept. of Neurology Albany Medical Center New Scotland Avenue Albany, NY 12208	20
Fazzini, Enrico, D.O. New York University Medical Center 530 First Avenue, Suite 9Q New York, NY 10016	20
Friedman, Joseph, M.D. Department of Neurology Roger Williams General Hospital 825 Chalkstone Avenue Providence, RI 02908	8

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Golbe, Lawrence I, M.D. Clinical Academic Building 125 Patterson Street Neurology Suite 6th Floor New Brunswick, NJ 08901-1977	13
Guttman, Dr. Mark 377 Church St., Suite 407 Markham, Ontario L6B 1A1 Canada	22
Hubble, Jean, M.D. Assistant Professor Department of Neurology Kansas University Medical Center 39th and Rainbow Blvd. Kansas City, KS 66103	16
Jankovic, Joseph, M.D. Professor of Neurology Baylor College of Medicine Dept. of Neurology 6550 Fannin Street, Suite 1801 Houston, TX 77030	14
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M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
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Paulson, George, M.D. Chairman, Department of Neurology 452 Means Hall Ohio State Univ. School of Medicine 1655 Upham Drive Columbus, OH 43210	7
Perlmutter, Joel S, M.D. Assoc. Professor of Neurology Washington Univ. School of Medicine Dept. of Neurology 660 South Euclid P. O. Box 8111 St. Louis, MO 63110	6
Pfeiffer, Ronald F, M.D. (3/17/93-6/19/94) Bertoni, John, M.D.,Ph.D. (6/20/94-present) University of Nebraska Medical Center Division of Neurology 42nd Street and Dewey Avenue Omaha, NE 68105	12
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Name and Address of Investigator	Number of Patients Randomized at Site
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Waters, Cheryl H, M.D., FRCP(C), FACP Assistant Professor of Neurology Chief, Division of Movement Disorders USC Movement Disorder Clinic Department of Neurology 1510 San Pablo St., Suite 615 Los Angeles, CA 90033	16
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Studies 19 and 22

Title: A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety, and tolerance of Pramipexole with concomitant treatment of levodopa (and decarboxylase inhibitor) in advanced Parkinson's disease.

Investigators:

Center	Location	Investigator(s)
19		
2	Austria	Schnaberth Pinter
7	Germany	Conrad
4	Germany	Gehlen
6	Germany	Glab
10	Germany	Koimel
9	Germany	Oertel
5	Germany	Poewe
22		
1	Denmark	Boas
2	Denmark	Boesen
3	Denmark	Boisen
4	Denmark	Dupont
5	Denmark	Hansen
6	Denmark	Sorensen / Mogensen
7	Denmark	Jensen / Magnussen
8	Denmark	Mikkelsen
9	Denmark	Worm-Petersen

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Objectives: The primary objective to assess the effect of Pramipexole (up to 5 mg) on Parkinsonian symptoms versus placebo in patients with advanced Parkinson's disease while on concomitant treatment with levodopa (and decarboxylase inhibitor). Effect is defined as a significant change in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS).

The secondary objective is to assess the safety and tolerance of Pramipexole in variable dose combinations with levodopa (and decarboxylase inhibitor).

Study Design: Multi-center, randomized, prospective, ascending dose, double-blind, placebo controlled study.

Treatments: Ascending dose in weeks one through seven followed by a 4 week maintenance period and a one week taper to discontinue. The maximum dose achieved will be the maximum dose without the patient suffering from intolerable side effects (maximum of 5.0 mg per day in divided doses i.e. 1.25 mg QID).

Treatment(s)	Pramipexole or Placebo	
Week	Dosage	Total Daily Dose
1	2 x 0.1 mg	0.2 mg
2	4 x 0.1 mg	0.4 mg
3	4 x 0.25 mg	1.0 mg
4	4 x 0.5 mg	2.0 mg
5	4 x 0.75 mg	3.0 mg
6	4 x 1.0 mg	4.0 mg
7	4 x 1.25 mg	5.0 mg

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Please see Table 1 and 2 for the Time and Events for studies 19 and 22, respectively.

Inclusion Criteria:

1. Men; women of non-child bearing potential;
2. Outpatients and Inpatients
3. Age: years (Age: years in study 22).
4. Patients with advanced idiopathic Parkinson's disease (classification according to ICD 9: 332.0) corresponding to stages II-IV according to the classification of Hoehn and Yahr.
5. Patients in whom the individual optimal dosage of levodopa (and decarboxylase inhibitor) causes disturbances such as akinesia, dyskinesia, dystonias, fluctuations.
6. Written informed consent.

Patients were to be maintained on their individual dose of L-dopa (and DCI).

If anticholinergics, amantadine, L-deprenyl, or tricyclic / tetracyclic antidepressant medications were used they should be maintained at a stable dose throughout the trial.

Exclusion Criteria:

1. Symptomatic forms of Parkinson syndrome (e.g. drug induced parkinsonism, post-encephalitic parkinsonism, Shy-Drager syndrome, Steele-Richardson-Olszewski-Syndrome).
2. Severe dementia
3. epilepsy
4. previous neurological operations

5. severe physical diseases
 6. AV block of 2nd or 3rd degree, sick-sinus syndrome, congestive heart failure, myocardial infarction within 6 months before the start of the study.
 7. Blood pressure above 180/100 mmHg (patients with a blood pressure below 180/100 mm Hg under concomitant treatment with saluretics, beta-blockers, may be included)
 8. Hypotension with systolic blood pressure below 100 mg Hg.
 9. Liver disease (SGPT > 82 U/l)
 10. Kidney disease (creatinine > 2.5 mg / 100 ml)
 11. Uncontrolled metabolic diseases
 12. Concomitant treatment with bromocriptine, lisuride, other dopamine agonist, apomorphine, MAO-A inhibitors, neuroleptics, alpha-methyldopa, reserpine, clonidine, guanabenz, calcium antagonists
 13. Women of child bearing potential (contraceptives are not allowed).

In addition to the above exclusion criteria, in study 22, patients who did not respond to dopamine agonists in the past were excluded from the study. Patients with a history of orthostatic hypotension were excluded.

Study Population:

Please see Table 3.

Outcome Measure: The primary efficacy measure was the change in UPDRS total score (not additionally defined in the protocol) from baseline to the final maintenance period. The total UPDRS score was calculated as the sum of the subscores for I - IV (I - mentation, behavior and mood, II - activities of daily living during "on" and "off" periods, III - motor examination during the "on" periods, and IV - complications of therapy).

Efficacy:

Study 19: An ITT-analysis performed with changes in the UPDRS total score from baseline (visit 2) to the end of the maintenance period (visit 11, week 11) showed a change of 20.1 points (SD=16.0) in the pramipexole treated group vs. A change of 5.9 points (SD=12.8) for the placebo group. The P-value of the Wilcoxon test was 0.0002. In this study the UPDRS sub-score I was not significantly influenced by pramipexole. Please see Table 4.

Study 22: An ITT-analysis performed with changes in the UPDRS total score from baseline (visit 2) to the end of the maintenance period (visit 9, week 11) showed a change of 16.9 points (SD=14.9) in the pramipexole treated group vs. A change of 9.0 points (SD=16.1) for the placebo group. The P-value of the Wilcoxon test was 0.0184. In this study the UPDRS sub-score IV (complications of therapy) was not significantly influenced by pramipexole. Please see Table 4.

In calculating the UPDRS scores, the method of LOCF was utilized. In cases where "on" or "off" scores were to be used and an "off" score was missing, the "on" was utilized. In 19, the number of scores missing was comparable in the two groups, as were the number of values missing from the most important visits (baseline and final maintenance visits). In contrast, the percent of missing values was substantially higher in the active drug group vs. the placebo group for study 22). This

difference was most notable for the final maintenance visit. Please see Table 5.

It is interesting to note that at one center (6, Sorensen and Mogensen) in study 22, the patients receiving Pramipexole, showed less improvement than the placebo group. This is the only center where this trend was noted.

Concomitant L-dopa Treatment: In study 19, treatment did not result in changes in the concomitant L-dopa (DCI). In contrast in study 22, the change (reduction in dose) from baseline to the end of the maintenance period was 150.7 mg/d in the pramipexole group compared to a change of 10.6 mg/d in the placebo group. Please see Table 6.

Safety: Please see the separate safety review for a more detailed evaluation. No deaths were reported in either study. In study 19, one patient in the Pramipexole group experienced angina pectoris which resulted in hospitalization. One patient in the placebo group experienced worsening of his Parkinsonian symptoms and developed papillary bladder carcinoma. He recovered from the former during the study and the latter during the follow-up. Eight patients withdrew from the study due to adverse events. Three from the active group and five from the placebo group. In former, one patient withdrew due to sedation/tiredness, one due to decreased blood pressure and confusion, and one due sleepiness and myoclonia. In study 22, There were three withdrawals due to adverse events, 1 from the Pramipexole group for orthostatic hypotension and 2 from the placebo group, 1 for angina pectoris and one for severe repetitive tachycardia. Please see Table 7.

Summary:

1. Patient Selection: Study 22 excludes patients who have not responded to dopamine agonists.
2. Demographics: In study 19 there is a disparity between the number of patients in the active vs. placebo groups. In addition, in this study, there is a higher percentage of male subjects in the placebo group. There is an imbalance in the treatment groups. The age, weight, duration of PD, and total UPDRS scores are comparable between the active and placebo groups in both studies. There is a greater percentage of Hoehn & Yahr stage IV patients in the placebo group vs. active group in both studies. This would suggest that the active groups had patients with less severe PD, and might be expected to do better than the placebo groups. Further suggestion of this is seen in the stratification based on L-dopa and other anti-Parkinson's disease medications, where the placebo group has a larger percent of patient's in the > 600 mg of L-Dopa groups. In study, 22, the stratification is based only on the amount of L-Dopa and does not include other anti-Parkinson's disease medications.
3. Exclusion Criteria: In study 22, patients who did not respond to dopamine agonists were excluded from the study. This exclusion has the potential to bias patient selection, in that patients are selected, who have previously demonstrated that they will benefit from a dopamine agonist. Another exclusion criteria included in study 22 was that of excluding patients with orthostatic hypotension. This is a frequent complication of Parkinson's disease, as well as a potential side effect several medications used to treat PD. These exclusion should be considered in preparation of the product labeling.
4. Efficacy: The primary endpoint analysis based on the protocols is the total UPDRS score. In both

studies, in either evaluable or ITT analysis, there is significant improvement in the UPDRS Total score. Improvement is seen in subparts II (activity of daily living), III (motor examination), and IV (complications). Patients receiving active drug had better scores in the Global Clinical Assessment and percent of off time during waking hours. There was no treatment effect with respect to the dyskinesia scale.

5. The mean daily dose of pramipexole was 3.59 and 4.59 in study 19 and 22, respectively.

Conclusion: Based on the primary outcome proposed in the protocols, change of the UPDRS Total score, the sponsor has demonstrated efficacy of the active drug, Pramipexole, in studies 19 and 22.

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Table 1. Time and Events Table for Study 19.

Events	Screening	baseline	Titration period							Maintenance period		Dose reduction period
			1	2	3	4	5	6	7	8	9	
Visit ^{a)}	1	2	3	4	5	6	7	8	9	10	11	12
Week ^{a)}	week		end of week							end of week		week
	-3	-1	1	2	3	4	5	6	7	9	11	12
Informed consent	X											
Demographic data	X											
Medical history	X											
Neurological examination ^{c)}	X										X	
Inclusion/exclusion criteria		X										
Randomization		X										
UPDRS, Hoehn & Yahr, Schwab-New England		X	X	X	X	X	X	X	X	X	X	
Dyskinesia Scale		X	X	X	X	X	X	X	X	X	X	
Discharge of patient record	X									X		
Evaluation of patient record		X									X	
BP, pulse	X	X	X	X	X	X	X	X	X	X	X	X ^{b)}
Electrocardiogram ^{c)}	X	X ^{b)}			X		X ^{b)}		X		X	X ^{b)}
Laboratory tests ^{c)}	X	X ^{b)}			X		X ^{b)}		X		X	X ^{b)}
Dispensing of study medication		X	X	X	X	X	X	X	X	X	X	X
Dosage of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Conclusion of participation - (Global Clinical Assessment ^{c)}											X	

- a) Visits in week -3, -1, 1, 2, 3, 4, 5, 6, 7, 9, 11 and 12 are mandatory if not otherwise stated.
- b) Only, if relevant changes at a previous visit compared to the screening/baseline value occurred.
- c) Investigations of week 11 should be performed at premature discontinuation.

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Table 2. Time and Events Table for Study 22.

SND 919: Time and events schedule of the study 838.008

Events	Treatment period													
	pre-treatment		dose-escalation				maintenance dose			dose-reduction				
visit (a)	1	2	3	4	5	6	7	8	9	10	11			
week (a)	end of week		end of week				end of week			week				
	-3	-1	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	x													
Demographic data	x													
Physical examination c)	x										x			
Medical history	x													
Neurological examination	x													
Inclusion/exclusion criteria		x												
Telephone randomization		x												
UPDRS c)		x	x	x	x	x	x	x	x	x	x	x	x	x
Fluctuations c)		x	x	x	x	x	x	x	x	x	x	x	x	x
Dyskinesia Scale c)		x	x	x	x	x	x	x	x	x	x	x	x	x
Patient record d)		<u>1 week</u> daily								<u>1 week</u> daily				
Adverse events c)	x	x	x	x	x	x	x	x	x	x	x	x	x	x
BP, pulse c)	x	x	x	x	x	x	x	x	x	x	x	x	x	x ^{b)}
Electrocardiogram c,f)	x	x ^{e)}			x	x ^{b)}	x	x	x	x	x	x	x	x ^{b)}
Routine laboratory investigations c)	x	x ^{e)}					x	x	x	x	x	x	x	x ^{b)}
Prolactin serum level g)	x	x ^{e)}					x	x	x	x	x	x	x	x ^{b)}
Delivery of the study medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dosage of the concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Global Clinical Impression c)		x												
Conclusion of participation c)														

- a) Visits in week -3, -1, 1, 2, 3, 5, 7, 9, 11 and 12 are mandatory if not otherwise stated.
- b) Only, if relevant changes occurred compared to the baseline value
- c) All investigation of week 11 should be performed also at premature discontinuation.
- d) Please, add to the case report forms a copy of the patient record of the reported "on" and "off" periods during waking hours and the severity of disability during "off" periods
- e) Repeat the investigation, if problems emerged at the 1st visit (Visit 2 = baseline).
- f) Please attach a copy of the ECG to the case record forms
- g) Blood will be drawn (6 - 7 ml) to determine prolactin serum levels

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Table 3.

Demographics Studies 19 and 22								
	Study 19				Study 22			
	SND 919 (Pramipexole)		Placebo		SND 919 (Pramipexole)		Placebo	
	No.	%	No.	%	No.	%	No.	%
Total No. Of Patients Treated	34		44		36		33	
Male	20	58.82	31	70.45	20	55.56	20	60.60
Female	14	41.18	13	29.55	16	44.44	13	39.39
White	33		43		36		33	
Oriental	1		0					
Unknown	0		1					
Age (Years) Mean	59.3		60.66		63.2		62.1	
Weight (kg) Mean	71.86		73.99		69.7		71.0	
Duration of PD in Years Mean	7.80		8.49		10.1		9.9	
Hoehn & Yahr Stages								
II	7	20.58	13	29.54	15	41.67	10	30.30
III	22	64.7	20	45.45	18	50	17	51.52
IV	5	14.7	11	25	3	8.33	6	18.18
Total Score of UPDRS Mea	53.60		50.24		51.9		56.7	
L-Dopa Treatment								
Other Anti-PD Medications								
Stratum 1 (600mg, no other meds)	5	14.71	7	15.91	14		11	
Stratum 2 (600mg, other meds)	15	44.12	16	36.36				
Stratum 3 (>600mg, no other meds)	4	11.76	8	18.18	22		22	
Stratum 4 (>600mg, other meds)	10	29.41	13	29.55				

Table 4.

Supportive Efficacy Studies (19 and 22)												
	Study 19						Study 22					
	Pramipexole (N34) Week			Placebo (N44) Week			Pramipexole (N36) Week			Placebo (N33) Week		
ITT	2	11	Diff.	2	11	Diff.	2	11	Diff.	2	11	Diff.
UPDRS - Total Mean Score (sum of I - IV)	53.7	33.6	20.1	50.2	44.4	5.9	51.9	35.0	16.9	56.7	47.7	9.0
UPDRS - I (mentation, behavior, mood)	1.5	0.8	0.7	1.1	1.2	-0.1	2.4	1.9	0.5	2.3	2.5	-0.2
UPDRS -II (activities of daily living)	13.0	8.6	4.4	12.7	11.7	1.1	13.4	9.9	3.4	14.9	14.2	0.7
UPDRS - III (motor exam.)	33.5	20.3	13.2	30.5	26.0	4.5	29.6	17.5	12.1	32.1	24.1	8.1
UPDRS - IV (complications)	5.7	3.9	1.8	5.9	5.5	0.4	6.6	5.6	1.0	7.4	7.0	0.4
Dyskinesia scale	2.70	2.12		3.70	2.77							
Evaluable (ITT - withdrawals, see table 7)	N29			N38			N30			N28		
UPDRS - Total Mean Score	52.3	29.7	22.6	47.4	41.2	6.2	50.9	32.2	18.7	57.1	46.2	10.9
UPDRS - I (mentation, behavior, mood)	1.4	0.8	0.6	0.9	1.1	-0.1	2.4	1.8	0.5	2.1	2.3	-0.2
UPDRS -II (activities of daily living)	12.7	7.7	5.0	11.8	10.5	1.3	12.7	9.0	3.7	14.9	14.0	0.9
UPDRS - III (motor exam.)	32.6	17.3	15.2	29.1	24.5	4.6	29.8	16.4	13.5	32.9	23.3	9.6
UPDRS - IV (complications)	5.7	3.9	1.8	5.6	5.1	0.5	6.1	5.1	1.0	7.2	6.7	0.5
Patient Record (% of waking off time)	32.97 (28)	20.69		32.7 2 (41)	34.6 1		32 (33)	26		43 (33)	40	
Mean Daily Dose	3.59 (29)			4.08 (38)			4.59 (32)			4.77 (21)		

Table 5.

Missing UPDRS Values*			
	Study 19		Study 22
	Pramipexole	Placebo	Placebo
Percent of Patients	16 (47%)	21 (47%)	7 (21%)
From Visit 2 (Baseline)	1	2	2
From Visit 9 (week 11) (End of Maintenance Period)	2	2	6

* Includes patients that dropped out of the trial and patients with missing values from only part of the UPDRS i.e. Part IV item no. 39.

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Concomitant L-dopa Treatment								
	Study 19				Study 22			
	Pramipexole		Placebo		Pramipexole		Placebo	
Visit	Mean (mg/d)	SD	Mean (mg/d)	SD	Mean (mg/d)	SD	Mean (mg/d)	SD
From Visit 2 (Baseline)	537.5	314.4	592.6	264.0	727.8	339.8	775.0	418.7
From Visit 9 (week 11) (End of Maintenance Period)	511.0	308.8	583.5	273.3	577.1	340.9	764.4	411.5

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Table 7.

Withdrawals (Adverse Events and Administrative) Studies 19 and 22				
	Pramipexole (N34) Baseline / Final Maintenance Visit	Placebo (N44) Baseline / Final Maintenance Visit	Pramipexole (N36) Baseline / Final Maintenance Visit	Placebo (N33) Baseline / Final Maintenance Visit
AE withdrawals	3 sedation / tiredness increased falls * drop BP / confusion drowsiness / myoclonia *during dose reduction period	5 nausea dizziness right bundle branch block felt inner restlessness influenza drowsiness dizziness arterial hypertension arterial hypertension (exclusion)	1 orthostatic hypotension	2 angina pectoris severe repetitive tachycardia
Admin. Withdrawals	1 withdrew consent	1 arterial hypertension	3 protocol violation withdrawal of consent lost to follow-up	1 protocol violation
Excluded due to treatment with increased amounts of anti-Parkinson's medications			2	2
Patient enrolled twice first to placebo then to Pramipexole	1			

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Study 18

This was designed to be a **single-blind**, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 48 patients were to be enrolled.

Patients were advanced PD patients on L-dopa who experienced motor fluctuations. Concomitant anticholinergics were allowed. Concomitant amantadine was allowed. Deprenyl was not allowed.

There was a 7-week dose-escalation phase, with a maximal daily dose of 4.5 mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced to a prior tolerated dose and that patient would begin the maintenance phase. Following dose-escalation, there was a 3 week maintenance period and then a 1 week dose reduction period.

Replacement of dropouts was allowed (p 5 of the protocol).

"Patients who drop from the study prior to completing at least two weeks of the maintenance dose interval...or are less than 75% compliant with the study drug...will be replaced."

Assessments included Parts II of the UPDRS and patient diaries of on-off time. The primary outcome was a dual outcome: mean change from baseline on Part II of the UPDRS at the end of maintenance and percentage (and severity) of off time. The protocol never specified whether UPDRS Part II would be averaged for the primary analysis, or divided into separate outcomes for on and off scores.

Results:

Fifty patients were randomized (26 pramipexole; 24 placebo) at 6 centers in the United States.

The results for the evaluable, observed case analysis is shown below: ["Observed case" seems to be a misnomer here since, by protocol, if a patient had not been in the maintenance phase for 2 weeks, that pt was to be replaced.] One patient (1001) was considered unevaluable because the baseline L-dopa dose was exceeded during the study.

Adjusted Change From Baseline,UPDRS II"off"

Pramipexole	3.50 (n=24)	
Placebo	0.25 (n=20)	p=0.11

Adjusted Change From Baseline,UPDRS II"on"

Pramipexole	1.04 (n=24)	
Placebo	0.80 (n=20)	p=0.90

When maintenance scores were averaged over 3 weeks (as opposed to using only the final maintenance score) and then compared to baseline, a statistically significant difference seemed to emerge in favor of pramipexole by the sponsor's report.

The percentage off time did not differ between the two treatment groups.

A trend toward reduced severity of off time was noted.

No significant difference on UPDRS Part III was found.

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Conclusions:

There was a trend toward reduced severity of off time as measured by patient diaries and UPDRS Part II "off" scores. When maintenance scores were averaged over 3 weeks and then compared to baseline, a statistically significant difference seemed to emerge in favor of pramipexole.

On the other hand, the percentage off time did not change for either treatment group. Also, the UPDRS Part II "on" scores did not differ for the two treatment groups.

The maintenance period here was only 3 weeks long, making any extrapolation from these results difficult.

One aspect of this study that is important is the exclusion of deprenyl as a concomitant medication. It may be important from the standpoint of drug interactions that trends in favor of pramipexole were seen in the absence of deprenyl.

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Study 20

This was designed to be a double-blind, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. Because of slow enrollment, only 19 patients (9 pramipexole; 10 placebo) were enrolled. For that reason, no meaningful efficacy results emerged from this study in patients with advanced PD. According to the sponsor, "there were no apparent differences between treatment groups in the UPDRS or subscores."

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Conclusions:

The sponsor has demonstrated the effectiveness of pramipexole in early Parkinson's Disease in the absence of L-dopa. Additionally, effectiveness has been shown in advanced Parkinson's Disease with concomitant L-dopa therapy.

Studies in Early Parkinson's Disease

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Four studies are summarized in the two tables below. A consistent improvement in UPDRS Part II (the activities of daily living scale) is shown across studies.

Likewise, a consistent improvement in UPDRS Part III is shown across studies. UPDRS Part III is referred to as the motor scale. I would argue that the scale captures the motor exam minus the domain of involuntary movements (to include dyskinesias).

Early Parkinson's Disease; No Concomitant L-Dopa

Change From Baseline on UPDRS Part II:

	Study 1	Study 4	Study 17	Study 21
Pramipexole	1.9	1.8	5.2	5.1
Placebo	-0.4	0.3	2.2	2.2

Change From Baseline on UPDRS Part III:

	Study 1	Study 4	Study 17	Study 21
Pramipexole	5	4.5	12.0	7.2
Placebo	-0.8	0.6	8.3	1.6

Studies in Advanced Parkinson's Disease

Four studies are summarized in the two tables below.

Note that UPDRS Part II (ADL) in these studies represents an average score of the "on" score and the "off" score. As such, without a per patient correction factor for amount of "on" time and "off" time, it must be interpreted carefully.

A consistent improvement is shown across studies.

Likewise, a consistent improvement in UPDRS Part III (the motor scale) is shown across studies. Again, I would argue that the scale captures the motor exam minus the domain of involuntary movements (to include dyskinesias).

Advanced Parkinson's Disease; Concomitant L-Dopa

Change From Baseline on UPDRS Part II (average of on and off score):

	Study 10	Study 18	Study 19*	Study 22
Pramipexole	2.7	2.1	4.4	3.5
Placebo	0.5	0.5	1.0	0.7

Change From Baseline on UPDRS Part III:

	Study 10	Study 18	Study 19*	Study 22
Pramipexole	5.6	3.1	13.2	12.1
Placebo	2.8	1.4	4.5	8.0

* Study 19 is the only study in advanced PD where daily dosage of L-dopa was not differentially reduced in the pramipexole group as compared to the placebo group

Given the presence of the on-off phenomenon in patients with advanced Parkinson's Disease, the effect of pramipexole on total amount of "on" time is important to evaluate. As mentioned above, a positive effect here may even be a prerequisite for meaningful interpretation of the primary outcome, UPDRS Part II. Unfortunately, 1) an operational definition of "on" and "off" time was not provided in the protocol and 2) the CRF only recorded "off" time without differentiating between the 2 alternatives, "on" versus "on with dyskinesias." The latter may not necessarily represent a better state than "off" (no operational definition provided, but potentially fairly benign according to the patient diaries) and should not be represented as such.

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Recommendations:

An approvable letter can be issued. Proposed labeling should point out the limitations of the data, as collected. Specifically, 1) UPDRS III does not encompass the entire motor exam and 2) a decrease in "off" time is not simply an increase in "on" time.

/S/

John Feeney, M.D. /
Medical Reviewer
September 13, 1996

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Review and Evaluation of Clinical Data

Safety Review

Application Information

NDA 20-667

Pharmacia & Upjohn

NDA Submission Date: December 28, 1995

Drug Name

Generic: Pramipexole

Proposed Trade Name: Mirapex™

Drug Characteristics

Pharmacological Category: Dopamine agonist

Proposed Indications: 1) Primary symptomatic treatment of Parkinson's disease.
2) Adjunctive treatment of Parkinson's disease.

Dosage Forms: Oral tablets in 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg

Proposed Use:

Pramipexole should be given T.I.D.. Dosages should be increased gradually from a starting dose of 0.375 mg/day and should not be increased any sooner than every 5-7 days. In most studies a 7 week dose escalation scheme was followed: 0.125 T.I.D., 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D., 1.25 T.I.D., and at the 7th week to the maximum dose of 1.5 T.I.D. Withdrawal should occur gradually over a 7-day period.

Safety Reviewers: John D. Balian, M.D. & James F. Knudsen, M.D., Ph.D.

Date of Review: November 13, 1996

1 Summary of Pramipexole Safety Review

Pharmacia & Upjohn is requesting approval to market pramipexole for the treatment of idiopathic Parkinson's disease (PD). Overall, the ISS summarized the safety experience for 1408 patients with about 815 person-years (PYs) of pramipexole use, most of it (800 PYs) coming from the PD trials. Both early therapy (ET) and advanced therapy (AT) PD patients had over 100 PYs of pramipexole exposure that occurred after the first year of use. In the completed PD studies, there were 245 ET and 176 AT patients who reached 4.5 mg/day, the maximum recommended daily dose. Of these 421 patients, 190 were exposed to this dose for at least 12 consecutive weeks.

In the clinical pharmacology studies, pramipexole had significant cardiovascular (CV) effects on healthy volunteers. Symptomatic orthostatic hypotension (OSH) was identified as a dose-related phenomenon, first evident following a single oral dose of 0.2 mg (first dose phenomenon). The OSH was reported as dose-limiting (0.4 mg/day was the maximum tolerated dose in study 26) for the normal volunteers. The time to onset of OSH varied from 30 minutes to 6 hours. The duration of OSH varied from 1 hour or less to at least 8 hours, depending upon dose. The magnitude of drug-induced changes in standing blood pressure and pulse rate could not be adequately assessed in all patients because of the inability to stand for vital sign measurements, but in those measured it was significant, with a decrease from baseline in SBP of up to 66 mg Hg and 30mmHg in DBP. The latter subject was unable to stand again for 8 hours and continued to experience nausea and asthenia for up to 12 hours. Overall, other symptoms associated with OSH were dizziness, asthenia, malaise, nausea, and increased sweating. There were no clinically significant changes from baseline in ECG parameters reported compared with placebo.

In the phase 2/3 studies, a separate review and analysis for the ET and AT patients was done (for this review) in order to adequately describe pramipexole associated AEs. In the 3 ET randomized controlled trials (RCT), the frequency of study dropout associated with non-serious AEs was comparable in the pramipexole and the placebo groups. The frequency of study dropout associated with serious AEs was 2% in pramipexole and 1% in the placebo patients, with only one pramipexole patient experiencing an AE that was CV in nature. The 3 most common AEs, irrespective of severity, associated with dropout in the 3 ET studies were: hallucinations, nausea and dizziness. Only 1 patient dropped out due to syncope. Overall, syncope as an AE was reported in 5 (1.3%) pramipexole-treated and 2 (1.0%) placebo treated patients. There were 4 deaths in pramipexole patients, 3 of which were CV in nature.

In the 4 AT RCTs, the frequency of study dropout associated with either serious or non-serious AEs was less in the pramipexole than in the placebo groups. None of the 18 patients exposed to pramipexole who had serious AEs had syncope, bradycardia, or orthostatic hypotension and only 3 patients had an event that could be considered CV in nature. There was no clear pattern of AEs associated with dropout. There were 8 deaths in pramipexole patients, 3 of which were CV in nature. Across the AT placebo controlled studies in the ISS,

only hallucinations and dry mouth were reported in more than 5% of pramipexole patients and were at least 2 times more frequent than in placebo. Syncope was reported in 2.2% of pramipexole AT patients compared to 3.4% of placebo patients.

Across all patients exposed to pramipexole in the development program, there were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, or aplastic anemia. Rhabdomyolysis was reported in one patient. One patient developed acute thrombocytopenia. There were no significant shifts in ECG parameters and laboratory analytes from baseline to study endpoint.

In summary, pramipexole use was not associated with increased risk for deaths, serious AEs, or dropouts in PD patients. While there was a clear increase in CV effects (syncope and OSH) attributable to pramipexole in the phase 1 healthy volunteers, no significant differences from placebo were observed in the phase 2/3 trials.

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2 Background

Boehringer Ingelheim (BI) in collaboration with the Pharmacia & Upjohn Company (Upjohn) developed pramipexole as a dopamine agonist for the "treatment of the signs and symptoms of idiopathic PD". Pramipexole is a synthetic amino-benzothiazole derivative with affinity for dopamine and α_2 receptors. It binds with highest affinity to the D₃ receptor subtype but it also binds the D₂ and D₄ receptors. It "stimulates fully" the dopamine receptors, with preclinical evidence of efficacy in animal models of Parkinson's disease (PD).

2.1 Overview of Safety Review

The sponsor had proposed for FDA approval to market pramipexole as primary therapy (referred in the NDA as monotherapy or early therapy {ET}) for Early Parkinson's Disease (EPD) and as adjunctive therapy (AT) for Advanced Parkinson's disease (APD), but at a pre-NDA meeting, the agency suggested that no specific referrals to monotherapy and adjunctive therapy be made, and instead a general claim for indication of "treatment of the signs and symptoms of idiopathic PD" be made.

In view of this, the sponsor's Integrated Safety Summary (ISS) provides pooled descriptions and analyses of the treatment emergent adverse events (AEs) without regard to ET or AT. The only separation of data in the ISS is that of data obtained from the so called "pivotal trials" or "the adequate and well controlled trials" and the rest of the data. These pivotal trials, consisting of 3 (studies M2730/0001, -/0004, and -/0010) double-blind, placebo-controlled, randomized controlled trials (RCTs) in PD, were designated as such for efficacy purposes, but the connotation and the analysis were then carried over by the sponsor to the safety analysis as well. The ISS contains 4 more similarly designed RCTs in PD, that were not designated as "pivotal" for efficacy purposes, and hence, for the safety review, the sponsor presents and analyzes these trials separately referring to them as "the other controlled PD trials".

Since the 2 populations identified by these indications could vary with respect to likelihood of background events because of differences in age, extent of underlying diseases, and other factors, we determined that it would be a better approach to separate the review and analysis of the ET and AT patient populations, wherever feasible. With the help of the sponsor a reanalysis of the data was performed. Since, there were no safety reasons to designate some studies as pivotal, data obtained from all similarly designed RCTs (3 studies from the ET trials and 4 from the AT trials) were used in the reanalysis.

This review, whenever possible reflects this separate (and not pooled) approach, except when specific findings from the "pivotal studies", after separating them into ET (trials 1 and 4) and AT (trial 10) are utilized.

2.2 Development of Pramipexole

According to the sponsor, development of pramipexole as a treatment for PD was pursued because preclinical studies suggested that it had effectiveness in reversing parkinsonian signs, no dopamine agonist is currently approved for monotherapy of PD, and pramipexole's "full dopamine agonism". Based upon this preclinical receptor profile, the sponsor hypothesized that pramipexole would have advantages in efficacy and/or safety when compared to approved dopamine agonists.

Pramipexole's clinical development program began in Europe with administration to healthy volunteers in January 1988. As of 1/1/96, pramipexole has not been marketed in other countries and there have been no foreign regulatory actions regarding its approval.

2.3 Pramipexole Preclinical Studies

Pramipexole binds to the D2 receptor subfamily, with highest affinity to the D₃ receptor subtype but it also binds the D₂ and D₄ receptors stimulating these receptors fully. In comparison, the ropinirole NDA review mentions bromocriptine and pergolide each with affinity for D1 and D2 receptor subtypes, and ropinirole and its metabolites with high affinity to the central D2 dopamine receptors, but not to D1.

In animal safety data, the no-toxic effect dose for pramipexole was reported to be 0.5 mg/kg/day for rats. The LD₅₀ of acute oral toxicity in mice was 1700 mg/Kg with signs of exophthalmos, piloerection, tremors, convulsions, and hypomotility. The LD₅₀ of acute IV toxicity in rats was 210 mg/Kg with signs of exophthalmos, dyspnea, convulsions, ataxia, and hypomotility. Autopsy in both cases revealed hemocongestion of major organs.

Chronic toxicology studies revealed mammary gland changes (proliferation of glandular epithelium) in female rats in the mid- (2 and 3 mg/kg/day) and high (8 and 15 mg/kg/day) dose groups. Other AEs noted were behavioral changes in both sexes, decreased body weight gain, and cholesterol and triglycerides in females in the lowest doses. With mid- and high-doses, body weight gain was reduced in both sexes. In addition, sporadic modest elevations in liver enzymes and decreases in potassium levels occurred. Hematologic AEs included mild thrombocytopenia. Organ changes included decrease in liver and thymus weights, and enlarged corpora lutea. Leydig cell hyperplasia was observed mainly in the low-dose groups and there were two adenomas observed in male rats (one control one pramipexole-treated).

Chronic toxicology studies in rhesus monkeys were significant for bradycardia and increased R-R and Q-T intervals observed in males of the mid-dose group.

The main findings observed in toxicology studies included retinal degeneration in

albino rats, CNS effects (increase in motor activity, agitation, ataxia, and tremors), and decreased prolactin secretion. Both male and female albino rats receiving long-term (2 year) pramipexole at mid- (2 mg/kg/day) and high (8 mg/kg/day) dose groups experienced dose-dependent retinal degeneration. The degeneration was characterized by loss of photoreceptor cells usually occurring late in treatment. Rats of the low dose group (0.3 mg/kg/day) and the control group were free of the AE. In other studies involving rats lasting only one year, and in long-term studies in other species (mice, swine, and monkeys) this syndrome was not recorded.

No reproductive abnormalities in mating, pregnancy, or pup development were noted in the low- and mid-dose groups of rats studied. In the high-dose, irregular estrus occurred in about one-half of the females, and the number of pregnancies that resulted in successful delivery decreased. Also the delivered pups had impaired growth during the lactation phase. The increase in the infertility and the impaired growth seen in the pups may be related to the drugs effect of inhibiting prolactin secretion. The teratogenicity data are scant due to the small number of pups, but no obvious effects were noted. Similar studies in rabbits were devoid of reproductive toxicities at doses up to 10 mg/Kg.

Mutagenicity studies were negative. Carcinogenicity studies in mice revealed no significant incidences of neoplastic lesions. Carcinogenicity studies in rats were significant for a higher incidence of Leydig cell adenomas in the mid- (2 mg/Kg/day) and (8 mg/Kg/day) high-dose groups. Leydig cell hyperplasia and testicular adenomas in rats were also observed in the ropinirole NDA review. Both sponsors attributed these to the reduced plasma prolactin that caused a reduction in Leydig cell LH receptors, which triggers a compensatory increase in LH production and release leading to Leydig cell hyperplasia and adenomas. (These Leydig cell LH receptors apparently are not present in humans).

Pramipexole rapidly crosses the blood-brain and blood-placental barriers in studied rats and is excreted in the milk of lactating mothers.

The opiate receptor activity of pramipexole was not investigated.

In summary, the main findings observed in the toxicology studies with pramipexole were related to retinal degeneration in albino rats, CNS effects, and reproductive effects possibly due to decreased prolactin secretion in rats (as the sponsor hypothesized).

2.4 Review of Safety Issues Identified in The Sponsor's Proposed Labeling

In the annotated labeling, pramipexole is described as a nonergot dopamine agonist with high specificity for the D2 subfamily receptors with a preferential affinity for D₃ receptors. The sponsor claims that by depressing dopamine synthesis, release, and

turnover, pramipexole reduces dopamine-induced neuronal degeneration in animals and alleviates parkinsonian motor defects.

In the current proposed label, pramipexole is indicated in "the treatment of the signs and symptoms of idiopathic Parkinson's disease", as was suggested by the agency at a pre-NDA meeting. In a communique dated October 31, 1996, the sponsor proposed a different text for the indications section to reflect our concentration of reviewing the AT and ET populations separately. The proposed text is: "Mirapex™ tablets are indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, both as first-line treatment (without levodopa) in early disease and in combination with levodopa for advanced Parkinson's disease".

The recommended starting dose is 0.375 mg/day in three divided doses, with a gradual increase every. . . days to a desired maintenance dose, with a maximum of 4.5 mg/day. Although abrupt discontinuations were uneventful, the sponsor recommends a gradual taper.

In the animal toxicology section, there is a mention of occurrence of Leydig cell adenomas in male rats, decreased fertility in female rats, and the excretion of drug-related material into breast milk.

Under the warnings section of the labeling, the sponsor mentions the occurrence of postural hypotension in patients treated with pramipexole and recommends gradual titration and careful adjustment of the dose. The sponsor claims that tolerance to the hypotension develops. Another AE mentioned under the warnings section is hallucinations: when used as monotherapy (EPD) 9% (34/377) of patients receiving pramipexole and 2% (5/222) of patients receiving placebo reported hallucinations. While in APD, this AE occurs more frequently, 21% (38/181) of patients receiving pramipexole in combination with carbidopa/levodopa vs 6% (10/178) of patients receiving placebo in combination with carbidopa/levodopa.

In the precautions section, the sponsor mentions that caution should be exercised when treating patients with renal insufficiency, and pramipexole may potentiate the dopaminergic side effects of levodopa and "may cause and/or exacerbate preexisting dyskinesia".

Under the AEs section of labeling, in pooled data for both ET and AT Parkinson's patients, 11% (out of 702) receiving pramipexole and 14% (out of 550) receiving placebo dropped out of the controlled studies due to AE occurrence. Hallucinations (3%), dizziness (2%), extrapyramidal syndrome (EPS) (1%), confusion (1%), somnolence (1%), postural hypotension (1%), and nausea (1%) were the most common reasons for withdrawal. These AE dropout risk estimates included all US and non-US experience and did not separate APD from EPD.

Table 1 provides a summary of AE risk estimates that were listed in the AE section of the proposed labeling that were observed in randomized placebo controlled ET and AT studies (pooled). In table 1, events are listed if they occurred in more than 1% of the patients where the event rate was more than 2 fold greater than placebo.

Table 1. Adverse events that occurred in more than 1% of and were more than 2 fold greater in pramipexole ET patients than with placebo. (Taken from sponsor's proposed labeling which uses data from studies 1, 4, and 10.)		
	pramipexole	placebo
	N=558(%)	N=400(%)
Decreased Weight	1.6	0.2
Peripheral Edema	4.1	2.8
Twitching	1.6	0.8
Hallucination	12.7	3.8
Somnolence	18.3	8.0
Akathisia	1.2	0.2
Decreased Libido	1.1	0.2
Myoclonus	1.1	0.5
Paranoid Reaction	1.1	0.5
Vision Abnormality*	2.9	0.2
Diplopia	1.2	0.5

*Floaters, visual spots, and peripheral vision disturbance.

Increased risk of somnolence and hallucination was associated with pramipexole's use.

In the patient information section, the sponsor is recommending that patients avoid driving automobiles and using heavy machinery until they know how pramipexole will effect them.

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3 Methods of Safety Review

As mentioned in section 2.1, the sponsor has provided pooled data in the ISS (without regard to ET or AT), and presented the data in several formats: (1) adequate and well controlled PD trials (studies 1, 4, and 10--the studies designated as pivotal to the efficacy of pramipexole); (2) all completed PD trials; (3) ongoing PD trials; (4) all completed schizophrenia trials; and (5) pooled data. In the ISS, no distinctions are made between US and non-US trials (although no clear differences in design are apparent) or in ET vs AT trials. Again, as noted in section 2.1, this review follows a different format: separate data presentation for the ET and AT trials. The review focused on deaths, serious AEs, dropout risk, dropouts associated with AE occurrence, and common AEs.

Using both the paper and electronic (CANADA) versions of the NDA, treatment emergent AEs occurring with pramipexole use were evaluated separately in ET and AT patients. To verify the accuracy of the primary data that was available for review, the information listed in the data listings, the CRFs, and the death narratives were cross checked for accuracy. To evaluate the consistency and accuracy of the AE coding (WHOART in the BI studies and COSTART in the Upjohn studies), subsumed investigator verbatims were compared to the corresponding preferred WHOART and COSTART AE codes. To further examine the validity of AE coding, selected WHOART and COSTART codes were reviewed in more detail. These codes were implicitly selected based upon the AE description in the proposed labeling, toxicity findings from preclinical testing, and findings noted during the NDA review. In view of the high incidence rates of syncope in the non-ergot dopamine agonist ropinirole (currently under review as an antiparkinson's drug), any supporting data for patients coded with the WHOARTs and COSTARTs "blackout", "faintness", "syncope, postural", "syncope, vasovagal", "symptomatic orthostatic hypotension", "circulation failure" were reviewed focusing on evidence of syncope or general CV events. Investigator verbatims for CV COSTART codes in studies 1, 4, and 10 were also reviewed to evaluate their specificity.

Since deaths were observed in the RCTs, before patients entered extensions, pramipexole mortality was compared to that in placebo separately for ET and AT patients. For the rate comparison, the sponsor used the exact number of days in computing person-years (PYs). PYs were estimated based on the medication records: the exact number of days were computed for each patient.

In addition to describing the mortality risks and rates, case summaries of all sudden or CV deaths were prepared by extracting data from the CRFs, narrative summaries and CRF tabulations. In addition, the CRFs, narrative summaries, and data tabulations were reviewed for the following groups of patients: (1) all deaths; (2) serious AEs; (3) AEs associated with dropout; (4) AEs coded as syncope, bradycardia, ventricular tachycardia/fibrillation or peripheral edema; and (5) patients

with any AEs suggestive of agranulocytosis, aplastic anemia, thrombocytopenia, serious skin reactions such as Stevens-Johnson Syndrome, hepatic failure or necrosis, renal failure or worsening of renal function, rhabdomyolysis, urolithiasis, hematuria or urosepsis, and retroperitoneal fibrosis or pulmonary fibrosis.

The AE experience observed in individual trials was contrasted to confirm that no major discrepancies in reporting occurred. The US and non-US data was not contrasted, but there were no clear differences in design or reporting.

4 Review of Findings

4.1 Description of the Pramipexole Development Program

Pramipexole was developed as a collaborative research effort between Boehringer Ingelheim (BI) and The Pharmacia Upjohn (Upjohn) companies. Clinical development of pramipexole is being conducted under the following INDs:

was submitted by BI on _____ to initiate Phase II clinical trials. On the sponsorship of the IND was transferred to Upjohn.

Since other indications (schizophrenia and depression) are not sought at this time, most analysis and review refers to the PD trials, without ignoring the data obtained from all trials. No other NDA's have been previously submitted.

Appendix 4.1.1 provides a listing of all studies included in the ISS. The ISS described pramipexole treatment emergent AEs based upon observations from 19 Clinical Pharmacology studies, 16 completed phase II-III clinical trials, and 15 ongoing trials.

Of the 19 clinical pharmacology studies involving 297 (260 PPX and 37 placebo) subjects, 17 were conducted in healthy volunteers, 1 (protocol 60) was conducted in volunteers with impaired renal function, and 1 (n=3) was conducted in APD patients.

Of the 16 completed phase II-III clinical trials (i) 9 (studies---#1, 4, 17, and 21 in ET and studies---#10, 18, 19, 20, and 22 in AT) were PD studies involving 1253 (702 PPX and 551 placebo) patients; and (ii) 7 were completed studies in schizophrenia involving 322 (177 PPX, 50 comparator, and 95 placebo) patients. There are also 15 ongoing studies: (i) 10 ongoing PD studies involving both controlled and uncontrolled studies, the controlled studies are blinded so an exposure number is not available, while the uncontrolled ongoing studies involve 1056 patients of which only 529 are uniquely exposed, the other 527 were enrolled in the completed controlled studies and exposed to PPX; (ii) 3 ongoing studies in schizophrenia; and (iii) 2 ongoing studies in

depression.

A tabulation of patient accountability of the completed studies is detailed in table 4.1.1:

	Number of Patients			
	Pramipexole	Placebo	Comparator	Total
Phase I (Clinical Pharmacology)	260	37	-	297
Phase II/III (PD Total)	702	550	-	1252
EPD	416	262	-	678
APD	286	288	-	574
Phase II/III (Schizophrenia Studies)	177	95	50	322
Total Phase II/III	1139	645	50	1871

The sponsor has given the following numbering system to the trials: M2730/00x, where x stands for the number of the study, i.e. 1, 2,---, 37, etc.. In this review, the final number (x) will be used to identify a study. The sponsor has selected three Phase II/III studies M/2730/0001 (study 1), M/2730/0004 (study 4), and M/2730/0010) (study 10) as the key studies for the evaluation of the effectiveness of pramipexole for the treatment of idiopathic PD (as discussed earlier, no specific referrals were made initially to either early or advanced PD in the indication). The sponsor chose these three trials since they met the criteria of adequate and well-controlled studies: studies with clear objectives, well defined methods of analysis, valid controls, and sufficient statistical power to allow a valid comparison with placebo.

As discussed earlier, the sponsor has presented safety data from all completed trials, but based the main safety analysis of this NDA submission on the 9 completed PD studies of phase II/III trials, and in particular the "pivotal" trials, pooling the data without regard to ET and AT populations. Again, as discussed earlier, the review did not follow this approach.

Of the 9 completed PD studies in phase II/III trials, 3 (studies 1, 17, and 18) were entirely conducted in the US, 2 (studies 4 and 10) were conducted in the US and Canada, and 4 (studies 19, 20, 21, and 22) were entirely foreign (non-US and non-Canadian) in conduct. All, except for study 20 were multicenter trials. Four trials (studies 1, 4, 21, and 17) were with patients not taking levodopa --defined as "early" PD-- while 5 (studies 10, 19, 20, 22, and 18) were with patients taking levodopa -- defined as "advanced" PD. Of note, the three pivotal studies (1 and 4 with EPD and

10 with APD) were US and Canadian in conduct.

The three pivotal or as the sponsor refers to them "the adequate and well-controlled" studies were multicenter, randomized, double-blind, and placebo-controlled in patients with PD who were not taking levodopa (defined as "early")--(protocols 1 and 4), or in patients with PD who were maintained on optimal doses of levodopa (defined as "advanced")--(protocol 10). Protocols 1 and 10 were flexible-dose studies during which patients received treatment with placebo or pramipexole from mg/day with an initial ascending dose phase (up to 7 weeks), followed by a 24 week maintenance phase, and a 1 week dose-reduction phase. Protocol 4 was a dose-response, parallel study where patients received pramipexole 1.5, 3.0, 4.5, 6.0 mg/day, or matching placebo. There was a 6 week ascending dose phase, followed by a 4 week maintenance phase at the targeted dose, and 4-8 day dose-reduction period. All other completed PD studies were also double-blind and placebo-controlled with the exception of two pilot studies (17 and 18), which were single-blind. Otherwise, there were no significant differences in design between ET and AT studies or the US and the foreign studies.

Patients from PD studies 1, 4, 10, 17, 18, 19, 20, and 22 were given the option of enrollment in extension studies (the current ongoing studies). Table VIII.G-15 in the ISS (page 8/3/47) enumerates the patients participating in more than one PD study. The total number of patients enrolled in the ongoing PD studies is 1056, 527 enrolled from the pramipexole arm, 371 from the placebo arm of the completed PD RCTs, and the rest are new enrollees.

The only phase 2/3 studies with comparative designs were in schizophrenia trials.

4.2 Summary of Pramipexole's Pharmacokinetics

Pramipexole is rapidly absorbed with an approximate bioavailability of 90% (indicating minimal first pass metabolism) and peak plasma concentrations occurring approximately hours after dosing. Renal excretion (> 80%) is the primary route of elimination as unchanged parent compound and the elimination half-life is 8.5 hours in young volunteers and 12 hours in older volunteers. Clearance in healthy female volunteers was lower than in healthy male volunteers. Clearance is decreased significantly in renally impaired patients. Protein binding was less than 20%.

Since pramipexole has minimal first pass metabolism, no in vitro or in vivo studies were performed to determine the presence of a P450 pathway.

Increases in C_{max} and AUC were proportional with dose over the range mg. Food decreased the rate of pramipexole absorption at steady state both in PD patients and healthy volunteers.

The sponsor conducted a study to explore the potential influence of age on renal processing (drug elimination) in study 0069. Age did not influence the absorption of pramipexole, nor the apparent volume of distribution after oral administration, however, as expected, the mean clearance for the elderly patients was approximately 30% lower than the young volunteers. Also, as a result of the reduction in glomerular filtration with increasing age, there was an increase in the elimination half-life from approximately 8.5 hours to 12 hours. In patients with renal insufficiency pramipexole total clearance and renal clearance decreased by 70% and 91%, respectively. The potential influence of hepatic insufficiency on pramipexole pharmacokinetics was not evaluated.

4.3 Description of the ISS Population

As table 4.1.1 in section 4.1 shows, in the 9 phase 2/3 completed PD RCTs, there were 702 patients who were exposed to pramipexole. Of these, 416 and 286 were observed in ET and AT studies, respectively.

Appendix 4.3.1 shows the demographics of the RCTs. In these trials there were no statistically significant differences between the pramipexole and placebo groups with respect to age, sex or race. The demographic characteristics of the combined ET and AT population were generally representative of the expected demographics of PD patients. In the pramipexole exposed group, the ages ranged from _____, with an average of around 62.8 years and the vast majority of patients (61%) were between _____ years old, while about 24% of the patients were >70 years of age. The overwhelming majority (96%) were Caucasian and 64% were male.

There was little difference in age between ET and AT patients across the ISS. AT patients had a longer duration of PD at baseline than that of ET patients; 9 years compared to _____ years. The average UPDRS Part II and III (the efficacy variables analyzed) were lower in the ET groups. AT patients had received l-dopa therapy for about 7 years and were rated in Hoehn and Yahr Stage II-IV at baseline, while by definition (protocol inclusion criteria) ET patients could not have received l-dopa therapy and were rated as Hoehn and Yahr Stage I-III.

Concomitant use of antiparkinsonian medications also varied between AT and ET patients and by study. As with l-dopa therapy, AT patients were not restricted in the extent of prior use of other dopaminergic therapy. However, both ET and AT patients were allowed continued use of amantadine, anticholinergic, and selegeline (l-deprenyl) therapy, but their dosage could not change. "Rescue" therapy with Sinemet was allowed, but exactly how this was applied was left up to each investigator.

Patients with clinically significant active cardiac disease were excluded from the trials. Disease co-morbidity prevalence was not compared in the ISS.

4.4 Review of Sponsor's AE Surveillance, Coding of AEs and Approach to Evaluating the Safety of Pramipexole.

According to the sponsor, surveillance for AEs occurred at each study visit in all studies. A treatment emergent AE was defined as any event or disease which was not present at baseline, or which if present increased in frequency or severity while in study, irrespective of any belief by the investigator regarding causality. Surveillance focused on all events including asymptomatic changes in laboratory findings, exacerbation of pre-existing conditions, intercurrent illnesses, and drug interactions.

Because of the dopamine agonist activity of pramipexole and because it caused hypotension and orthostatic hypotension in phase 1 studies, supine and standing BPs were collected across phase 2 and 3 studies. Patients were checked for postural changes by comparing 5 minute supine BPs with 1 minute standing BPs. In phase 2/3, while the method of BP measurement was standardized across studies, the timing of BP measurement with respect to drug dose was not standardized, unlike the phase 1 studies, where supine and standing BP were measured at specific time points following dosing. This sponsor uses postural hypotension and orthostatic hypotension interchangeably.

In coding the AEs, BI used the WHOART dictionary while Upjohn used the COSTART dictionary. As Upjohn took overall responsibility of the submission, it reassigned the WHOART preferred terms to COSTART preferred terms.

Because certain investigator verbatims were judged to be related to an event of particular interest, some specific coding rules were applied. The investigator verbatims "blackout spells", "fainting", "syncopal spells", "cardiovascular collapse", and "orthostatic collapse" were coded with the COSTART "syncope". The investigator verbatims "drowsiness", "sleepiness", and "sedation" were coded with the COSTART "somnolence".

There were instances of coding inconsistencies. For example, the adverse event descriptive term "fall" was subsumed under the COSTART terms gait abnormality, ataxia, and accidental injury. Other adverse events listed under more than one COSTART terms were "dizziness on standing", "faintness upon standing", and "lightheadedness". These were subsumed under COSTART terms postural hypotension of the cardiovascular body system, as well as under the COSTART term dizziness related to the CNS body system. The minor inconsistencies are not likely to influence the analysis, and overall, the sponsor's coding approach was found to be appropriate.

In reviewing the NDA, it appears that the approach described by the sponsor to ascertaining and describing treatment emergent AEs was followed in all studies. In addition to having the investigator code AEs as to degree of medical severity, the

sponsor identified AEs meeting the regulatory definition of serious. The ISS defines concurrent illness as any illness that occurred prior to study entry. These conditions were considered treatment emergent AEs if the conditions worsened during the course of the study.

The NDA summarized deaths, serious AEs, and overall dropouts from completed and ongoing studies using a cutoff date of 1/31/95. Patients had a unique identifier and most patients were counted only once except where placebo patients entered a pramipexole extension (371 patients). Two patients in the ISS were randomized to receive placebo but ended up not receiving any treatment.

In the ISS, the sponsor described common AE occurrence by focusing on AEs considered causally related to pramipexole. Potential causality was defined as a greater than 10% increase and greater than placebo. Since dose escalation was used in all clinical studies, a dose response analysis could have been confounded by time since first exposure. In addition, The sponsor counted some patients more than once in this analysis. Patients that had an increase in clinical severity (mild, moderate and severe) at different doses could have been counted as many as three times, but such patients were counted once within a corresponding dose. AE occurrence was also described by time since first exposure. In this analysis, patients were counted only once with the date of first occurrence used to calculate time.

To evaluate potential modification of risk attributable to pramipexole by concurrent medications, underlying diseases, or in demographic subgroups, AEs that occurred $\geq 5\%$ were used to calculate relative risk (RR). Percentages of occurrence were calculated separately for ET and AT patients. The following concurrent medications were selected: selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricyclic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and tocopherol. Concurrent illnesses defined as present at baseline, were coded to respective COSTART terms. The following concurrent diseases were selected: arthritis, CV disease, constipation, depression, dizziness, hypercholesterolemia, hypertension, insomnia, and prostate disease.

Appendix 4.15.1 shows the hematology, chemistry, and urinary laboratory analytes with predefined limits that were set as normal ranges. The sponsor identified patients with laboratory analytes at or above the value of potential clinical concern. For hepatic enzymes, clinical concern was set at 2.5 times the ULN. All study protocols required at least baseline and ending laboratory determinations with some studies requiring more frequent blood sampling. A complete listing of patients who dropped out associated with any laboratory analyte abnormality was provided.

All ET and AT studies had 12 lead electrocardiograms (ECGs) performed. All studies had a screening ECG, but the frequency of follow-up ECGs varied from only one

follow-up in study 4 to 6 follow-ups in study 10. All ECGs were available for review.

4.5 Audit Findings and Specificity of the AE Coding.

The investigator verbatims listed in the CRFs of the 17 deaths and from a sample of AE withdrawals and serious AEs were congruent with those in the data tabulations and described in the narrative summaries. Conversely, the narrative summaries, while providing more clinical detail, particularly about past medical history, described AEs that were generally identified in the CRF.

In general, the COSTART coding of the investigator verbatims seemed reasonable except for the few instances mentioned in section 4.4. Of special note are the AEs of "dizziness on standing", "faintness upon standing", and "lightheadedness" which were listed under more than one COSTART term: postural hypotension or dizziness. Because of the coding inconsistencies (AEs listed under more than one COSTART term), the specificity of "orthostatic hypotension" may likely be reduced. The protocol definition of orthostatic hypotension for all studies in the ISS was defined as a decrease in systolic BP of 20 mm Hg and/or a decrease in diastolic of 10 mm Hg, irrespective of presence of symptoms.¹ However, in the ISS, the COSTART code "orthostatic hypotension" also was used to code postural symptoms (dizziness on standing) with or without objective change in BP. This approach appears to have been applied because several patients, particularly in the phase 1 studies, could not have their standing BPs measured because of orthostatic symptoms and in some cases, syncope. While this approach may increase the sensitivity of the code to identify clinically significant events, its specificity most likely has been reduced (increasing false positives) biasing any difference between pramipexole and a comparison group towards the null. Of course, the sensitivity of the code probably varied across studies anyway, since BP was measured irrespective of the timing of dose for some studies.

Other COSTART codes were also applied in a non-specific way. Several reports of falls associated with use of pramipexole have been coded as "gait abnormality", "ataxia", or "accidental injury".

In addition to a general check of the validity of data submitted in the NDA, the supine and standing BPs that were recorded for studies 1, 4, and 10 were also reviewed and nothing unusual in the reporting system was found. This review focused on obvious inconsistencies and biases and didn't use formal sampling to statistically test for potential bias.

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¹ We will use this definition to reflect objective orthostatic hypotension in subsequent discussion.

4.6 Extent of Exposure

4.6.1 Extent of Exposure, Overall and Stratified by Duration of Use

In the 16 completed RCTs, a total of 879 unique patients were exposed to PPX for a total of 274.4 patient years. Table 4.6.1.1 displays patient exposure in patient years:

Type of Trial		Pramipexole	Placebo
Phase II/III (Completed PD Trials)	N	702	551
	Patient Years	258.8	225.5
Phase II/III (Completed Schizophrenia Trials)	N	177	95
	Patient Years	15.9	9.3
Total Phase II/III Completed Trials	N	879	646
	Patient Years	274.4	234.8
All Phase II/III Trials-- Completed and Ongoing	N	1408	
	Patient Years	815	

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Appendix 4.6.1.1 is a detailed (separated by disease type) table of the number of patients and estimated Person-Years (PYs) of pramipexole use. PYs were estimated based on the medication records: the exact number of days were computed for each patient and are presented here in 0-24 months, >6-24 months, and >12-24 months intervals.

Overall (including the extension trials that are ongoing), there were 1419 pramipexole patients observed in phase 2/3 studies. Dose information is not available on 11 patients, therefore a total of 1408 patients with 815 PYs of pramipexole use are included in the exposure data, most of it (800 PYs) coming from the PD trials.

4.6.2 Extent of Exposure by Dose

Appendices 4.6.2.1 and 4.6.2.2 show the mean and maximum dose exposures of ET and AT patients by weeks. Table 4.6.2.1 displays the number of pramipexole patients achieving ≥ 4.5 mg total daily dose (the maximum dose recommended):

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Table 4.6.2.1
 Pramipexole Patients Achieving $\geq$ 4.5 mg Total Daily Dose

Population	Number of Patients Achieving $\geq$ 4.5 mg at any Time During Study	Number of Patients Achieving $\geq$ 4.5 mg for $\geq$ 12 Consecutive Weeks	Total Number of Pramipexole Patients Exposed
Completed Studies			
All Patients	474	190	879
All PD Patients	421	190	702
All AT Patients	176	85	286
All ET Patients	245	105	416
All Schizophrenia Patients	53	0	177
Completed + Ongoing Studies			
All Patients	1034	552	1408
All PD Patients	981	552	1231
All AT Patients	377	248	556
All ET Patients	604	304	675
All Schizophrenia Patients	53	0	177

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As the above table indicates, in the phase 2/3 completed and ongoing studies, 1034 of the 1408 patients and 981 of the 1231 PD patients studies achieved the highest dose of 4.5 mg/day (604 ET and 377 AT patients). Of the 1034 patients that reached 4.5 mg/day, 552 were exposed to this dose for more than 12 consecutive weeks. In the completed PD studies, 421 of the 702 PD patients achieved the highest dose of 4.5 mg/day (245 ET and 176 AT patients). Of the 421 patients that reached 4.5 mg/day, 190 were exposed to this dose for more than 12 consecutive weeks.

4.6.3 Extent of Dosing in Selected Demographic Groups

There was no difference in the total daily pramipexole dose between ET and AT patients based on gender or age. There were too few non-white patients to generalize about any dosing differences by race. Dose was not described as a function of concurrent medications or by baseline co-morbidity. Tables 4.6.3.1-4 display these findings:

Table 4.6.3.1. AT Patients: Pramipexole Total Daily Dose (mg) by Sex						
Sex	N	Mean	Std Dev	Std Err	Min	Max
Male	149	3.75	1.30	0.11	0.2	5.0
Female	86	3.56	1.44	0.16	0.375	5.0

Studies Included: M27300010, M27300019, M27300020, M27300022

Table 4.6.3.2. ET Patients: Pramipexole Total Daily Dose (mg) by Sex						
Sex	N	Mean	Std Dev	Std Err	Min	Max
Male	229	3.77	1.49	0.19	0.0	6.0
Female	126	3.57	1.51	0.13	0.375	6.0

Studies Included: M27300001, M27300004, M27300021

Table 4.6.3.3. AT Patients: Pramipexole Total Daily Dose (mg) by Age						
Age	N	Mean	Std Dev	Std Err	Min	Max
≤ 45	11	3.36	1.56	0.47	0.75	5.0
46-55	45	3.70	1.47	0.22	0.2	5.0
56-65	78	3.74	1.32	0.15	0.375	5.0
66-75	87	3.71	1.30	0.14	0.4	5.0
> 75	14	3.33	1.47	0.39	0.375	5.0

Studies Included: M27300010, M27300019, M27300020, M27300022

Table 4.6.3.4. ET Patients: Pramipexole Total Daily Dose (mg) by Age						
Age	N	Mean	Std Dev	Std Err	Min	Max
≤ 45	28	3.91	1.55	0.29	1.5	6.0
46-55	61	3.32	1.59	0.20	0.75	6.0
56-65	108	3.76	1.41	0.14	0.0	6.0
66-75	130	3.83	1.48	0.13	0.0	6.0
> 75	28	3.48	1.57	0.30	0.0	6.0

Studies Included: M27300001, M27300004, M27300021

* Only patients who entered the maintenance interval are included

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4.7 Phase 1 Safety

The sponsor has divided the 19 phase 1 studies into 3 types: 3 basic PK studies (29, 30, and 47); 7 studies with "factors affecting PK" (60--ongoing, 61, 62, 63, 64, 65, and 69); and 9 safety and tolerance studies (3, 23, 25, 26, 27, 28, 31, 51, and 73). In the 19 phase 1 studies of the ISS, there were 13 single-dose studies with the pramipexole dose ranging from 0.1-0.4 mg, while in the 6 multiple-dose (with maximum duration of 30 days) studies the pramipexole dose ranged from 0.375-4.5 mg/day. Eight of the single-dose (25, 28, 29, 30, 51, 61, 64, and 65) and 2 of the multiple-dose (62 and 63) were crossover. Four of the studies investigated different pramipexole formulations: study 29 compared pramipexole given intravenously (IV) to an oral solution and a tablet form; study 73 was an eye drop formulation; studies 30 and 62 compared two planned marketed formulations; and study 31 was a transdermal formulation.

All 9 safety and tolerance studies, except for study 73, were conducted in healthy, young males. Study 73, the ocular study, enrolled 6 males and 6 females. The age range in this group was

Two of the basic PK studies were conducted in healthy males, while the other enrolled males and females. The age range in this group was years.

Two of the 7 studies with "factors affecting PK" were conducted in males, another four enrolled males and females, while the age-gender study (60), is currently ongoing and is enrolling elderly (up to 80 years of age) patients of both sexes.

There was only one phase 1 trial with patient (APD) volunteers with N of 3.

Across the phase 1 studies, no deaths or serious AEs were reported.

In the 9 safety and tolerance studies, one placebo patient and 3 pramipexole patients discontinued due to orthostatic hypotension. In studies 25 (single dose), 26, and 3 (both multiple dose), symptomatic orthostatic hypotension (OSH) was identified as a dose-related phenomenon and dose-limiting (maximum tolerated dose of 0.4 mg for study 26). OSH was evident following a single oral dose of 0.2 mg (first dose phenomenon) in study 26.

The time to onset of OSH varied from 30 minutes to 6 hours. The duration of OSH varied from 1 hour or less to at least 8 hours depending upon dose. The magnitude of drug-induced changes in standing blood pressure and pulse rate could not be adequately assessed in all patients because of the inability to stand for vital sign measurements. Changes from baseline observed in the vital signs of three subjects recorded drops in the SBP, DBP, and HR as follows: subject 1, a decrease of 66 mg/Hg in SBP, no change in DBP, and a decrease of 36 bpm in HR; subject 2, a

decrease of 35 mg/Hg in SBP, a decrease of 30 mg/Hg in DBP, and no change in HR (30 minutes after administration of 0.4mg); and subject 3, a decrease of 17 mg/Hg in SBP, a decrease of 26 mg/Hg in DBP, and an increase of 16 bpm in HR. Subject 2 was unable to stand again for 8 hours and continued to experience nausea and asthenia for up to 12 hours. Other symptoms associated with OSH were dizziness, asthenia, malaise, nausea, increased sweating.

There were no clinically significant changes from baseline in ECG parameter reported during the evaluation periods compared with placebo, but one pramipexole patient discontinued due to a "non-serious" atrial tachycardia.

In the 10 PK studies, 9 volunteers discontinued: 1 patient (#26, study 60) for GI bleeding; 2 due to increases in BP; 2 for not feeling well; 1 due to abdominal colic; 1 due to irritability after receiving one dose of Sinemet; and 2 due to nausea and vomiting. In protocol 63, there were 6 patients (#s 1, 3, 5, 7, 9, and 10) who had orthostatic symptoms and 8 patients (#s 1, 2, 3, 5, 7, 8, 9, and 10) who had decreases of systolic BP of more than 20 mm Hg. These changes occurred during the ascending phase of the pramipexole dosing. Also in protocol 65, 2 patients reported dizziness and nausea on standing with some reduction of standing BP at 3 hours post-dosing.

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In the safety and tolerance studies, a slight PR interval increase in the ECGs were noted, upon standing.

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There were no changes of clinical importance observed in the laboratory parameters. Serum prolactin concentrations were measured in 2 phase 1 studies in healthy volunteers and statistically significant decreases were noted at the first sampling time (30 minutes post dose), maximum effect was reached at 2-4 hours post dose, and were still significantly decreased compared to baseline at 8 hours post dose.

Appendix 4.7.1 summarizes the AEs observed in non-patient volunteers. In these volunteers headache, asthenia, abdominal pain, pain, chills, infection, malaise, back pain, pallor, postural hypotension, vasodilatation, nausea, anorexia, vomiting, constipation, dyspepsia, flatulence, diarrhea, dizziness, nervousness, somnolence, insomnia, concentration impaired, agitation, rhinitis, sweating, pruritis, and decrease in creatinine clearance occurred at a percentage difference of > 5% (pramipexole n=240 and placebo n=69). There were 3 reports of syncope in the pramipexole treated healthy volunteers and none in the placebo.

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4.8 Mortality in Phase 2/3 Studies

4.8.1 Pramipexole Mortality Compared to Placebo

Through January 31, 1995, there were 17 deaths observed in the development program, of which, 15 cases (deaths or the event leading to death) occurred within 30 days of the last dose of pramipexole or placebo. Of the 17 deaths, 14 occurred with pramipexole and of the 14, 10 occurred in the AT studies and 4 in the ET studies. There was 1 pramipexole death within 30 days of last use in study 1, and 3 deaths in study 10. Table 4.8.1.1 shows the estimated mortality rates for pramipexole and placebo separately in ET and AT patients, and in Schizophrenia patients:

Table 4.8.1.1. Rate of Mortality Observed					
	Deaths	N	PYs	Rate / 100 PYs	RR** 95% CIs
Completed Trials					
ET Patients					
Pramipexole	1	416	139.64	0.72	0.80 (0.051, 12.65)
Placebo	1	262	111.61	0.90	
AT Patients					
Pramipexole	3	286	119.14	2.52	2.874 (0.303, 27.23)
Placebo	1	289	113.94	0.88	
Schizophrenia					
Pramipexole	0	117	15.59	0.0	
Placebo	0	95	9.22	0.0	
Completed and Open-Label Ongoing Trials					
ET Patients					
Pramipexole	4	675	363.12	0.11	not applicable#
Placebo	1	262	111.61	0.9	
AT Patients					
Pramipexole	8	556	436.30	1.83	not applicable#
Placebo	1	289	113.94	0.88	
Schizophrenia					
Pramipexole	0	117	15.59	0.0	
Placebo	0	95	9.22	0.0	

** Rate Ratio (Relative Risk) of Pramipexole is defined as: (Death/PYs of PPX)/ (Death/PYs of Placebo)

Because all patients in the ongoing part received pramipexole.

Three patients in study 0012 died but are not included in this table because the randomization codes, # of patients, and drug exposure data were not available. Among these patients, two (#23 and 424) received PPX (and died more than 30 days after the day of the last dose), one (#118) received placebo.

In the completed ET trials, the 6-month mortality risk was 0.24 per 100 patients (1/416) for pramipexole and 0.38 (1/262) for placebo. In the completed AT trials, the 6-month mortality risk was 1.1 per 100 patients (3/286) for pramipexole and 0.4 per 100 patients (1/289) for placebo.

The pramipexole mortality rate per 100 PYs was 3.5 fold greater in AT compared to ET pramipexole exposed patients, but equivalent in the placebo patients. In either ET or AT patients, pramipexole mortality was less than that observed with ropinirole (see Ropinirole NDA review; in a recent publication² describing mortality of the Honolulu Heart Study cohort, the mortality rate in year olds who developed PD was about 5 per 100 PYs.)

There were no deaths reported in the schizophrenia and depression (completed or ongoing) studies. There were no deaths reported in the 19 Phase 1 studies.

4.8.2 Description of Deaths Observed During Pramipexole's Use

Of the 14 pramipexole deaths, 8 were potentially CV in nature. These 8 deaths are summarized below.

Patient 2433 was a 72YOM who entered the ET study 0001. Parkinson's Disease had been diagnosed 6 months previously. The patient's medical history included coronary artery disease (CAD), myocardial infarction (MI) and triple coronary artery bypass graft surgery (CABG) in 1991, and congestive heart failure (CHF) with resultant liver disease. At baseline, the patient's vital signs were normal. His baseline ECG showed first-degree heart block, left atrial pathology, an old inferior myocardial infarction, poor R-wave progression, and nonspecific ST-T wave changes. The baseline chest X-ray showed moderate cardiomegaly, minimal scarring in the left lung, and emphysematous changes in the upper lobes. During the study, the patient concomitantly received hydrochlorothiazide and lisinopril. The patient was receiving pramipexole 3 mg per day when, on day 29, he experienced mild nausea, which he attributed to an empty stomach. The investigator considered this to be possibly

² Morens DM. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic parkinson disease. Am J Epidemiology 1996; 144:400-404.

follow-up telephone call by study staff that evening, the patient stated that the nausea had resolved. On day 32, the patient had an MI and died. The investigator considered these medical events to be unrelated to study medication. Autopsy revealed cause of death to be an MI.

Patient 1065 was a 72YOM who entered the AT study 0010. He had a 5 year history of PD. The patient was maintained on carbidopa-levodopa. Past medical history was significant for an asymptomatic chronic aortic valve murmur with aortic stenosis since 1988, and drug allergies to penicillin and erythromycin. The patient had never smoked and consumed an average amount of ethanol. On dosing day 29 (pramipexole 3.0 mg/day) the patient complained of shortness of breath. The patient was admitted to the hospital and diagnosed with severe pneumonia and severe CHF. While in the hospital, the patient was treated with erythromycin as well as other antibiotics for the pneumonia. He was also given furosemide for CHF. After 7 weeks in the hospital, the pneumonia apparently resolved. The patient was then discharged from the hospital and transferred to a rehabilitation center. After 4 days the patient's condition deteriorated and he was admitted to the coronary intensive care unit. A doppler was done and it indicated destruction of 2 heart valves. The patient died. The patient's wife stated that he died of pulmonary edema (CHF). The investigator indicated neither was related to study drug. The cause of death was coded as CHF.

Patient 1021 was a 64YOM who entered the AT study 0010. He had a 12 year history of PD who began study medication on 10/5/93. Past medical history included dementia, hallucinations, leg cramps, and lightheadedness with an unknown onset date. The initial ECG at study entry showed normal sinus rhythm without evidence of a past infarct. Medication at entry included carbidopa-levodopa 50/200 and amantadine. The patient was an ex-smoker who had not consumed ethanol. At Visit 16, the patient had an ECG per protocol which showed an old inferoposterior wall MI with laboratory results showing a CPK level of _____ and AST (SGOT) at _____. The MB fraction of the CPK was elevated at _____. The patient apparently had an asymptomatic infarct some time prior to this study visit. In the morning the patient was found dead at home by his wife. The investigator felt that the patient had an infarct of severe intensity as the cause of death although there was no autopsy performed.

Patient 2227 was a 71YOM who entered the ET study 0001 followed by the open-label phase of the study (0002). He was diagnosed with PD 2 years prior to entry in the double-blind phase. The patient's relevant medical history included hypertension, which started 2 years prior to entry in the double-blind phase. During the study, he concomitantly received L-deprenyl 10 mg per day. During the maintenance-dose interval of the double-blind phase, he received pramipexole 2.25 mg per day. In the open-label phase, he completed the ascending-dose interval and entered the maintenance-dose interval receiving pramipexole 0.75 mg per day. The patient's clinic visit on day 60 was unremarkable. The following day (day 61), the patient

went for a walk and subsequently died at home from a possible pulmonary embolism (PE). There were no precipitating adverse events. The investigator considered the PE to be unrelated to the study medication. There was no autopsy performed to document the occurrence of PE.

Patient 2441 was a 80YOM who entered the ET study 0001 followed by the open-label phase of the study (protocol 0002). He was diagnosed with PD 4 years prior to entry in the double-blind phase. The patient's relevant medical history included angina pectoris, CAD, and bypass surgery (all 14 years prior to entry in the double-blind phase), hyperlipidemia (9 years), and shortness of breath and lightheadedness of unknown etiology (1 year). At the first study visit, the patient's ECG showed minimal voltage of LVH, possibly due to an inferior infarct approximately 3 years prior to entry in the double-blind period, and occasional ventricular complexes. He received no concomitant medications for PD during the study. He completed the ascending-dose interval of the open-label phase and entered the maintenance-dose interval receiving pramipexole 4.5 mg per day. On day 126 the patient was hospitalized because of severe chest pain. Prior to admission to the hospital, the patient had taken nitroglycerin sublingually and his symptoms had resolved. Results of an ECG showed atrial fibrillation. The patient was treated with diltiazem (bolus and IV drip) and normal sinus rhythm was restored. His CPK values remained normal, and CK-MB was . He was discharged from the hospital on day 129. The following day (day 130), the patient collapsed and died. The cause of death was reported as probably a massive M.I. The chest pain, atrial fibrillation, and M.I. were considered by the investigator to be unrelated to the study medication.

Patient 36 was a 65YOM who entered the AT open-label/ongoing study 0014. He had PD for a duration of 21 years which was treated with levodopa/decarboxylase inhibitor and biperiden. Patient history included mild cardiac insufficiency, and swallowing difficulties. He was also receiving hydrochlorothiazide/amiloride for cardiac insufficiency, and trimethoprim/sulfamethoxazole, and acetylcysteine for bronchitis. The patient was receiving pramipexole 4.0 mg/day and levodopa/benserazide, and biperiden. The patient suffered from dyspnea on 12/20/93 which was suspected to be related to a mild cardiac failure: this was treated with furosemide and then amiloride. The episodes of dyspnea reappeared. A lung embolism was suspected but not confirmed on a pulmonary scintigraphy. A relapsing bronchitis possibly due to aspiration because of Parkinson's disease-related swallowing difficulties was diagnosed. The patient was hospitalized from 8/16/94 to 8/20/94 and the diuretic discontinued. On 8/11/94 recurrent syncopes occurred, sometimes obviously following episodes of dyspnea. The neurologist interpreted these syncopes as most probable of the pressor-postpressor type. As a consequence of these events, the daily dose of pramipexole was reduced from 4.0 to 3.0 mg/day by the patient. The patient died on 9/1/94 following syncope. The family doctor stated cardiovascular arrest was the cause death. No autopsy was performed.

Patient 23 was a 75YOM who entered the AT ongoing study 0012. Patient history included posterior M.I., multiple bypass surgery, pulmonary emphysema, extra heart beats, and left anterior hemiblock. Concomitant medications included dihydroergotamine mesylate for low blood pressure, triamterene/hydrochlorothiazide for edema, and acetylsalicylic acid for the condition following the bypass surgery. Pramipexole was reduced from 2.25 mg/day to 0.75 mg/day from 10/20/94 to 10/31/94 due to moderate visual hallucinations. He had extra heartbeats on 10/22/94 which were treated with potassium. On 11/9/94 he had moderate dyspnea. Pramipexole was increased again to 2.25 mg/day on 11/10/94. Severe global heart insufficiency was reported on 11/20/94 and required patient hospitalization on 11/25/94. Torasemide treatment began on 11/22/94 and Dihydroergotamine Retard® and Isoptin 80® (verapamil) were discontinued. Study medication was discontinued. He was discharged from the hospital. He died at home of unknown cause. The investigator assessed that there is no reasonable possibility that the global heart insufficiency was caused by the study drug.

Patient 424 was a 76YOM who entered the AT ongoing study 0012. He had Parkinson's disease since 1985. Patient history included acute M.I. and ischemic heart disease. The patient was a known asthmatic for 10 years on chronic bronchodilator therapy. The patient was admitted to the hospital due to shortness of breath on 7/29/94. The patient was diagnosed with hyper-inflated chest with wheezes and breathlessness due to acute infective exacerbation of asthma. Pramipexole was discontinued. The patient was treated with bronchodilators, prednisolone, and erythromycin and was discharged. The patient was readmitted to the hospital with acute breathlessness. The patient was diagnosed with left ventricular failure secondary to ischemic heart disease and exacerbated chest infection. The patient's condition deteriorated with evidence of heart failure and he died. The cause of death was chronic obstructive airway disease with left ventricular failure. Although there was no autopsy to confirm.

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4.9 All-Cause and AE Dropout Risks

4.9.1 ET Studies

Table 4.9.1.1 shows the reasons for study dropout in ET patients (completed double-blind placebo-controlled PD trials) by treatment groups.

Reason For Discontinuation	Number (%) of Patients			
	Pramipexole (N=388)		Placebo (N=235)	
	N	%	N	%
Adverse Events	46	11.9	25	10.6
Lack of efficacy	1	0.3	8	3.4
Protocol Violation	1	0.3	0	0
Lost to Follow-up	3	0.8	0	0
Other	5	1.3	5	2.1
Total Patients	56	14.4	38	16.2

Using a data cutoff date of 1/31/95, the all-cause dropout risk was 14.4% (56/388) in pramipexole ET patients compared to 16.2% (38/235) in placebo.

There were differences in reasons for dropout by treatment group. The AE dropout risk was 11.9% with pramipexole (46 patients) compared to 10.6% with placebo (25 patients). A larger percentage of patients was withdrawn from study because of lost to follow-up with pramipexole than placebo and the opposite was the case for lack of efficacy.

The all-cause dropout risk and AE dropout risk associated with pramipexole use was variable across ET studies. In study 1, the all-cause dropout risk was 17% (28/164) for pramipexole and 20% (34/171) for placebo treated patients. In pramipexole treated patients, the AE dropout risk was 13% (22/164) compared to 14% (24/171) with placebo. In study 21, the all-cause dropout risk was 18% (2/11) for pramipexole and 23% (3/13) for placebo treated patients, and these dropouts were due to AEs.

In study 4, the all-cause dropout risk was 6 times greater with pramipexole, 12% (25/213) than with placebo 2% (1/51). This difference was mostly due to a difference in dropouts associated with AEs. In pramipexole treated patients, the AE dropout risk was 10% (22/213) compared to 0% (0/51) with placebo. This

difference in AE dropout risk seems to be due to the fact that study 4, as mentioned earlier was a dose-response tolerability study and reached doses of 6.0 mg/day in one of its arms. Clinical intolerance occurred more at this highest dose, whereas in the other protocols the maximum dose reached was 4.5 mg/day.

The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

4.9.2 AT Studies

Table 4.9.2.1 shows the reasons for study dropout in AT patients (completed double-blind, placebo-controlled PD trials) by treatment groups.

Table 4.9.2.1 Premature discontinuations: AT Trials (10, 19, 20, & 22)				
Reason For Discontinuation	Number (%) of Patients			
	Pramipexole (N=260)		Placebo (N=265)	
	N	%	N	%
Adverse Events	30	11.5	42	15.8
Lack of efficacy	0	0	1	0.4
Protocol Violation	1	0.4	2	0.8
Lost to Follow-up	0	0	2	0.87
Other	9	3.5	7	2.6
Total Patients	40	15.4	54	20.4

The all-cause dropout risk was 15.4% (40/260) in pramipexole AT patients compared to 20.4% (54/265) in placebo.

The AE dropout risk was 11.5% with pramipexole (30 patients) compared to 15.8% with placebo (42 patients).

The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

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4.10 Clinical Characteristics of AEs that were Associated with Dropout

Across all phase 2/3 studies, 127 pramipexole patients dropped out of study associated with a serious AE occurrence. No separate lists were provided for the dropouts due to serious AEs for the ET patients and AT patients. Appendix 4.11.1 provides a listing of all serious AEs associated with dropout across all studies. These events were reviewed using the narrative summaries and other supporting data. Overall, there were no cases of agranulocytosis, aplastic anemia, serious skin reactions such as Stevens-Johnson Syndrome, hepatic failure or necrosis, and renal failure or worsening of renal function that were associated with dropout. One patient was discontinued for immune thrombocytopenia and 3 more because of elevated CPKs, with one patient experiencing rhabdomyolysis. Cases are discussed in 4.11 along with other serious AEs.

4.10.1 Clinical Characteristics of AE Dropouts in ET Patients

4.10.1.1 Serious AEs Associated with Dropout in ET Patients

The serious AE dropout risk in ET patients using pramipexole was 2.1% (8/388), while 1.3% (3/235) using placebo. Based upon a review of the investigator verbatims of the 8 patients with serious AEs associated with pramipexole dropout in ET patients, 1 had an AE that was cardiovascular in nature, and this patient eventually expired, (this patient# 2433, study 1 is summarized in the mortality section 4.8.2). The 7 remaining patients were recorded under investigator verbatims of drowsiness (associated with an MVA), decreased platelets, abdominal pain, somnolence (ran off the road in car), paranoid psychosis, sensory hallucinations, and confusion/hallucination.

4.10.1.2 Most Common AEs associated with Dropout in ET Patients

Table 4.10.1.2.1 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% of patients:

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Table 4.10.1.2.1
ET Patients
Adverse Events Which Caused Study Termination
Occurring with Frequency > = 1%

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	388	235
CONFUS	4 (1.03)	0 (0.00)
DIZZINESS	8 (2.06)	2 (0.85)
EXTRAPYR SYND	6 (1.55)	15 (6.38)
HALLUCIN	12 (3.09)	1 (0.43)
HEADACHE	5 (1.29)	0 (0.00)
NAUSEA	8 (2.06)	1 (0.43)
SOMNOLENCE	6 (1.55)	0 (0.00)

Studies included M/2730/0001, M/2730/0004, and M/2730/0021

Hallucinations, nausea, dizziness, somnolence, EPS, headache, and confusion were the only AEs associated with dropout in more than 1% of pramipexole patients. They also occurred at least 2 times more frequently than with placebo. Based upon our review of all dropouts from studies 1, 4, and 21, only 1 patient (patient 182, pramipexole exposed) dropped out due to syncope (0.3%).

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4.10.2 Clinical Characteristics of AEs Associated with Dropout in AT Patients

4.10.2.1 Serious AEs Associated with Dropout in AT Patients

The serious AE dropout risk in AT patients using pramipexole was 3.1% (8/259), while 2.3% (6/266) using placebo. Based upon a review the investigator verbatims of the 8 patients with serious AEs associated with pramipexole dropout in AT patients, 2 had AEs that were cardiovascular in nature (patient #s 1021 and 1065) and both were discussed in the mortality section 4.8.2.

4.10.2.2 Most Common AEs associated with Dropout in AT Patients

Table 4.10.2.2.1 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% of AT patients:

Table 4.10.2.2.1
AT Patients
Adverse Events Which Caused Study Termination
Occurring with Frequency $\geq 1\%$

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	260	264
CONFUS	3 (1.15)	6 (2.27)
DIZZINESS	3 (1.15)	4 (1.52)
DYSKINESIA	5 (1.92)	2 (0.76)
EXTRAPYR SYND	4 (1.54)	13 (4.92)
HALLUCIN	7 (2.69)	1 (0.38)
HYPOTENS POST	6 (2.31)	3 (1.14)

Studies included M/2730/0010, M/2730/0019, M/2730/0020, and M/2730/0022

Hallucinations, dyskinesia, and postural hypotension were associated with dropout in more than 1% of pramipexole patients and occurred 2 times more frequently than with placebo. No pramipexole patients dropped out because of syncope, while 3 patients (#s 1399, 1411, and 1302) dropped out because of syncope, all from protocol 10.

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4.11 Serious AEs Associated with Pramipexole

In the ISS, serious AE risks were not described separately for ET and AT patients, as noted earlier a separate analysis was performed for this review. In the 3 ET RCTs the serious AE risk was 5.1% (20/388) with pramipexole and 5.5% (13/235) with placebo. Of these 20 pramipexole patients with serious AEs, 7 were CV in nature. One of these 7 was discussed in the mortality section, of the remaining 6, 2 were MIs, 2 were angina pectoris, and 1 each of pulmonary embolism and left ventricular dysfunction (reported as dyspnea).

Seven of the remaining 13 patients with serious non-CV AEs in the ET studies, were described under section 4.10.1.1. Of the remaining 6 patients, 2 had prostate cancer and 1 patient each were reported to have the following: fractured hip, thyroid nodule, basal cell carcinoma, and early rectal cancer.

In the 4 AT RCTs, the serious AE risk was 7% (18/259) with pramipexole and 7.5% (20/266) in placebo. Of the 18 patients with serious AEs, 3 were CV in nature, of which 2 have been discussed in section 4.8.2, and the other (patient 30, study 19) was reported to suffer from angina pectoris and stenocardia. The remaining 15 patients were reported to have the following: pneumonia, dyskinesia, fractures, somnolence, bladder cancer, paranoia, nausea, neck pain, CPK elevation, increase of periods, back pain, abdominal pain, confusion, and multiple myeloma.

The patients coded with dyspnea had other ongoing AEs such as CHF or pneumonia.

Appendix 4.11.1 provides a listing of all serious AEs occurring in pramipexole and placebo patients. There were no serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, or seizures. Several cases are worth summarizing for their possible association with the study medication.

Cardiovascular

In ongoing study #0036, patient #663 experienced severe orthostatic hypotension after the initial dose of pramipexole. This patient was a 72 YOWM () with a history of PD diagnosed in 1994 and treated with selegiline and levodopa-carbidopa. Concomitant medications were numerous and included: estrogen, Cyproterone, entrophen for prostatic CA, lactulose for constipation and phenazo-pyridine and lorazepam. He did not smoke. The patient received one dose of pramipexole (0.125mg). One hour following initial dose, the patient was reported to have experienced what was termed "severe orthostatic hypotension", with symptoms characterized by feeling faint and lightheadedness. He appeared pale with a rapid pulse. The supine blood pressure was () and the standing blood pressure was reported to be essentially 0. The patient was unable to stand for 3.5 hours post-dosing. When able to stand, his standing blood pressure was () The ECG reading was reported to be normal. The patient was admitted to

the hospital for overnight observation, bedrest and IV fluids. The next day the patient was discharged but complained of lightheadedness and dizziness. Study medication was discontinued following the first dose. Incidentally, the patient had no previous history of symptomatic orthostatic hypotension. At baseline his supine vital signs were upon standing they were The investigator indicated that the event was probably related to study medication.

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Hematologic

Patient #130 (protocol 0004) discontinued on study day 47 because of severe (life threatening) thrombocytopenia. The baseline platelet count was cells/mm³; on day 40 the count was /mm³. This was a 72 year old male who was on a 4.5mg per day of pramipexole. The narrative summary and CRF (Volume 576) of the patient revealed that this was a patient who had Parkinson's disease diagnosed approximately 4 years previously. This patient had a past medical history of hypertension (since 1994) and received nifedipine during the study. He began treatment with nifedipine 216 days prior to study entry. On day 40 as mentioned previously the platelet count had decreased significantly. The hemoglobin value and WBC count were unchanged from baseline. On day 43, repeat laboratory results showed a platelet count of cells/mm³. The patient was discontinued from the study. On day 47 the platelet count was cell/mm³. On day 55 bone marrow aspiration showed a slight hypercellularity and trilineal hyperplasia, indicating no bone marrow suppression. The patient was followed by a hematologist. The investigator considered the decreased platelet count to be possibly related to study medication and/or nifedipine. No further information is available on this patient.

Respiratory

Patient #30 (study 0004) was a 77 YOM with pre-existing heart disease and left ventricular dysfunction. The patient had a history of hypertension and coronary arteriosclerosis since 1987 and had cardiac bypass surgery in 1988. During this study, he concomitantly received nifedipine and acetylsalicylic acid and deprenyl for Parkinson's disease. At baseline his vital signs and ECG were normal. On day 8, he began reporting moderate edema in his left ankle but no cardiac symptoms. The patient was receiving 3mg/day of pramipexole when on day 32 he began having dyspnea. On day 36 while receiving 4.5mg/per day of pramipexole the patient was hospitalized because of continued dyspnea. He was found to have pulmonary congestion and ventricular dysfunction. He was discontinued from the study. On day 50, he underwent cardiac bypass surgery. On day 99, the patient was discharged from the hospital.

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Serious Laboratory Abnormalities

Patient 1092 was a 49 YOWM () with a 5 year history of Parkinson's (carbidopa-levodopa Rx) on multiple medications. Patient had episodes of dizziness, lightheadedness, dyspnea and pain in neck, back and chest for 4 days (7/12/93) prior to a blood pressure reading on 7/16/93 which revealed asymptomatic hypotension (supine vs = and standing vs =) compared with baseline readings of: for supine and) for standing. Seven days (7/23/93) after the orthostatic hypotension at the next laboratory determination an increase in CPK was noted and he was hospitalized diagnosed and treated for rhabdomyolysis. He had a marked increase in CPK-). The CPK was fractionated and found to be His baseline on 6/25/93 was Patient also had other abnormal laboratory results reflecting release of intracellular contents from skeletal muscle injury, e.g., LDH, AST and uric acid (escaped muscle purine catabolism). His CPKs decreased when drug was stopped. The narrative summary contained in volume 102 stated that patient had multiple bruises. This information was not seen in the CRF.

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4.12 AEs Associated with a Change in Pramipexole Dose

AEs that were associated with a reduction in pramipexole dose were similar to the pattern seen with discontinuations.

4.13 AE Risks Associated with Pramipexole Use Irrespective of Severity

4.13.1 Overall

4.13.1.1 ET Patients

Appendix 4.13.1.1.1 lists AEs that were reported in $\geq 1\%$ of ET patients assigned pramipexole in placebo controlled ET studies.

Table 4.13.1.1.1 lists the AEs that were reported at twice the rate of placebo and $\geq 1\%$ (the rest of the AEs in appendix 4.13.1.1.1 were comparable to or less frequent than placebo):

Table 4.13.1.1.1
ET Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	388	235
Fever	4 (1.03)	1 (0.4)
Nausea	107 (27.6)	42 (17.9)
Constipation	53 (13.7)	14 (6.0)
Anorexia	17 (4.4)	5 (2.1)
Dysphagia	7 (1.8)	1 (0.4)
Weight decrease	7 (1.8)	1 (0.4)
Somnolence	85 (21.9)	21 (8.9)
Insomnia	66 (17)	27 (11.5)
Hallucination	35 (9)	6(2.6)
Confusion	16 (4.1)	3 (1.3)
Amnesia	14 (3.6)	4 (1.7)
Hypesthesia	11 (2.8)	2 (0.9)
Akathisia	6 (1.5)	0
Thinking Abnormal	6 (1.5)	1 (0.4)
Libido Decreased	5 (1.3)	0
Myoclonus	5 (1.3)	1 (0.4)
Vision Abnormality	10 (2.6)	0 (0.00)

Studies included M/2730/0001, M/2730/0004, and M/2730/0021

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Somnolence (21.9%), constipation (13.7%), and hallucinations (9.0%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.13.1.2 AT Patients

Appendix 4.13.1.2.1 lists AEs that were reported in $\geq 1\%$ of AT patients assigned pramipexole in placebo controlled AT studies.

Table 4.13.1.2.1 lists the AEs that were reported at twice the rate of placebo and $\geq 1\%$ (the rest of the AEs in appendix 4.13.1.2.1 were comparable to or less frequent than placebo):

Table 4.13.1.2.1
AT Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	260	264
Chest Pain	8 (3.1)	4 (1.5)
Dry Mouth	17 (6.5)	7 (2.7)
Peripheral Edema	6 (2.3)	2 (0.8)
CPK Increase	3 (1.2)	1 (0.4)
Twitching	6 (2.3)	0
Bursitis	4 (1.5)	1 (0.4)
Myasthenia	3 (1.2)	0
Dyskinesia	123 (47.3)	83 (31.5)
Hallucination	43 (16.5)	10(3.8)
Paranoid Reaction	5 (1.9)	1 (0.4)
Delusions	3 (1.2)	1 (0.4)
Sleep Disorder	3 (1.2)	0
Rhinitis	7 (2.7)	3 (1.3)
Pneumonia	5 (1.9)	0
Diplopia	3 (1.2)	0
Urinary Frequency	15 (5.8)	7 (2.7)
Vision Abnormality	8 (3.1)	2 (0.8)

Studies included M/2730/0010, M/2730/0019, M/2730/0020 and M/2730/0022

Hallucinations (16.5%), urinary frequency (5.8%), and dry mouth (6.5%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.13.2 Dose Response

4.13.2.1 Dose Response in ET Patients

Appendix 4.13.2.1.1 shows the effect of dose on AE risk for AEs that were reported in at least 10% of ET patients using pramipexole (irrespective of frequency in placebo). The sponsor's analysis was broken down not by individual doses but by phases: ascending, maintenance, and taper phases of the dosing cycles. The largest risk reported was during the ascending phase of the dosing. AEs shown are: asthenia, headache, infection, pain, constipation, nausea, dizziness, insomnia, and somnolence.

Since study 4 was designed as a specific dose response study, its dose-relatedness of adverse events was assessed separately. This study was performed in 264 patients with early Parkinson's disease. In this study patients were randomized equally to target dosages of 0, which was a placebo, 1.5mg; 3.0mg; 4.5mg or 6.0mg per day of pramipexole. (Doses given orally on a t.i.d. schedule with a six week dose escalation period and a four week maintenance period). With increasing dosages of pramipexole, there were more adverse events reported in the digestive system (nausea 15% (8/54), 17% (9/54), and 20% (11/55) for the 1.5 mg/day, 4.5mg/day, and 6.0mg/day doses, respectively) and the CNS (somnolence and insomnia) in the maintenance phase of the study. Vital signs were measured at each visit and time of last dose recorded, but the BP measurements were not timed to last dose.

4.13.2.2 Dose Response in AT Patients

Appendix 4.13.2.2.1 shows the effect of dose on selected AEs in AT patients following a similar approach as in ET patients. The sponsor's analysis was broken down not by individual doses but by phases: ascending, maintenance, and taper phases of the dosing cycles. The largest risk reported, here as well was during the ascending phase of the dosing. The AEs shown include dyskinesia, nausea, orthostatic hypotension, confusion, and hallucination.

No specific dose-response design studies were performed in the AT patients.

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4.13.3 AE Occurrence and Plasma Concentration

Pramipexole plasma concentration was not measured at the time of AE occurrence in either ET or AT patients.

4.13.4 AE Risk by Time Since First Exposure

Appendix 4.13.4.1 shows risks for AEs reported in $\geq 10\%$ of ET patient by time since first exposure.

Appendix 4.13.4.2 shows risks for AEs reported in $\geq 10\%$ of AT patients by time since first exposure.

In general, the findings agree with those observed for dose response. The most frequently reported AEs, here as well occurred with the lower doses, which correspond with the ascending phase of the dosing.

4.13.5 AE Risk and Concurrent Medication Use

The sponsor examined the effect of concurrently used medications on AE risk that might be attributable to pramipexole for both ET and AT patients. AEs were selected if reported in at least 5% of a study population and concurrent medications were selected if their extent of use was at least 10%. The concurrent medications selected were selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricyclic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and tocopherol.

4.13.5.1 AE Risk and Concurrent Medication Use In ET Patients

When examining the RRs (pramipexole compared to placebo), there were no differences of any consequence observed in the AE occurrence between the different concurrent medications analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.13.5.2 AE Risk and Concurrent Medication Use In AT Patients

When examining the RRs (pramipexole compared to placebo), there were no differences of any consequence observed in the AE occurrence between the different concurrent medications analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.13.6 AE Risk by Age, Gender and Race

Data from the pivotal trials were pooled in the ISS. For this review a subgroup analysis of AE risk by age and gender for the ET and AT trials was performed. Appendices 4.13.6.1-2 and 4.13.6.3-4 display the age (< 45, , and >75) and gender based analyses for AEs reported with a frequency of > 5% with analyses of relative risk (RR-relative rate for pramipexole/rate of placebo). A summary of findings in the appendices follows:

In the age analysis of the ET patients, when examining the RRs (pramipexole compared to placebo), there were no major differences observed in the AE occurrence between the different age groups analyzed. A search did not identify an RR that was two-fold greater than any comparison. However, there was a specific pattern of increasing RR with increasing age for the reported AE Hallucination.

In the age analysis of the AT patients, when examining the RRs (pramipexole compared to placebo), there were no major differences observed in the AE occurrence between the different age groups analyzed. A search did not identify an RR that was two-fold greater than any comparison. However, there was a specific pattern of increasing RR with increasing age for the reported AE Hallucination (even more prominent than with the ET patients).

In the gender analysis of the ET patients, depression was reported at a > two-fold higher RR in males than in females; and hallucination was reported at a > two-fold higher RR in females than in males. Other AEs were comparable.

In the gender analysis of the AT patients, dyspepsia was reported at a > two-fold higher RR in males than in females; and hallucination and urinary frequency were reported at a > two-fold higher RR in females than in males. Other AEs were comparable.

There were too few non-white patients exposed to pramipexole to examine variation in risk by race.

4.13.7 AE Risk for Selected Underlying Diseases

To describe any potential modification in pramipexole risk for patients with selected underlying (concurrent) diseases, The sponsor used a similar approach to that with concurrently used medications and for demographic subgroups. Concurrent disease was defined as illness present at baseline. Concurrent diseases that occurred in $\geq 5\%$ of pramipexole patients were used to calculate the relative risk. The concurrent diseases selected for study were arthritis, CV disease, constipation, depression, dizziness, hypercholesterolemia, hypertension, insomnia, and prostate disease.

When examining the RRs (pramipexole compared to placebo) in ET patients, there were no differences of any consequence observed in the AE occurrence between the different concurrent illnesses analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

When examining the RRs (pramipexole compared to placebo) in AT patients, there were no differences of any consequence observed in the AE occurrence between the different concurrent illnesses analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.14 AE Risk During Tapering

There were no significant differences in the AEs reported during tapering. In protocols where dose reduction was followed, no AEs could be attributed to drug withdrawal. There seemed to be more AEs (tremor, EPS, and hypokinesia) consistent with worsening of PD.

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4.15 Changes in Laboratory Parameters Associated with Pramipexole Use

Here again, the sponsor primarily presented pooled analysis of the "adequate and well-controlled studies", 0001, 0004 (the studies in early PD patients) and 0010 (the study in advanced PD patients), without disregarding the other 6 PD studies. This portion of the review will follow the sponsor's approach. However, it should be noted that the individual ET and AT study reports were reviewed. Appendix 4.15.1 displays the laboratory criteria used by the sponsor as normal values; values outside these predefined limits were flagged. Appendix 4.15.2 summarizes the data of laboratory values with abnormal shifts (outside these predefined limits) in the 3 pivotal trials.

Hematology

Except for lymphocytes, the incidence of hematologic laboratory values exceeding predefined limits for pramipexole-treated patients was less than that of placebo patients and/or was lower than 1%. Approximately 3% of the pramipexole-treated patients (16/547) vs approximately 2% of placebo-treated patients (7/394) had lymphocyte values lower than the predefined limits. There was no statistically significant differences between the groups (Sponsor's Fishers' Exact Test, $p=0.292$).

There were no statistically significant changes in mean hematologic values for the pramipexole and placebo groups separately and when compared to each other across the baseline values. There was no evidence of dose-relatedness (1.5mg/day to 6.0mg/day in protocol 0004) for the hematologic analytes measured: HgB, WBC, and platelets.

For the other PD studies there were 2 pramipexole-treated patients (1.5%) who had spurious low lymphocyte values outside the predefined limits during treatment compared with 3 (2.2%) of the 137 placebo-treated patients.

In the PD studies one patient (patient #130, protocol 0004) out of 702 of the pramipexole-treated patients discontinued due to thrombocytopenia (case discussed in section 4.11). One placebo-treated patient (0.3%) discontinued because of leukopenia. In the completed schizoprenia studies, as well as the ongoing studies in Parkinson's disease, there were no reports of discontinuations because of hematologic laboratory values. In the review of deaths and serious AEs, no cases of aplastic anemia or agranulocytosis were found.

Blood Chemistry Parameters

Appendix table 4.15.2 summarizes all patients with laboratory data exceeding predefined limits in the pooled adequate and well-controlled studies. The proportion of patients which moved from a predefined normal GGT and CPK value to a higher abnormal value were 2% and 3.5%, respectively, in the pramipexole treated patients. These shifts were similar in the placebo treated patients. About 1% of the pramipexole treated patients had shifts to

abnormal values for AST and ALT. This was not observed for placebo. The incidence of shifts in other analytes (both for placebo and pramipexole treated patients) were less than 1% and clinically not significant.

A summary of patients with elevated CPKs is located in Appendix table 4.15.3. It enables one to appreciate the wide range of dispersion in values for both treatment groups. In the pooled database 19 (3.5%) of the pramipexole treated patients compared with 9 (2.3%) of the placebo treated patients had CPK values which exceeded predefined limits. There was no statistically significant difference between the two groups, (sponsor's Fishers' Exact Test, $p=0.335$).

Of the 19 pramipexole treated patients with elevated CPKs, 13 were reported in the 2 early Parkinson's studies and 6 in the advanced Parkinson's study 0010. In the placebo group, there were 5 reports in the early and 4 reports in the advanced. The AT study 0010, reported a statistically significant mean change elevation from baseline in total CPKs in the pramipexole group compared to the placebo group (+21.31 vs -1.28, $p<0.003$). The ET dose-response study (protocol 0004), also reported a mean change from baseline greater in the pramipexole than placebo group for both the ascending and maintenance phases at all doses other than the 4.5mg/day dose. Table 4.15.1, which displays the mean changes from baseline to endpoints for CPKs during the dosing periods for protocol 0001, can be considered representative of all PD studies:

Group	Ascending*		WEEKS Maintenance		Reduction
	4	7	8	16	
					24
Pramipexole	+24	+27	+32	+31	+30
Placebo	+9.5	+1.0	+8.0	+6.0	+13

+ = Dosing phases

In the 6 studies designated other controlled studies, only the laboratory analyte CPK exceeded predefined limits (shifts to abnormal). Five (7%) of the 76 pramipexole patients exceeded predefined limits compared with none of the 83 placebo patients evaluated. For three of the five pramipexole patients, the abnormal values were spurious. For the other two patients their endpoint values remained elevated: one patient started with a high baseline CPK value of 257 u/L (normal range: u/L) and at endpoint it was 336 u/L. The remaining patient (No. 20, Protocol 0020) was a 58-year old man with a CPK value of 86 u/L at baseline, at day-22 value of 219, and an endpoint value (day 48) of 3498 u/L. The patient was discontinued because of this elevated CPK. Although the patient had many other adverse events, a cause for the elevated CPK could not be identified by the investigator. Myopathy was not reported. After drug discontinuation, the CPK had returned to within the normal range.

As discussed in previous sections (serious and dropouts), a careful assessment for rhabdomyolysis was performed (by examining individual CRFs) and one patient was found that experienced rhabdomyolysis. The case is discussed in the serious AEs section.

Patients with increased GGTs are summarized in Appendix table 4.15.3. Of the 11 patients with GGT values outside the predefined limits during treatment, 5 had baseline elevations and 6 had post baseline elevations. Four pramipexole treated patients, from protocol 10, (number 1061, 1118, 1171, and 1226) had GGT values which ranged from : u/L (NR: 0-65 u/L). In all cases patients had clinically significant elevations of other liver enzymes as well (either AST or ALT values). In the placebo group one patient (number 1242) was identified with clinically significant elevations in GGT (value was 268 u/L). Mean changes in GGT levels from baseline were examined and there were no statistically significant differences between pramipexole and placebo.

Four patients (#s 182, 1171, 1021, 1092) had elevated ASTs and 4 patients (#s 1171, 1061, 1226, 1118) had elevated ALTs. Data are summarized in appendix table 4.15.3. The following patients reported values which were $\geq 2.5 \times \text{ULN}$: patient #171 in protocol 0010 (AST, ALT and GGT); patient #1118, (ALT and GGT) and patient #1226, (ALT and GGT).

In protocol 10 (AT trial), there were statistically significant mean change elevations of ALT and AST from baseline in the pramipexole treated patients. Table 4.15.2 displays these differences:

Visit number	Laboratory analyte	Mean change from Baseline		
		Pramipexole	Placebo	p-value
18	ALT IU/L	+5.14	0.28	0.005
	AST IU/L	+2.43	0.02	0.02
19	ALT IU/L	+4.3	-0.9	0.001
	AST IU/L	+1.8	-0.7	0.01

There were no differences in mean changes from baseline to designated endpoints between the treatment groups with respect to AST and ALT values in protocols 1 or 4 (ET trials).

One patient in protocol 0010 (patient #1226, CRF in volume 610) withdrew from pramipexole treatment because of the adverse event hepatitis and abdominal pain. He had elevated hepatic enzymes and is discussed in this section. Patient #1226 was a 67-year old white male with a past medical history significant for a cholecystectomy, kidney stones and removal of skin cancer. The patient had Parkinson's disease since 1964 treated with

antiparkinsonian medication including bentsropine emsylate and carbidopa-levodopa. When the patient was seen for visit 5, the liver tests were noted to be markedly elevated with GGT at u/L (upper normal u/L) as well as elevated AST, ALT, and alkaline phosphatase (values could not be read from the CRF). Repeat liver function test at visit 6 showed further increases in AST and LDH (once again, the values were illegible). The dose level of study medication was increased as per protocol to dose level 5. At visit 7, a general hepatitis A screen was reported to be positive. However, further workup indicated patient did not have active hepatitis (only past exposure). Further additional workup for hepatitis B and C was reported to be negative. At visit 8, additional LFTs were done demonstrating continuing elevations and these values were noted to be as follows: AST value on visit 8 was u/L (), ALT was u/L on visit 8 and GGT value on visit 8 was u/L (). Study medication was discontinued. Patient was referred to a gastroenterologist who felt that the patient's elevated LFTs were drug-related. Within 30 days of discontinuing medication, normalization of LDH, AST and ALT occurred. Throughout the total time period that LFTs were elevated total bilirubin levels remained within the normal range. Based upon the patient's course and normalization of laboratory abnormalities following discontinuation of study drug, the abnormal LFTs appeared to be possibly related to the pramipexole. The patient did enter the open-label pramipexole study five months later. There were no reports of elevated LFTs.

As mentioned in the dropouts section, in the PD trials 3 pramipexole-treated patients and 1 placebo-treated patient discontinued because of chemistry AEs. These patients (pramipexole and placebo) discontinued because of increases in CPK, and were discussed earlier. In the completed schizophrenia studies, 1 out of 177 pramipexole-treated patients discontinued because of chemistry values considered abnormal (CPK increase--information on this patient is not available at this time) and 1 placebo-treated patient out of 95 discontinued due to an elevation in ALT. In the ongoing studies in Parkinson's disease, 1 out of 1,056 pramipexole-treated patients, discontinued (elevation in CPK). Patient #049 (protocol 0012 CRF in vol 667) discontinued because of increased CPK, pain in arm and back and dyskinesia.

Urine Analysis

Appendix table 4.15.2 lists the incidence of clinically significant urinalysis laboratory values exceeding predefined limits in the adequate and well-controlled studies. With the exception of urinary protein, the incidence of abnormalities for pramipexole-treated patients was less than that of placebo patients and/or was lower than 1%. In the pramipexole-treated patients 2.2% of the patients (8/364) vs 1% of the placebo-treated patients (2/219) had an abnormal laboratory urinary protein value which was abnormally high. Seven of the 8 pramipexole patients with urine protein values outside predefined limits also had protein in their urine at baseline.

There were no statistically significant changes in mean urinalysis analytes values for the pramipexole and placebo groups compared with baseline values.

In the other controlled studies, the only value that was higher in the pramipexole-treated group compared to the placebo-treated group was the WBC in the urine where 25% of the pramipexole-treated patients (13/53) vs 10% of the placebo-treated patients (5/50) had values outside exceeding the predefined limits. There were no discontinuations reported.

There was no reporting in the ISS of urinary crystals. However, a review of numerous CRFs revealed that uric acid and calcium oxalate crystals were reported in pramipexole treated patients.

4.16 Changes in Vital Signs Associated with Pramipexole Use

Special attention was focused upon vital sign monitoring as a result of a clinical hold placed on the original IND because of reports of hypotension. In the phase 2/3 studies BP measurement was not timed relative to the time of dosing, but vital signs were checked at every visit.

As displayed in appendices 4.13.1.1.1 and 4.13.1.2.1, although there was little difference between pramipexole groups and placebo groups in the incidence of orthostatic hypotension, there was a great disparity between the ET and AT groups: 7.7% of ET patients taking pramipexole reported orthostatic hypotension and 52.7% of AT patients reported the same AE. A similar disparity between ET and AT placebo groups was noted.

A total of six (1%) of the pramipexole treated patients compared with 1 (0.3%) of the placebo treated patients discontinued treatment due to vital signs. Five (1 ET and 4 AT) of the six events were due to orthostatic hypotension.

4.17 Changes in ECG Parameters Associated with Pramipexole Use

Across the development program, there were no consistent changes in ECG or AEs that suggested that pramipexole had deleterious effects on cardiac function. Most studies had extensive ECG monitoring, and these did not reveal differences in incidence of any changes in ECG between pramipexole and placebo.

In the 3 adequate and well-controlled studies 0.5% (3/558) of the pramipexole treated patients compared with 0.2% (1/400) of placebo treated patients discontinued because of ECG abnormalities. Overall in the completed controlled studies in Parkinson's disease, 0.4% (3/702) of the pramipexole compared with 1% (4/551) of placebo treated patients discontinued because of ECG abnormalities.

The 3 pramipexole treated patients (patient numbers 114, 98 and 91) who discontinued from

protocol 0004 reported ECG abnormalities of palpitations, tachycardia, and an irregular heart rate (arrhythmia) that were not causally related to pramipexole. The 1 placebo patient (patient # 1399) was from protocol 10.

4.18 Dyskinesia

The Parkinson's Dyskinesia Scale (PDS) was used by investigators to characterize the severity of abnormal movements in patients. There was no difference in the PDS over time between treatment groups.

4.19 Review of Special Studies

4.19.1 Withdrawal Potential

Pramipexole is not a controlled substance. Pramipexole has not been systemically studied in animals or humans for its potential for abuse, tolerance or physical dependence; and receptor binding studies for the opiate receptors were not performed.

In protocols where dose reduction for one week was followed, no AEs could be attributed to drug withdrawal. Symptoms such as tremor, EPS, asthenia, hypertonia, gait abnormality, and hypokinesia during dose reduction were attributed to the underlying PD. In the clinical trials and in the labelling, the sponsor recommends that patients discontinue treatment gradually over a one-week period, despite instances of patients discontinuing abruptly or tapered at a rate faster than recommended exhibiting no withdrawal symptoms.

4.19.2 Interaction Studies

Four phase I studies were conducted to evaluate drug interactions of pramipexole with other drugs.

The potential interactions between probenecid, pramipexole, and cimetidine were investigated in six male and six female volunteers according to a three treatment crossover design (study 0061). This study demonstrated that concomitant therapy with drugs secreted by the cationic-transport system of the renal tubules may necessitate dose reduction of pramipexole.

In a modified and crossover design study (study 0063) of five male and four female volunteers, the pharmacokinetics of pramipexole and levodopa administration were examined. Pramipexole did not alter the extent of levodopa absorption, but there were differences in levodopa C_{max} (42% increase) and T_{max} (71% decrease) suggesting a faster rate of absorption, although the small number of subjects and the high degree of variability produced precluded a definitive estimate of the magnitude of this change. Titration of the levodopa dose to the individual patients optimum therapeutic response may be required

during concomitant treatment with pramipexole.

The sponsor did not perform drug metabolism studies. The rationale was that the high bioavailability (>90%) indicates no first pass effect and hence no phase 1 oxidative metabolism of the drug.

4.20 Human Reproduction Data

No pregnancy exposures were observed with pramipexole. Preclinical studies with high doses (1.5 mg/Kg/day) revealed embryo toxicity demonstrated by post-implantation loss, late embryonic deaths, and decreased fetal weights). No teratogenic effects were observed at any dose.

4.21 Human Carcinogenicity Potential

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Pramipexole was not carcinogenic in the drug safety studies except for a 2 year study in rats, in which Leydig cell adenomas were found. The sponsor attributes the Leydig cell hyperplasia and increased number of adenomas to pramipexole-induced hypoprolactinemia. Because of the common occurrence of Leydig cell tumors in rats, the agency's cancer assessment committee (CAC) no longer requires mentioning of such tumors in the labelling.

4.22 Overdose Experience

There were no reports of intentional overdoses. There was only one report of an unintentional overdose in a patient with a 10-year history of schizophrenia. He took 11mg/day of pramipexole. No adverse events were reported.

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5 Summary of the Safety Experience in the Pramipexole Development Program

5.1 General Comments

Overall, the pramipexole development program has included adequate short and long-term pramipexole use to evaluate its safety separately in ET and AT patients. There appears to have been enough experience at 4.5 mg per day, the maximum recommended dose, to evaluate the relative safety of that dose.

Follow-up of patients was good with few patients lost to follow-up. The clinical data provided was sufficient in most cases to describe the general character of most treatment emergent AEs.

On balance, there was little difference between pramipexole and placebo in the ET and AT patient populations. All cause study dropout risk for the ET patients was reported to be 14.4% in the pramipexole treated patients and 16.2% in the placebo, while 15.4% and 20.4%, respectively for the AT patients. Dropout risk due to AEs for the ET patients was reported to be 11.9% in the pramipexole treated patients and 10.6% in the placebo, while 11.5% and 15.8%, respectively for the AT patients. Dropout risk due to serious AEs for the ET patients was reported to be 2.1% in the pramipexole treated patients and 1.3% in the placebo, while 3.1% and 2.3%, respectively for the AT patients. Serious AEs for the ET patients was reported at 5.1% in the pramipexole treated patients and 5.5% in the placebo, while 7.0% and 7.5%, respectively for the AT patients. Mortality rate for the ET patients was reported at 0.34 in the pramipexole treated patients and 0.34 in the placebo, while 1.1% and 0.4, respectively for the AT patients.

The events that were reported in more than 5% of pramipexole ET patients that were at least 2 times more frequent than in placebo were hallucinations and somnolence, while hallucinations and dry mouth in AT patients.

As a point of interest the OSH risk in the ET patients was reported at 7.7% in the pramipexole treated patients and 8.9% in the placebo, while 52.7% and 48.1%, respectively for the AT patients. Risk for syncope in the ET patients was reported at 1.3% in the pramipexole treated patients and 0.9% in the placebo, while 1.5% and 2.7%, respectively for the AT patients.

5.2 Cardiovascular System

In the preclinical studies, pramipexole lowered blood pressure and heart rate, especially in anesthetized animals. Results of experiments with antagonists indicated that the cardiovascular effects are related to the compound's main mechanism of action, (i.e., agonist at dopamine D2 receptors). This seems to be, however, primarily a first-dose effect. No (in rats) or little (in rhesus monkeys, especially after repeated doses) hypotensive

activity was found after oral administration to conscious animals. No interaction with l-deprenyl or L-dopa plus carbidopa could be observed on cardiovascular parameters.

In clinical pharmacology studies, pramipexole was associated with dose-related symptomatic orthostatic hypotension (OSH) in normal subjects beginning at the 0.2 mg dose and a dose-limiting phenomenon at a 0.4 mg/day dose in some studies. OSH occurred after the first dose in some volunteers and as early as 30 minutes at the highest doses. The duration of OSH varied from 1 hour or less to 8 hours, postural syncope occurred in some subjects. The magnitude of the drug-induced changes in standing blood pressure and pulse rate could not always be assessed because subjects were unable to stand for vital sign measurements. There were no clinically significant changes in ECG measurements during the evaluation periods.

In the phase 2/3 trials, there were exclusion criteria of not enrolling patients with active CV disease. The CV events that were most strongly associated with pramipexole use in the phase 1 trials were not consistent with findings in the phase 2/3 trials. In the ET studies, study dropouts and AE dropouts were similar in the pramipexole and placebo groups. Only one of the serious AE dropouts was CV in nature. There were 20 serious AEs reported in patients exposed to pramipexole and 7 were CV in nature, but none reported syncope or orthostatic hypotension. There were 5 syncopes reported in patients exposed to pramipexole and 2 in patients exposed to placebo.

In the AT studies, pramipexole was not associated with increases in study dropouts either overall or that associated with AEs. There was no clear pattern of AEs associated with dropouts. None of the 18 patients with serious AEs and exposed to pramipexole had syncope or orthostatic hypotension. There were 4 syncopes reported in patients exposed to pramipexole and 7 in patients exposed to placebo.

Overall, irrespective of severity there were 7 reports of dropouts due to the AE orthostatic hypotension in pramipexole treated patients in the combined ET, AT studies (1 and 6, respectively) compared with 3 reports in the placebo group in the combined ET, AT studies (0 and 3, respectively). Overall, there were few reports of symptomatic orthostatic hypotension, but two placebo and one pramipexole treated patients reported syncope as an AE and were discontinued. Of special interest is an ongoing double-blind, placebo-controlled study (protocol 55), where the CV effects of pramipexole in PD is being evaluated by performing the valsalva maneuver and tilt table testing.

ECG recordings in animals revealed bradycardia with a corresponding increase in the R-R interval. Other than bradycardia, there was no evidence in animals or humans that pramipexole affected cardiac conduction or was associated with dysrhythmias.

The 8 deaths that were potentially CV in nature, none could be attributed to any CV effect that pramipexole may have had.

In summary, the CV effects of OSH in healthy normal volunteers appear to result from the dopaminergic activity of pramipexole. Despite the benign clinical picture observed for pramipexole, we must keep in perspective its reported pharmacologic mechanism of action as a D₂ and alpha₂ agonist as well as the fact that in the studies, patients with significant underlying CV disease were excluded from participation. The CV effects of pramipexole may be detrimental in patients with advanced Parkinson's disease who may have impaired autonomic nervous system (Shy Drager Syndrome), impaired cardiovascular function, cardiovascular diseases which could be exacerbated by hypotension, in conditions such as hypovolemia and dehydration, and in conditions associated with abnormal early diastolic ventricular filling. Moreover, many elderly patients have resting cerebral blood flow that is close to the threshold for cerebral ischemia and thus, relatively small acute blood pressure reductions may produce cerebral ischemic symptoms such as dizziness, syncope, or falls.

5.3 Central Nervous System

In the animal studies, aside from behavioral changes, there were few significant CNS effects induced by acute treatment with pramipexole. The animal models demonstrated the sedating properties of pramipexole. At various ranges of dosing, ataxia was not reported. Pramipexole did not lower the threshold for seizures. Animal pharmacology studies to determine opiate-like activity for pramipexole were not performed, but there was no evidence of withdrawal.

Adverse events reported from the phase 1 studies were frequently related to the CNS (most frequently dizziness) and did not include any event not seen in phase 2/3 studies.

Reports of CNS AEs were more frequent in the AT group than in the ET group. The following events were considered drug-related in patients with early Parkinson's disease: hallucinations, somnolence, insomnia, and confusion. In the patients with advanced Parkinson's disease the following were considered drug-related: hallucinations, dyskinesia, and confusion. Parenthetically, M.V.A.s occurred in some patients treated with pramipexole and was attributed to somnolence.

There was no evidence of opiate - type withdrawal during the dose-reduction phase in the phase 2/3 studies.

In summary, the CNS adverse effects are known side effects of dopamine agonists. Pramipexole may exacerbate preexisting dyskinesia and potentiate the dopaminergic side effects of such drugs as levodopa.

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5.4 Dermatological

There was no increase in the risk for rash. There were no hospitalizations for serious skin reactions in the pramipexole-treated patients.

5.5 Gastrointestinal

Preclinically, like other dopamine agonists, pramipexole induced emesis and the effect was blocked with a dopamine antagonist. Pramipexole inhibited gastrointestinal transit time, which in individuals older than 70 years of age may exacerbate an already existing situation. Nausea and vomiting were frequently reported in the Phase 1 studies. Two patients dropped out because of these events.

In phase 2/3, the AEs nausea and constipation featured prominently in the ET studies, but not in the AT. Other common causes of nausea, M.I.s and hepatitis were not reported in the patients who discontinued pramipexole use.

In summary, nausea as an AE should not be minimized. The potent influence of nausea on vasopressin release and subsequent antidiuretic effect is well established and may have important clinical consequences, particularly in the elderly P.D. patient.

5.6 Genitourinary/Renal

In animal studies, conflicting results were obtained in assessments of the renal effects of pramipexole in rats with respect to effect on urinary volume and electrolyte excretion. Contrasting effects were reported for pramipexole in conscious and anesthetized animals and may have been due to the anesthesia, dose, or strain of rats. The effectiveness of the D₁ antagonist against pramipexole suggest that the renal effects of pramipexole may be mediated by D₁ receptors. Noteworthy is the fact that both D₁ and D₂ receptors are associated with the renal vascular and tubular systems in humans. Moreover, alpha₁ receptors are found in the collecting tubules of humans.

In the Phase 1 studies, one pramipexole-treated patient dropped out because of renal colic. There were no reports of hyperuricemia or urinary crystals.

In the Phase 2/3 studies, twice as many AT pramipexole-treated patients reported genitourinary AEs than ET pramipexole-treated patients. There were no differences between the placebo groups. In the AT group, urinary frequency was reported by four times as many pramipexole-treated patients as ET pramipexole-treated patients. The placebo AT and the placebo ET groups were similar. A review of CRFs indicated the presence of calcium oxalate and uric acid crystals in some of the pramipexole treated patients, but these were not analyzed in the data presented by the sponsor and hence difficult to quantitate.

In summary, pramipexole is eliminated through the kidney and patients with renal insufficiency should be cautioned about dosing. Moreover, a normal serum creatinine level may mask renal dysfunction in frail older persons with low muscle mass. Creatinine clearance estimations may be a more useful measure of renal function in this age group of PD patients.

5.7 Hematologic

In animal studies, pramipexole was associated with thrombocytopenia in _____ percent of female rats.

In phase 2/3 studies, there was one case of severe thrombocytopenia which appeared to have been caused by an immune mechanism possibly associated with pramipexole. Of note is the fact that other sulfa-containing drugs also have been implicated in acute thrombocytopenia.

5.8 Metabolic Endocrine

Serum prolactin was decreased in both animals and humans in the preclinical and Phase 1-3 studies during exposure to pramipexole. Dopamine agonists are known to influence the lactotrope and prolactin secretion.

Overall, in the ET and AT studies, dropouts were infrequent. Most of the dropouts were due to elevated CPK levels and occurred more frequently in the pramipexole than the placebo groups.

As discussed previously, more pramipexole-treated patients than placebo-treated patients had reports of CPK levels exceeding predefined limits. The fractionation of CPK was not usually carried out in the studies. Of the 19 reports of elevated CPKs in pramipexole-treated patients, 13 occurred in the ET protocols and 6 in the AT protocols. In the placebo groups, the distribution was 5 and 4, respectively for the above protocols. Dyskinesia did not appear to be a contributing factor to elevated CPKs in all cases.

In summary, CPK increases above baseline occurred in pramipexole and placebo-treated patients. Exposure adjusted rates (per 100 patient-years) were more than twice as high for pramipexole-treated patients compared with placebo. The increases in CPK levels were often preceded by changes in blood pressure and not always preceded by reports of physical over activity and/or excessive muscular exertion. In at least one pramipexole-treated patient, increases in CPK were associated with rhabdomyolysis.

5.9 Musculoskeletal

There was one case of rhabdomyolysis associated with pramipexole. Preclinically, there

were no reports of adverse events associated with this system.

5.10 Respiratory

Preclinically, there were no respiratory effects noted with pramipexole. In Phase 2/3 studies, there was no evidence of pulmonary fibrosis with pramipexole. Pulmonary fibrosis has been reported infrequently with dopamine agonists of different chemical structures. The present database had limited power to have detected any pulmonary fibrosis cases even assuming this condition can be diagnosed accurately.

There was an increase in respiratory AEs in the pramipexole AT patients compared with placebo, whereas the reverse was true in the ET patients. More AT pramipexole-treated patients reported respiratory AEs than ET pramipexole-treated patients. Once again, the reverse was true for the placebo-treated patients. AT pramipexole-treated patients may have been at greater risk for pneumonia. There were no reports of pneumonia in placebo or ET patients. Similarly, there were no reports of pneumonia in the preclinical data base.

5.11 Special Senses

Preclinically, retinal degeneration occurred in albino rats. There were no reports of similar ocular findings in humans. In the phase 2/3 trials a higher incidence of "vision abnormalities" were reported in the pramipexole treated patients. The investigator verbatims of these abnormalities included flashing light in eyes, visual disturbance, seeing spots, visual flickering, floaters, trouble reading small print, white comet shooting forward in front of eye and decreased visual acuity. Some of the reported AEs are possibly related to visual hallucinations. No special eye examinations were conducted on these patients.

6 Conclusion

Since, the overall tolerance and safety profile for pramipexole is good, from the safety point of view pramipexole is approvable. The adverse event profile for pramipexole was similar to that frequently seen with dopamine agonists. In the completed controlled studies in Parkinson's disease, adverse events in the nervous, digestive and cardiovascular systems were most common. Patients with advanced Parkinson's disease who were older and on concomitant levodopa therapy often had higher reporting frequencies of adverse events than the patients with early Parkinson's disease. The adverse events emerged more often during the dose-ascending phase. Overall, there were no distinguishing pattern of adverse events by age except for hallucinations (more frequently in pramipexole patients over 65 years of age). Overall, there were no distinguishing pattern of adverse events to separate males and females except of hallucinations (more frequent in females).

In the cardiovascular system reports of adverse events were times more frequent in the AT placebo and pramipexole-treated patients than in the ET placebo and pramipexole-treated

patients. Orthostatic hypotension was the most frequently reported CV adverse event in both the ET and AT groups and it was reported with several orders of magnitude more frequently in the AT patients than in the ET. It is important to note that, most of the reports of orthostatic hypotension in phase 2/3 were asymptomatic in contradistinction to the phase 1 trials. Pramipexole was not associated with an increased risk of syncope in either the ET or AT patients.

Across the ISS, the overall pramipexole mortality was 5 fold greater in AT compared to ET patients and 3 fold greater in AT compared to ET placebo treated patients. Five of 8 CV deaths occurred in the AT group. CV deaths might be expected from the advanced age of the patient population.

Significant, usually transient, elevations of serum enzymes such as CPK, GGT, AST and ALT occurred in pramipexole-treated patients. The laboratory abnormalities were rarely associated with clinical symptoms; however, rhabdomyolysis was reported in one pramipexole-treated patient who had markedly elevated CPKs. The relationship to pramipexole therapy is uncertain; the patient may have suffered from acute exertional rhabdomyolysis.

In conclusion, when the dose of pramipexole is slowly titrated and individualized to obtain optimum response, pramipexole is a safe treatment for patients with Parkinson's disease.

6.1 Suggested Follow-up Issues

- (1) The sponsor should perform in vitro studies to determine the absence of phase I oxidative metabolism. Even in the absence of a P450 pathway, inhibition studies should be performed to evaluate potential drug-drug interactions.
- (2) Explore the ET and AT database for the incidence of urinary crystals such as uric acid and calcium oxalate.

7 Labeling Recommendations

Clinical Pharmacology section:

- (1) The sponsor should mention that pramipexole possesses alpha-two agonist activity.
- (2) The claim that pramipexole reduces dopamine-induced neuronal degeneration is not based on scientific data and should be deleted.

Warnings section:

(1) The sponsor's claim in labeling that tolerance to the AE of orthostatic hypotension develops is not based on scientific evidence and should be deleted.

(2) The sponsor should mention that postural hypotension has been observed after the first dose of pramipexole in a few patients.

(3) The mention of hallucinations is appropriate, but it should be stressed that the elderly and possibly females seem to be at a higher risk.

Adverse Events section:

(1) The 1% table should be redone and two tables reflecting the ET and AT patient populations.

Other Adverse Events section:

(1) The sponsor should note the occurrence of rhabdomyolysis and thrombocytopenia under Rare events.

/S/
John D. Balian, M.D.

11/13/96
Date

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/S/
James F. Knudsen, M.D., PhD

11/13/96
Date

Clinical Reviewers, Safety Group
Div. of Neuropharmacologic Drug Products

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Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
Phase I - Clinical Pharmacology (Basic Pharmacokinetic Studies, Studies in Factors Affecting Pharmacokinetics, and Safety & Tolerance Studies)								
M/2730/0003 Phase I	United States: 1	8/93-10/93	Dose escalation of pramipexole in healthy volunteers: Evaluation of tolerance development to blood pressure and hormone effects	PPX PBO		q8h	7-15 days	24 PPX 12 PBO
M/2730/0023 Phase I	Switzerland: 1	8/90-8/91	A case control study to investigate the influence of varying single doses of pramipexole (SND 919 CL 2Y) measuring Parkinsonian symptoms with a tracking device in patients with advanced PD	PPX		Single dose	Single dose	3 PPX
M/2730/0025 Phase I	Germany: 1	1/88-3/88	Phase I tolerance and preliminary PK: single-dose, dose-escalating, placebo-controlled, double-blind, healthy volunteers	PPX PBO		Single dose	Single dose 2 doses per volunteer	15 PPX 9 PBO
M/2730/0026 Phase I	Germany: 1	5/88-6/88	Phase I tolerance and preliminary PK: multiple-dose, placebo-controlled, double-blind, healthy volunteers	PPX PBO	0.3	TID (q8h)	7 days	8 PPX 4 PBO

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M/2730/0027 Phase I	Germany: 1	8/88-11/88	Phase I tolerance and preliminary PK: single-dose, placebo-controlled, double-blind, pharmacological effects (ie, hormone levels, psychopharmacological evaluations) healthy volunteers	PPX PBO		Single dose	Single dose 2-3 dose/volunteer	15 PPX 9 PBO

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0028 Phase I	Germany: 1	6/88-7/88	A four-way crossover dose and time pharmacodynamic response study of pramipexole given orally as a single dose to healthy male volunteers	PPX PBO		Single dose	Single dose 4-way crossover	12 total
M/2730/0029 Phase I	Germany: 1	4/89-4/89	Phase I PK and bioavailability study: single-dose, open-label, 3-way crossover, healthy volunteers	PPX PPX PPX	0.1 (IV) 0.3 tablet 0.3 solution	Single dose	Single dose 3-way crossover	12 total
M/2730/0030 Phase I	Germany: 1	10/90-12/90	Phase I PK and metabolism of radiolabeled [¹⁴ C] PPX, single-dose, open-label, 2-way crossover, healthy volunteers	PPX PPX	0.1 (IV) 0.3 (oral solution)	Single dose	Single dose 2-way crossover	6 total
M/2730/0031 Phase I	Germany: 1	7/90-9/90	Phase I tolerability and PK study of transdermal PPX in healthy volunteers	PPX PBO Patch Study		Continuous transdermal application	14 days	10 PPX 6 PBO
M/2730/0047 Phase I	United States: 1	3/94-4/94	Phase I steady state PK study: multiple-dose, dose-escalating, open-label, healthy volunteers	PPX		Q8h	22 days	16

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0051 Phase I	England: 1	6/94-11/94	Cardiovascular affects of pramipexole in healthy volunteers and for 0051 their antagonism by domperidone. Randomized, double-blind, four-way crossover, placebo-controlled study	PPX + PBO DOM + PBO PPX + DOM PBO + PBO	0.25 30 0.25 PPX + 30 DOM	Single dose	Single dose 4-way crossover	14 total
M/2730/0060 Phase I	United States: 1	11/94-ongoing	Phase I PK study in volunteers with impaired renal function: single-dose, open-label, parallel	PPX	0.25	Single dose	Single dose	26
M/2730/0061 Phase I	United States: 1	1/95-2/95	Phase I PK study: influence of probenecid and cimetidine on PPX PK, single-dose, 3-way crossover, healthy volunteers	PPX PPX + Probenecid PPX + Cimetidine	0.25 0.25 PPX + 2000 Probenecid 0.25 PPX + 1200 Cimetidine	Single dose PPX 1000 then 500 q6h 300 q6h	Single dose 3-way crossover 4 days 4 days	13 total
M/2730/0062 Phase I	Germany: 1	1/95-4/95	Phase I bioavailability study of clinical and final tablet formulations: 2 x 2 crossover, open-label, multiple-dose, healthy volunteers	PPX	0.375 escalating to 4.5	q8h	30 days	24 total

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M/2730/0063 Phase I	United States: 1	2/95-3/95	Phase I PK study of PPX and carbidopa/levodopa: open-label, modified crossover, multiple-dose PPX, single-dose carbidopa/levodopa, healthy volunteers	PPX carbidopa / levodopa	25/250	q8h Single dose	20 days Single dose	10 total

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0064 Phase I	United States: 1	3/95-3/95	Phase I PK evaluation of co-administration with selegiline: single-dose PPX, multiple-dose selegiline, 2-way crossover, open-label, healthy volunteers	PPX Selegiline	0.25 5	Single dose BID	Single dose 3 days	12 total
M/2730/0065 Phase I	England: 1	6/95-6/95	Phase I PK food interaction study; single-dose, open-label, 2-way crossover, healthy volunteers	PPX	0.25	Single dose	Single dose	12 total
M/2730/0069 Phase I	United States: 1	1/95-1/95	Phase I PK influence of age and gender on PPX PK: single-dose, open-label, healthy volunteers	PPX	0.25	Single dose	Single dose	38
M/2730/0073 Phase I Innovex: F=061 Basotherm GmbH No: IP- Nr 211.1)	Germany: 2	6/93-6/93	Study to investigate the tolerability of SND 919 CL eye drops (0.00625, 0.02, and 0.05%) in ascending order after single instillation into the eye of healthy volunteers	PPX PPX PPX PBO	1.8 µg 6 µg 15 µg	Single dose eye drops	Single dose	3 3 3 3
Parkinson's Disease Studies/Early								

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TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0001 Phase III	United States: 26	7/93-1/95	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in early Parkinson's disease (Part I) and to assess long term safety with open-label pramipexole (Part II)	PPX PBO		TID	up to 32 weeks	164 PPX 171 PBO
M/2730/0002 Phase III	United States: 26	1/94-ongoing	Multicenter, open-label study in pts with early PD	PPX		TID	up to 27 months	281 PPX

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0004 Phase III	Canada: 5 United States: 15	3/94-12/94	Parallel group, placebo controlled, dose-response tolerability, safety and efficacy study of pramipexole in early Parkinson's disease	PPX PBO	1.5, 3, 4.5, 6	TID	11 weeks	213 PPX 51 PBO
M/2730/0005 Phase III	Austria: 2 Belgium: 2 Denmark: 3 Germany: 3 Italy: 9 Spain: 5 Sweden: 3 United Kingdom: 3	9/93-ongoing	A European double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in early Parkinson's disease (Part I) and to assess long term safety with open-label pramipexole (Part II)	PPX PBO		TID	up to 9 months	176 blinded
M/2730/0006 Phase III	Austria: 2 Belgium: 2 Denmark: 3 Germany: 3 Italy: 9 Spain: 5 Sweden: 3 United Kingdom: 3	2/94-ongoing	Open-label study (Follow-up to M/2730/0005)	PPX		TID	up to 29 months	41 PPX
M/2730/0016 Phase III	Canada: 5 United States: 15	6/94 - ongoing	Long term safety study of open-label pramipexole in early Parkinson's disease (extension of M/2730/0004 and M/2730/0017)	PPX		TID	up to 38 months	223 PPX
M/2730/0017 Phase II	United States: 4	3/91-7/92	An ascending dose tolerance and efficacy study of SND 919 in early Parkinson's disease	PPX PBO		TID	up to 11 weeks	28 PPX 27 PBO

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Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0021 Phase II	England: 6	1/92-6/93	A study to assess the efficacy and safety of the maximally tolerated oral dose of SND 919 (pramipexole) in patients with early Parkinson's disease	PPX PBO		TID	up to 12 weeks	11 PPX 13 PBO
Parkinson's Disease Studies/Advanced								
M/2730/0010 Phase III	Canada: 4 United States: 22	6/93-1/95	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in advanced Parkinson's disease (0679) and to assess long-term safety with open-label pramipexole (0979)	PPX PBO		TID	up to 32 weeks	181 PPX 179 PBO
M/2730/0011 Phase III	Canada: 4 United States: 22	6/93 - ongoing	Long-term safety open-label study (Follow-up to M/2730/0010)	PPX		TID	up to 29 months	305 PPX
M/2730/0012 Phase III	Austria: 4 Denmark: 3 England: 8 France: 14 Germany: 18 Italy: 6 Scotland: 1	9/93 - ongoing	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in advanced Parkinson's disease (838.021) and to assess long-term safety with open-label pramipexole (838.022)	PPX PBO		TID	up to 32 weeks	236 blinded

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M/2730/0013 Phase III	Austria: 4 Denmark: 3 England: 8 France: 14 Germany: 18 Italy: 6 Scotland: 1	6/94 - ongoing	Long-term safety open-label study (Follow-up to M/2730/0012)	PPX		TID	up to 29 months	88 PPX

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0022 Phase II	Denmark: 9	9/90-6/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 in advanced Parkinson's disease	PPX PBO		QID	up to 12 weeks	36 PPX 33 PBO
M/2730/0036 Phase III	Austria: 2 Canada: 12 Germany: 8 Netherlands: 4 Slovakia: 2 United Kingdom: 9	5/94-ongoing	A double-blind, placebo-controlled, randomized, multicenter trial to compare the safety, tolerance and efficacy of oral administration of pramipexole up to 4.5 mg and bromocriptine up to 30 mg in advanced Parkinson's disease	PPX PBO		TID	up to 9 months	124 blinded
M/2730/0055 Phase II	Italy: 1	9/94-12/95	A double-blind, placebo-controlled parallel-group study of the evaluation of some cardiovascular and biochemical effects of pramipexole in L-dopa stable responders in Parkinson's disease patients	PPX/PBO PPX + DOM PBO + DOM	0.25 0.25 + 20 0 + 20	Single dose TID	Single dose then 7-day repeated dose interval	6 blinded
Depression Studies								
M/2730/0037 Phase II	Germany: 2	12/93-ongoing	Tolerability of pramipexole in patients hospitalized for major depressive disorder. An open study to assess the maximum tolerated dose of pramipexole with repeated dosing	PPX		TID	up to 28 days	23 PPX

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M/2730/0014 Phase II	Denmark: 8 Germany: 4 New Zealand: 1 Switzerland: 2	11/91- ongoing	An open, uncontrolled, multi-center study to assess the effects, safety and tolerability of SND 919 in advanced Parkinson's disease (1st follow-up study of study no. 838.033 in Switzerland, Austria, Germany; study no. 383.008 in Denmark; study no. 838.005 in New Zealand)	PPX		QID	up to 3 years	89
M/2730/0018 Phase II	United States: 6	5/91-11/92	An ascending dose tolerance and efficacy study of SND 919 in advanced Parkinson's disease	PPX PBO		TID	up to 11 weeks	26 PPX 24 PBO
M/2730/0019 Phase II	Austria: 1 Germany: 7 Switzerland: 2	2/91-8/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 with concomitant treatment of levodopa (and decarboxylase-inhibitor) in advanced Parkinson's disease	PPX PBO		QID	up to 12 weeks	34 PPX 43 PBO
M/2730/0020 Phase II	New Zealand: 1	8/91-9/92	A double-blind, placebo-controlled, randomized, parallel-group study to assess the efficacy and safety of SND 919 in patients with advanced Parkinson's disease	PPX PBO		TID	up to 16 weeks	9 PPX 10 PBO

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M/2730/0022 Phase II	Denmark: 9	9/90-6/92	A double-blind, placebo-controlled, randomized, multicenter study to assess the effects, safety and tolerance of SND 919 in advanced Parkinson's disease	PPX PBO		QID	up to 12 weeks	36 PPX 33 PBO
M/2730/0036 Phase III	Austria: 2 Canada: 12 Germany: 8 Netherlands: 4 Slovakia: 2 United Kingdom: 9	5/94-ongoing	A double-blind, placebo-controlled, randomized, multicenter trial to compare the safety, tolerance and efficacy of oral administration of pramipexole up to 4.5 mg and bromocriptine up to 30 mg in advanced Parkinson's disease	PPX PBO		TID	up to 9 months	124 blinded
M/2730/0055 Phase II	Italy: 1	9/94-12/95	A double-blind, placebo-controlled parallel-group study of the evaluation of some cardiovascular and biochemical effects of pramipexole in L-dopa stable responders in Parkinson's disease patients	PPX/PBO PPX + DOM PBO + DOM	0.25 0.25 + 20 0 + 20	Single dose TID	Single dose then 7-day repeated dose interval	6 blinded
Depression Studies								
M/2730/0037 Phase II	Germany: 2	12/93-ongoing	Tolerability of pramipexole in patients hospitalized for major depressive disorder. An open study to assess the maximum tolerated dose of pramipexole with repeated dosing	PPX		TID	up to 28 days	23 PPX

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M/2730/0043 Phase II	United States: 2	11/94- ongoing	Pramipexole in the treatment of outpatients with major depression: a dose response study	PPX PBO		BID	up to 9 weeks	30 blinded

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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Schizophrenia Studies, Phase II								
M/2730/0007 Phase II	United States: 3	1/94- ongoing	Pilot trial of pramipexole in the treatment of tardive dyskinesia; single-blind	PPX		BID	up to 12 weeks	5 PPX
M/2730/0015 Phase II	Hungary: 4	1990-1992	Double-blind, randomized, PBO-controlled, preliminary safety and efficacy study in pts with schizophrenia (negative symptoms)	PPX PBO		TID	11 weeks	28 PPX 30 PBO
M/2730/0024 Phase II	France: 17	1991-1992	Double-blind, randomized, multicenter, clinical trial to explore the effects of pramipexole in three doses in patients with acute schizophrenia: a haloperidol-treated group control study	PPX HAL	15	TID	6 weeks	79 PPX 22 HAL
M/2730/0033 Phase II	Germany: 4	1989-1991	Efficacy and safety of pramipexole in patients with acute schizophrenic psychoses in an open, randomized study controlled by the usual antipsychotic treatment of the participating centers	PPX HAL PER FLU	30 600 15	TID	4 weeks	34 PPX 18 HAL 10 PER 1 FLU

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0034 Phase II	Czechia: 2 Slovakia: 1	9/91-11/92	Double-blind, placebo- and haloperidol-controlled clinical study to determine the tolerability and effectiveness of pramipexole in acute exacerbations of schizophrenia (Protocol 837.009) Czech and Slovak Republics, M/2730/0034, Boehringer Ingelheim, Investigators: Vinar, Svestka, and Konikova)	PPX HAL PBO		TID	4 weeks	22 PPX 22 HAL 22 PBO
M/2730/0048 Phase II	Germany: 1	1990-1992	Double-blind, controlled clinical study to compare the safety and efficacy of pramipexole, haloperidol, and placebo in schizophrenic patients (Protocol 837.001 Germany, M/2730/0048, Boehringer Ingelheim, Investigators: Heinrich and Klieser)	PPX HAL PBO		TID	4 weeks	8 PPX 6 HAL 6 PBO
M/2730/0049 Phase II	Germany: 2	1991-1992	Double-blind, randomized multicenter clinical trial to compare the efficacy and tolerance of pramipexole in patients with schizophrenia characterized by a placebo-treated group	PPX PBO		TID	up to 12 weeks	5 PPX 4 PBO
M/2730/0050 Phase II	United States: 20	11/94- ongoing	Dose-response study in the treatment of negative symptoms of schizophrenia with pramipexole	PPX HAL	10	BID	up to 13 weeks	4 blinded

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Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0067 Phase II	Austria: 2 Germany: 3	1/94- ongoing	An open-label, dose escalation study in schizophrenia in patients treated orally with pramipexole added to a maintenance therapy with haloperidol	PPX + HAL	PX + 5-20 HAL	BID	up to 28 days	5
M/2730/0079	Austria: 3	10/91-2/92	Double-blind, randomized, parallel-group, multicenter study to assess the efficacy and safety of three fixed doses of pramipexole and one dose of haloperidol in patients with acute exacerbations of schizophrenia.	PPX HAL	15	TID	up to 47 days	2 PPX 1 HAL

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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Appendix 4.3.1

Demographics ET patients (Protocols 1 and 4)			
Characteristic		Pramipexole	Placebo
Age (years)	N	377	222
	Mean +/- SD	62.6 +/- 10.49	61.6 +/- 11.61
	Range		
Weight (lbs)	N	364	220
	Mean +/- SD	170.8 +/- 34.17	166.8 +/- 35.18
	Range		
Sex	Male N (%)	243 (64)	130 (59)
	Female N (%)	134 (36)	92 (41)
Race	Caucasian N (%)	363 (96)	210 (95)
	Black N (%)	5 (1)	5 (2)
	Other N (%)	9 (2)	7 (3)

Demographics AT patients (Protocol 10)			
Characteristic		Pramipexole	Placebo
Age (years)	N	181	178
	Mean +/- SD	63.4 +/- 9.70	63.2 +/- 9.60
	Range		
Weight (lbs)	N	181	178
	Mean +/- SD	162.6 +/- 31.43	160.6 +/- 36.13
	Range		
Sex	Male N (%)	119 (66)	115 (65)
	Female N (%)	62 (34)	63 (35)
Race	Caucasian N (%)	172 (95)	171 (96)
	Black N (%)	3 (2)	4 (2)
	Other N (%)	6 (3)	3 (2)

Demographics All Completed PD Studies (Protocols 1, 4, 10, and 17-22)			
Characteristic		Pramipexole	Placebo
Age (years)	N	701	550
	Mean +/- SD	62.8 +/- 9.99	62.2 +/- 10.25
	Range		
Weight (lbs)	N	687	546
	Mean +/- SD	166.4 +/- 32.78	163.5 +/- 34.9
	Range		
Sex	Male N (%)	452 (64)	348 (63)
	Female N (%)	250 (36)	203 (37)
Race	Caucasian N (%)	672 (96)	531 (96)
	Black N (%)	9 (1)	9 (2)
	Other N (%)	21 (3)	11 (2)

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Appendix 4.6.1.1. Number of Patients and Estimated Person-Years in Patients with pramipexole Use up to 2 Years				
	Completed Trials		Completed + Ongoing Trials	
	N	Person-Years	N*	Person-Years
Phase I				
Healthy Volunteers+	250	--	276	--
PD Patients (0023)	3	--	3	--
Phase 2/3 (PD and Schizophrenia)				
All Patients@	879	274.37	1408	815.00**
0-24 Months	879	274.37	1349	662.32
>6-24 Months	286	175.87	543	488.84
>12-24 Months	0	--	178	223.96
All PD Patients#	702	258.78	1231	799.42**
0-24 Months	702	258.78	1172	646.74
>6-24 Months	286	175.87	543	488.84
>12-24 Months	0	--	178	223.96
ET Patients&	416	139.64	675	363.12
0-24 Months	416	139.64	675	363.12
>6-24 Months	137	84.66	312	269.98
>12-24 Months	0	--	91	113.82
AT Patients&&	286	119.14	556	436.30**
0-24 Months	286	119.14	497	283.62
>6-24 Months	149	91.21	231	218.86
>12-24 Months	0	--	87	110.14
Schizophrenia Patients!	177	15.59	177	15.59
0-24 Months	177	15.59	3	15.59
>6-24 Months	0	--	0	--
>12-24 Months	0	--	0	--

* Patients were counted only once

** Includes 59 AT pramipexole patients with continued use beyond 24 months (total of 34.68 additional PY)

+ All completed Studies are 3, 25, 26, 27, 28, 29, 30, 31, 47, 51, 61, 62,63, 64, 65, 69, and 73; one ongoing study (0060)

@ All completed studies are: 1,4, 10, 17, 18, 19, 20, 21, 22, 15, 24, 33, 34, 48, and 49; all open-label ongoing studies are: 2, 6, 11, 13, 14, and 16.

All AT + All ET studies

& All completed ET studies are 1, 4, 17, and 21; all open-label ongoing ET studies are 2, 6, and 16.

&& All completed AT studies are 10, 18, 19, 20, and 22; all open-label ongoing AT studies are 11, 13, and 14.

! All completed schizophrenia studies are 15, 24, 33, 34, 48, and 49.

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Appendix 4.6.2.1

Duration of Exposure by Mean Dose ET Patients (Protocols 1 and 4)													
Mean Daily Dose (mg)	Number (%) of Patients												
	Duration of Pramipexole Exposure in Weeks												Total
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	
>0-1.5	3 (<1)	3 (<1)	6 (2)	5 (1)	5 (1)	1 (<1)	3 (<1)	55 (15)	0	14 (4)	0	0	95 (25)
>1.5-3.0	0	0	0	0	1 (<1)	2 (<1)	6 (2)	95 (25)	2 (<1)	12 (3)	0	0	118 (31)
>3.0-4.5	0	0	0	0	0	0	1 (<1)	41 (11)	8 (2)	107 (28)	6 (2)	0	163 (43)
>4.5-6.0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1 (<1)
Total	3 (<1)	3 (<1)	6 (2)	5 (1)	6 (2)	3 (<1)	10 (3)	192 (51)	10 (3)	133 (35)	6 (2)	0	377

Duration of Exposure by Mean Dose AT patients (Protocol 10)													
Mean Daily Dose (mg)	Number (%) of Patients												
	Duration of Pramipexole Exposure in Weeks												Total
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	
>0-1.5	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	1 (<1)	0	1 (<1)	1 (<1)	19 (10)	0	0	30 (17)
>1.5-3.0	0	0	0	0	0	2 (1)	3 (2)	4 (2)	6 (3)	27 (15)	0	0	42 (23)
>3.0-4.5	0	0	0	0	0	0	0	1 (<1)	4 (2)	100 (55)	4 (2)	0	109 (60)
>4.5-6.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	3 (2)	6 (3)	11 (6)	146 (81)	4 (2)	0	181

Duration of Exposure by Mean Dose All Completed PD Studies (Protocols 1, 4, 10, and 17-22)													
Mean Daily Dose (mg)	Number (%) of Patients												
	Duration of Pramipexole Exposure in Weeks												Total
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	
>0-1.5	6 (<1)	8 (1)	9 (1)	8 (1)	8 (1)	5 (<1)	5 (<1)	66 (9)	1 (<1)	33 (5)	0	0	149 (21)
>1.5-3.0	0	0	0	0	1 (<1)	4 (<1)	15 (2)	117 (17)	27 (4)	39 (6)	0	0	203 (29)
>3.0-4.5	0	0	0	0	0	0	1 (<1)	106 (15)	25 (4)	207 (29)	10 (1)	0	349 (50)
>4.5-6.0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1 (<1)
Total	6 (<1)	8 (1)	9 (1)	8 (1)	9 (1)	9 (1)	21 (3)	290 (41)	53 (8)	279 (40)	10 (1)	0	702

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Appendix 4.6.2.2

Duration of Exposure by Maximum Dose ET Patients (Protocols 1 and 4)													
Maximum Daily Dose (mg)	Number (%) of Patients												
	Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	3 (<1)	3 (<1)	6 (2)	4 (1)	3 (<1)	0	3 (<1)	50 (13)	0	7 (2)	0	0	79 (21)
>1.5-3.0	0	0	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)	52 (14)	1 (<1)	14 (4)	0	0	73 (19)
>3.0-4.5	0	0	0	0	1 (<1)	1 (<1)	2 (<1)	49 (13)	9 (2)	112 (30)	6 (2)	0	180 (48)
>4.5-6.0	0	0	0	0	0	1 (<1)	3 (<1)	41 (11)	0	0	0	0	45 (12)
Total	3 (<1)	3 (<1)	6 (2)	5 (1)	6 (2)	3 (<1)	10 (3)	192 (51)	10 (3)	133 (35)	6 (2)	0	377

Duration of Exposure by Maximum Dose AT Patients (Protocol 10)													
Maximum Daily Dose (mg)	Number (%) of Patients												
	Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	1 (<1)	1 (<1)	3 (2)	1 (<1)	1 (<1)	0	0	1 (<1)	0	13 (7)	0	0	21 (12)
>1.5-3.0	0	0	0	0	1 (<1)	2 (1)	1 (<1)	2 (1)	3 (2)	20 (11)	0	0	29 (16)
>3.0-4.5	0	0	0	0	0	1 (<1)	2 (1)	3 (2)	8 (4)	113 (62)	4 (2)	0	131 (72)
>4.5-6.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	3 (2)	6 (3)	11 (6)	146 (81)	4 (2)	0	181

Duration of Exposure by Maximum Dose All Completed PD Studies (Protocols 1, 4, 10, and 17-22)													
Maximum Daily Dose (mg)	Number (%) of Patients												
	Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	6 (<1)	8 (1)	9 (1)	7 (<1)	5 (<1)	3 (<1)	3 (<1)	57 (8)	0	20 (3)	0	0	118 (17)
>1.5-3.0	0	0	0	1 (<1)	3 (<1)	3 (<1)	10 (1)	63 (9)	8 (1)	34 (5)	0	0	122 (17)
>3.0-4.5	0	0	0	0	1 (<1)	2 (<1)	5 (<1)	98 (14)	31 (4)	225 (32)	10 (1)	0	372 (53)
>4.5-6.0	0	0	0	0	0	1 (<1)	3 (<1)	72 (10)	14 (2)	0	0	0	90 (13)
Total	6 (<1)	8 (1)	9 (1)	8 (1)	9 (1)	9 (1)	21 (3)	290 (41)	53 (8)	279 (40)	10 (1)	0	702

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Appendix 4.7.1
Number (%) of Healthy Volunteers with Adverse Events in the Phase I Studies
AEs for Pramipexole (Alone) and Placebo (Alone) Treatments
AEs Occurring $\geq$ 1%

Body System & Event	Pramipexole ^a (N=240)	Placebo ^b (N=69)
Body as a Whole		
Headache	63(26%)	6(9%)
Asthenia	62(26%)	14(20%)
Pain abdominal	18(8%)	2(3%)
Pain	11(5%)	0(0%)
Chills	7(3%)	2(3%)
Infection	5(2%)	0(0%)
Malaise	5(2%)	0(0%)
Pain back	5(2%)	0(0%)
Abdomen enlarged	4(2%)	0(0%)
Pain chest	3(1%)	0(0%)
Injection site reaction	3(1%)	0(0%)
Cardiovascular		
Pallor	15(6%)	1(1%)
Hypotension postural	8(3%)	2(3%)
Vasodilatation	8(3%)	2(3%)
Palpitations	3(1%)	0(0%)
Syncope	3(1%)	0(0%)
Digestive		
Nausea	63(26%)	5(7%)
Anorexia	20(8%)	1(1%)
Vomiting	15(6%)	0(0%)
Constipation	12(5%)	0(0%)
Dyspepsia	12(5%)	0(0%)
Flatulence	11(5%)	1(1%)
Diarrhea	8(3%)	0(0%)
Dry mouth	4(2%)	1(1%)

^a Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0029, 0030, 0031, 0047, 0051, 0061, 0062, 0064, 0065, 0069, 0073. Protocols 0023 (PD patients), 0060 (ongoing study) and 0063 (concomitant L-dopa) not included. AEs counted once per patient during pramipexole treatment.

^b Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0031, 0051, 0073. AEs counted once per patient during placebo treatment.

Appendix 4.7.1
Number (%) of Healthy Volunteers with Adverse Events in the Phase I Studies
AEs for Pramipexole (Alone) and Placebo (Alone) Treatments
AEs Occurring $\geq$ 1%

Body System & Event	Pramipexole ^a (N=240)	Placebo ^b (N=69)
Nervous		
Dizziness	50(21%)	3(4%)
Nervousness	11(5%)	0(0%)
Insomnia	10(4%)	3(4%)
Somnolence	7(3%)	1(1%)
Concentration impaired	6(3%)	0(0%)
Agitation	5(2%)	0(0%)
Tremor	4(2%)	0(0%)
Confusion	3(1%)	1(1%)
Respiratory		
Rhinitis	15(6%)	5(7%)
Pharyngitis	6(3%)	2(3%)
Hiccups	3(1%)	0(0%)
Skin		
Sweating	23(10%)	0(0%)
Pruritus	10(4%)	5(7%)
Rash	5(2%)	1(1%)
Special Senses		
Vision abnormal	3(1%)	1(1%)
Urogenital		
Creatinine clearance dec.	10(4%)	0(0%)

^a Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0029, 0030, 0031, 0047, 0051, 0061, 0062, 0064, 0065, 0069, 0073. Protocols 0023 (PD patients), 0060 (ongoing study) and 0063 (concomitant L-dopa) not included. AEs counted once per patient during pramipexole treatment.

^b Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0031, 0051, 0073. AEs counted once per patient during placebo treatment.

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Appendix 4.11.1
 All Serious Non-Fatal Adverse Experiences Reported up to Cut-off Date of 1/31/95
 For the Phase II/III Pramipexole Studies

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Body	M27300001	67	Male	0		208	ALLERGIC REACTION	ALLERG REACT
		59	Male	0		120	CHEST PRESSURE/PAIN	PAIN CHEST
		41	Male	0		153	CHEST PAIN	PAIN CHEST
		61	Male	4.5		102	CHEST PAIN	PAIN CHEST
		73	Male	>		255	CHEST PAIN	PAIN CHEST
				>		259	LOW BACK PAIN	PAIN BACK
				>		259	MALAISE	MALAISE
		56	Female	4.5		178	CHEST PAIN	PAIN CHEST
		69	Male	0		14	INCREASED WEAKNESS	ASTHENIA
		M27300002	72	Male	-		325	CHEST PAIN
	60		Male	-		-	BACK PAIN	PAIN BACK
	75		Male	-		240	CONCUSSION	INJURY ACCID
				-		241	FEVER	FEVER
	68		Female	-		28	BROKEN ANKLE	INJURY ACCID
	64		Male	-		-	NAEVUS R PARIETAL AREA	ANOMALY CONGEN
	64		Male	-		238	SWELLING ALL OVER	EDEMA GENERAL
	69		Male	-		2	BACK STRAIN/PAIN	INJURY ACCID
				-		2	RIB CONTUSIONS	INJURY ACCID
				-		2	ROLLOVER MOTOR VEHICLE ACCIDENT	INJURY ACCID
	M27300004	70	Male	6		36	FRACTURE RIGHT HIP	INJURY ACCID
		70	Male	4.5		30	FRACTURED RIGHT HIP	INJURY ACCID
	M27300006	69	Male	-		-	TRAUMATIC BURN	INJURY ACCID
				-		25	TRAUMATIC BURN ON THORAX, HANDS, FACE	INJURY ACCID
	M27300010	70	Female	3.75		119	FALL-R WRIST FX	INJURY ACCID
		57	Male	0.75		14	NECK PAIN	PAIN NECK
				0.75		14	NECK PAIN RADIATING IN L ARM	PAIN NECK
		71	Female	0		113	BROKEN HIP	INJURY ACCID
		73	Male	-		74	FALL	INJURY ACCID
				-		74	FALL IN HOME FRACTURED RIBS X3	INJURY ACCID
		56	Male	4.5		58	DEEP LACERATION PIP JOINT LT INDEX FINGER	INJURY ACCID
		54	Male	0		66	L LEG PAIN	PAIN
		69	Male	4.5		158	BACK PAIN RADIATING TO LEFT EXTREMITY	PAIN BACK
				4.5		158	BK PN RAD TO LFT EXTR WITH LFT FT WEAKNESS	PAIN BACK
59		Male	0		80	BACK PAIN	PAIN BACK	
			0		198	CHEST PAIN	PAIN CHEST	
			0		138	GROIN PAIN	PAIN	
46	Male	0		60	CELLULITIS RLE	CELLULITIS		

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term	
Body	M27300010	60	Male	-		223	ABDOMINAL PAIN	PAIN ABDO	
		66	Male	0		49	BACKPAIN	PAIN BACK	
		59	Male	0		44	HERNIA RT INGUINAL	HERNIA	
				0		44	HERNIA, RT INGUINAL	HERNIA	
			63	Male	0		43	CHEST PAIN	PAIN CHEST
	M27300011	62	Male	-			109	ACCIDENT	INJURY ACCID
		75	Male	-			230	FALL	INJURY ACCID
		57	Male	-			66	INFECTION AT SURGICAL WOUND	INFECT
				-			-3	INGUINAL HERNIA	HERNIA
		65	Female	-			37	FALL	INJURY ACCID
		67	Male	-			124	FALL	INJURY ACCID
		63	Female	-			41	FRACTURE RIGHT FOREARM	INJURY ACCID
		65	Female	-			167	OVERDOSE	OVERDOSE
		69	Male	-			176	BACK PAIN	PAIN BACK
		69	Male	-			104	FALL	INJURY ACCID
		74	Male	-			178	CHEST PAIN	PAIN CHEST
			77	Male	-		5	CHEST PAIN	PAIN CHEST
	M27300013	60	Female	-			113	BROKE LEFT ARM	INJURY ACCID
		74	Male	-			89	FALL	INJURY ACCID
		53	Male	-			-	LUMBAGO	PAIN BACK
	M27300014	59	Male	-			281	SEVERE CHEST PAIN	PAIN CHEST
		64	Male	-			-	BACK PAIN	PAIN BACK
		64	Female	-			-	PAINS IN THE LEFT INGUINAL REGION	PAIN ABDO
		75	Female	-			624	FRACT. COLLI FEM. DXT	INJURY ACCID
				-			624	FRACT. COLLISI DXT	INJURY ACCID
		58	Female	-			38	INTRA-ARTICULAR RADIUS-FRACTURE TROCHANTER MAJOR	INJURY ACCID
				-			19	INTRAARTIKUL. FRACTURE DISTAL RADIUS LEFT 200792	INJURY ACCID
54		Male	-			-	PAIN IN THE BACK	PAIN BACK	
74		Female	-			204	FEVER	FEVER	
			-			214	PAIN	PAIN	
M27300016	69	Female	-			802	ACCIDENT HOUSEHOLD*	INJURY ACCID	
			-			747	PAIN	PAIN	
	59	Female	-			282	PAIN	PAIN	
	67	Male	-			119	CHEST PAIN	PAIN CHEST	
	76	Male	-			106	BRACHIAL PLEXUS INJURY LEFT ARM	INJURY ACCID	
			-			-	CELLULITIS R LEG	CELLULITIS	
		-			97	CELLULITIS RIGHT LEG	CELLULITIS		
		74	Female	-		254	PERIPELVIC CYST ON SKIN	CYST	

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Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term	
Body	M27300018		68	Male	0	17	CHEST TIGHTNESS	PAIN CHEST	
	M27300024		39	Male	-	12	ATTEMPT OF SUICIDE BY STRANGULATION	SUICIDE ATTEMPT	
			37	Male	-	2	ATTEMPT OF SUICIDE	SUICIDE ATTEMPT	
			41	Female	-	30	SUICIDE ATTEMPT	SUICIDE ATTEMPT	
			54	Female	-	8	BP COLLAPSED	SHOCK	
Cardiovascular	M27300001		75	Male	0	89	ATRIAL FLUTTER	FLUTTER ATR	
			59	Male	0	120	CORONARY ARTERY DISEASE	CORONARY ART DIS	
					0	120	SINUS ARRHYTHMIA	ARRHYTHMIA ATR	
					0	120	UNSTABLE ANGINA	ANGINA PECTORIS	
			67	Male	0	10	ATRIAL FIBRILLATION	FIBRILLAT ATR	
					0	10	INTERMITTENT TACHYCARDIA	TACHYCARDIA	
			72	Male	0	183	DEEP VEIN THROMBOSIS	THROMBOPHLEB DEEP	
			77	Female	4.5	114	ACUTE MYOCARDIAL INFARCT	INFARCT MYOCARD	
			59	Male	0	202	BRADYCARDIA	BRADYCARDIA	
					0	202	HYPOTENSION	HYPOTENS	
		M27300002		67	Male	-	94	ATRIAL FIB.	FIBRILLAT ATR
				72	Male	-	30	ABDOMINAL AORTIC ANEURYSM	ANOMALY VASCUL
				59	Male	-	-	CORONARY ARTERY DISEASE	CORONARY ART DIS
				68	Male	-	214	ANGINA	ANGINA PECTORIS
				75	Male	-	241	ATRIAL FIBRILLATION	FIBRILLAT ATR
						-	241	IRREGULAR HEART RATE	ARRHYTHMIA
				60	Female	-	118	ANGINA	ANGINA PECTORIS
				64	Male	-	238	CONGESTIVE HEART FAILURE	HEART FAIL
				79	Male	-	126	ATRIAL FIBRILLATION	FIBRILLAT ATR
		M27300004		77	Male	4.5	36	LEFT VENTRICULAR DYSFUNCTION	HEART FAIL LEFT
				60	Male	0	9	MYOCARDIAL INFARCTION	INFARCT MYOCARD
				70	Male	6	42	BILATERAL PULMONARY EMBOLUS	EMB PULM
		M27300010		63	Male	0	43	PALPITATIONS	PALPITAT
			75	Female	0	21	SYNCOPE X2	SYNCOPE	
	M27300011		67	Female	-	77	LEFT PONTIVE INFARCT	CEREBROVASC ACCID	
			66	Male	-	190	DVT	THROMBOPHLEB DEEP	
			74	Male	-	178	ATRIAL FIB	FIBRILLAT ATR	
	M27300013		70	Male	-	50	ATRIAL FIBRILLATION	ARRHYTHMIA ATR	
			53	Male	-	33	LIPOTHYMIA	SYNCOPE	
	M27300014		59	Male	-	270	SEVERE M.I.	INFARCT MYOCARD	
					-	566	UNSTABLE ANGINA	ANGINA PECTORIS	
			65	Male	-	150	ARRHYTHMIA	ARRHYTHMIA	
					-	-	MYOCARDIAL DECOMPENSATION	HEART FAIL	
					-	170	MYOCARDIAL DECOMPENSATION	HEART FAIL	
					-	-	TACHYCARDIA	TACHYCARDIA	
			63	Male	-	664	EMBOLISM CEREBRAL	EMB CEREBR	
					-	665	HEART BLOCK AV	AV BLOCK	
					-	662	INTERMITTENT AURICULAR FLUTTER WITH 2:1 VENTRICULAR ACTIVATION	ARRHYTHMIA ATR	

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Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term	
Cardiovascular	M27300014	53	63	Male	-	662	INTERMITTENT AURICULAR FLUTTER WITH 2:1-VENTRICULAR ACTIVATION	ARRHYTHMIA ATR	
						665	SUSPICION OF AV-BLOCK 2.3 DEGREE UNDER THERAPY WITH ISOPTIN AND DIGOXIN	AV BLOCK	
						182	MYOCARDIAL INFARCTION	INFARCT MYOCARD	
						-	ANGINA PECTORIS	ANGINA PECTORIS	
				71	Female	-	-	HEART FAIL	
				69	Female	-	-	HEART FAIL	
				70	Male	-	-	HEART FAIL	
		M27300015		52	Male	1.5	28	MYOCARDIAL INFARCTION	INFARCT MYOCARD
		M27300016		67	Male	-	119	MYOCARDIAL INFARCTION	INFARCT MYOCARD
			69	Male	-	10	SYNCOPE	SYNCOPE	
		M27300018		68	Male	0	17	PALPITATIONS	PALPITAT
			17				PREMATURE VENTRICULAR CONTRACTIONS (PVCs)	ARRHYTHMIA VENT	
			74				MI	INFARCT MYOCARD	
	M27300019		65	Male	5	43	STENOCARDIA	ANGINA PECTORIS	
		42				STENOCARDIA DSYMNOEA	ANGINA PECTORIS		
	M27300020		67	Male	4.5	75	INFECTED HAEMATOMA ON (R) HAND	HEM	
	M27300022		70	Female	+	-	ANGINA PECTORIS	ANGINA PECTORIS	
	M27300024		54	Female	-	8	SYNCOPE	SYNCOPE	
Digestive	M27300001		69	Male	>	236	EARLY RECTAL CANCER	CARCINOMA GI	
		236				WORSENING OF POLYPS-COLON	GI DIS		
		69				BOWEL OBSTRUCTION	OBSTRUCT INTEST		
		69				DIARRHEA	DIARRHEA		
		90				SMALL BOWEL OBSTRUCTION	OBSTRUCT INTEST		
		259				DYSPEPSIA	DYSPEPSIA		
		259				PANCREATIC CANCER	CARCINOMA GI		
		M27300010		70	Female	3.75	119	NAUSEA	NAUSEA
			87				ESOPHAGEAL SPASM	CARDIOSPASM	
			51				GI BLEED (PROB GASTIC ULCER)	HEM GI	
			223				NAUSEA	NAUSEA	
			101				COLITIS	COLITIS	
			100				CONSTIPATION	CONSTIP	
			101				DIARRHEA	DIARRHEA	
			53				CONSTIPATION (WORSENER)	CONSTIP	
	M27300011		57	Male	-	157	BOWEL IMPACTION	IMPACT FECAL	
		M27300018					60	Male	<

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Endocrine	M27300001		45	Female	1.5	72	THYROID NODULE	NEOPL THYR
Hemic and Lymphatic	M27300004		72	Male	4.5	40	DECREASED PLATELETS	THROMBOCYTOPENIA
	M27300010		77	Male	3.75	118	LUMBAR RADICULOPATHY (MULTIPLE MYELOMA)	MYELOMA
Metabolic and Nutritional	M27300001		73	Male	>	255	WEIGHT LOSS	WEIGHT DEC
			69	Male	0	16	DECREASED POTASSIUM	HYPOKALEM
	M27300002		75	Male	-	241	DEHYDRATION	DEHYDRAT
						241	ELEVATED CPK	CREATINE PK INC
	M27300010		49	Male	-	22	ELEVATED CPK	CREATINE PK INC
						22	HOSPITALIZATION DUE TO ELEVATED CK(CPK)	CREATINE PK INC
M27300020		58	Male	4.5	47	ELEVATED SERUM CK	CREATINE PK INC	
Musculo-Skeletal	M27300002		60	Male	-	177	MRSA INFECTION OF T10-T11,T12	OSTEOMYELITIS
	M27300010		69	Male	4.5	158	LEFT FOOT WEAKNESS	MYASTHENIA
	M27300011		67	Female	-	229	INCREASED RT SIDE WEAKNESS	MYASTHENIA
			77	Female	-	-75	ARTHRITIC PAIN(SPINAL STENOSIS)	ARTHRITIS
	M27300014		63	Male	-	-	OSTEOPOROSIS	OSTEOPOROSIS
		62	Male	-	-	DEG. MENISKOPATH	JOINT DIS	

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Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Nervous	M27300001	59	Male	0.75	14	DROWSINESS	SOMNOLENCE	
				1.5	16	DROWSINESS	SOMNOLENCE	
		59	Male	0	202	DIZZINESS	DIZZINESS	
				0	202	LIGHTEADEDNESS	DIZZINESS	
			69	Male	0	14	WORSENING PARKINSON'S DISEASE	EXTRAPYR SYND
	M27300002	67	Male	-	93	ACUTE SEIZURE ACTIVITY	CONVULS	
		65	Male	-	70	INCREASED VISUAL HALLUCINATION	HALLUCIN	
				-	70	WORSENING OF PARKINSON'S DISEASE	EXTRAPYR SYND	
		67	Male	-	95	LEFT HEMISPHERIC INFARCT (INSULAR CORTEX)	INFARCT CEREBR	
	M27300004	62	Female	3	28	SEVERE SOMNOLENCE RAN OFF ROAD IN HER CAR	SOMNOLENCE	
		71	Male	1.5	61	CONFUSION	CONFUS	
				1.5	61	HALLUCINATIONS	HALLUCIN	
	M27300010	65	Male	+	-	NUMB TINGL ACHE WEAK(CER RADICULOPATHY)	NEUROPATHY	
		68	Female	-	15	PARANOIA	PARANOID REACT	
				-	15	VISUAL HALLUCINATIONS	HALLUCIN	
		71	Female	0	113	DIZZINESS	DIZZINESS	
		75	Female	0	51	CONFUSION	CONFUS	
				0	51	PARANOIA	PARANOID REACT	
		74	Male	4.5	123	INCREASED OFF PERIODS	EXTRAPYR SYND	
		75	Male	0	108	RIGHT CEREBRAL INFARCT(BET 7-15-94 + 7-22-94)	INFARCT CEREBR	
	M27300011	72	Male	0.75	74	CONFUSION	CONFUS	
75		Male	-	136	PSYCHOSIS	PSYCHOSIS		
			-	106	TIA	ISCHEMIA CEREBR		
36		Male	-	5	AKINETIC	AKINESIA		
65		Female	-	101	INCR DYSKINESIAS	DYSKINESIA		
M27300013	71	Male	-	119	CONFUSION	CONFUS		
	52	Male	-	-6	PARANOIA	PARANOID REACT		
	79	Female	-	-	INCREASE OF PARKINSON SYNDR.	EXTRAPYR SYND		
			-	-	INCREASE OF PARKINSON SYNDROM	EXTRAPYR SYND		
M27300014			-	1	INCREASE OF PARKINSON SYNDROMS	EXTRAPYR SYND		
	63	Female	-	999	AGGRAVATION OF PARKINSON'S SYMPTOMS	EXTRAPYR SYND		
	72	Male	-	460	AGGRAVATION OF PARKINSON'S SYMPTOMS	EXTRAPYR SYND		
	64	Male	-	207	PAINFUL DYSKINESIA	DYSKINESIA		
	55	Female	-	2	DIZZINESS, NAUSEA FAINTING	DIZZINESS		

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term	
Nervous	M27300014		59	Male	-	-	PARKINSONISM AGGRAVATED	EXTRAPYR SYND	
			65	Male	-	150	PARKINSONISM AGGRAVATED	EXTRAPYR SYND	
			54	Female	-	337	INCREASED PARKINSONISM	EXTRAPYR SYND	
			50	Male	-	106	ANXIETY	ANXIETY	
			74	Female	-	32	WORSENING OF PARKINSON	EXTRAPYR SYND	
			52	Male	-	597	LUMBAR NERVE ROOT COMPRESSION	NEURALGIA	
						597	LUMBAR NERVE ROOT COMPRESSION	NEURALGIA	
							RELAPSE OF		
				70	Male	-	-	HALLUCINATIONS	HALLUCIN
								SEVERE "OFF-PERIODS"	EXTRAPYR SYND
			74	Female	-	-	LONG AND PAINFUL OFF-PERIODS, INNER RESTLESS	EXTRAPYR SYND	
		M27300015		35	Male	+	-	ACUT PSYCHOTIC SYMPTOMS	SCHIZOPHRENIC REACT
						1.5	37	EXAC. OF PSYCHOSIS WITH HALLUCIN.	SCHIZOPHRENIC REACT
						2	33	REHOSPILIZ. BEC. OF PRAEPSY. SIGNS	SCHIZOPHRENIC REACT
						+	-	REHOSPITALISATION	SCHIZOPHRENIC REACT
				53	Male	0	34	EXACERBATION OF PSYCHOSIS	SCHIZOPHRENIC REACT
			49	Female	+	-	INCREASED HALLUCINATORY BEHAVIOR	HALLUCIN	
					+	-	RESTLESSNESS, AGRESSIVITY	HOSTILITY	
		M27300016	74	Female	-	-	32	NEUROPATHY	NEUROPATHY
	M27300018	48	Male	<	<	-21	DYSTONIA	DYSTONIA	
-20						SEVERE OFF PERIOD(WORSENING OF DISEASE)	EXTRAPYR SYND		
	M27300019	47	Male	+	0	-	INCREASE OF BLOCKAGES	EXTRAPYR SYND	
						59	INCREASING OFF PERIODS	EXTRAPYR SYND	
						-	WORSENING OF PARKINSON.-BLOCKAG.	EXTRAPYR SYND	
	M27300020	67	Male	1.5	4.5	18	FALL WITH (R) HUMERUS	GAIT ABNORM	
						45	CONFUSION	CONFUS	
						45	HYPERSOMNOLENCE	SOMNOLENCE	
	M27300021	54	Male	-	-	58	HALLUCINATION (VISUAL/AUDITORY)	HALLUCIN	
						36	PARANOID PSYCHOSIS	PSYCHOSIS	
	M27300022	62	Female	2	-	37	DYSKINESIA	DYSKINESIA	
	M27300024	37	Male	-	-	-1	ACUTE ANGUISH	AGITATION	
Nervous	M27300024	39	Male	-	-	40	EPILEPTIC CRISES	CONVULS	
		41	Female	-	-	25	STATE OF DEPRESSION	DEPRESSION	

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Respiratory	M27300001		42	Female	>	126	BILATERAL PNEUMONIA	PNEUMONIA
						106	R MIDDLE LOBE PNEUMONIA	PNEUMONIA
	M27300002		77	Male	-	164	SHORTNESS OF BREATH	DYSPNEA
	M27300004		77	Male	3	32	DYSPNEA	DYSPNEA
	M27300010		72	Male	3	30	PNEUMONIA	PNEUMONIA
						71	PNEUMONIA	PNEUMONIA
	M27300011		71	Male	-	33	DYSPNEA	DYSPNEA
	M27300014		67	Male	-	6	PNEUMONIA	PNEUMONIA
						-	BRONCHITIS	BRONCHITIS
						-	DYSPNEA	DYSPNEA
						-	TACHYPNOEA	HYPERVENTIL
						657	EXACERB. COPD WITH BRONCHIAL SUPERINFECTION	EMPHYSEMA
						443	EXACERB. COPD WITH BRONCHITIS	EMPHYSEMA
	73	DYSPNOE	DYSPNEA					
70	OEDEMA PULMONEUM	EDEMA LUNG						
M27300022		67	Female	4	71	ACUTE PNEUMONIA	PNEUMONIA	
Skin	M27300001		70	Male	0.375	1	BASAL CELL CARCINOMA OF L EAR	CARCINOMA SKIN
						106	SKIN CANCER-LEFT CHEEK	CARCINOMA SKIN
	M27300002		78	Female	-	-	SKIN CANCER-LEFT CHEEK	CARCINOMA SKIN
						191	MELANOMA	MELANOMA SKIN
	M27300014		59	Male	-	0	EXCISION OF MELANOMA (R) FLANK, (L) THIGH	MELANOMA SKIN
Special Senses	M27300014		42	Female	-	-	BLEPHAROSPASM	EYE DIS

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Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Urogenital	M27300001	70	Male	4.5	222	PROSTATE CANCER	CARCINOMA PROSTATE	
		72	Male	0	174	ADVANCED BLADDER TRABECULAE	UG DIS	
				0	197	BLADDER CANCER	CARCINOMA BLADDER	
				+	-	CYSTITIS	CYSTITIS	
				+	-	OBSTRUCTED PROSTATE	PROSTAT DIS	
		61	Male	4.5	215	CA OF PROSTATE	CARCINOMA PROSTATE	
	M27300002	67	Male	-	70	WORSENING BPH	PROSTAT DIS	
		70	Male	-	-	PROSTATE CANCER	CARCINOMA PROSTATE	
		61	Male	-	-	CA OF PROSTATE	CARCINOMA PROSTATE	
	M27300004	68	Female	+	-	BREAST MALIGNANT NEOPLASM, FEMALE	CARCINOMA BREAST	
	M27300010	75	Male	0	83	ABNORMAL URINE COLOR	URIN ABNORM	
				0	101	ACUTE URINARY RETENTION	URIN RETENT	
	M27300011	72	Male	>	32	MASS R KIDNEY	CARCINOMA BLADDER	
		68	Male	-	28	UTI	INFECT URIN TRACT	
		57	Male	-	97	ACUTE URINARY RETENTION	URIN RETENT	
		66	Male	-	209	HEMATURIA	HEMATURIA	
	M27300014	77	Male	-	62	HEMATURIA	HEMATURIA	
		71	Male	-	-	PROSTATIC CARCINOMA*	CARCINOMA PROSTATE	
		63	Male	-	463	PROSTATE CANCER	CARCINOMA PROSTATE	
		46	Male	-	-	SPASTIC BLADDER / INCONTINENS	INCONTIN URIN	
M27300016	66	Male	-	53	HYDROCELE	EPIDIDYMITIS		
	43	Female	-	125	FIBROIDS	UTER FIBROID ENLARGE		
			-	106	PRE-CANCER CELLS IN UTERUS	CARCINOMA ENDOMETR		
			-	117	VAGINAL BLEEDING	HEM VAGINAL		
	69	Male	-	12	PROSTATIC HYPERTROPHY	PROSTAT DIS		
	74	Female	-	-	URINARY FREQUENCY	URIN FREQUENCY		
M27300019			-	-	URINARY URGENCY	URIN URGENCY		
			-	272	UTERINE DESCENSUS	UTER DIS		
	47	Male	+	-	BLADDER CARCINOMA	CARCINOMA BLADDER		
		0	77	PAPILLARY BLADDER CARCINOMA	CARCINOMA BLADDER			

Note: mglvl = '+' indicates onset date missing; '<' onset prior to date of first dose; '>' onset after date of last dose; '-' dose level not available

Appendix 4.13.1.1.1

% and 95% C.I. of Patients with Adverse Events (TES Reported in >= 1% of the Patients in the Pramipexole Group)
 Group: All Double-Blind Placebo Controlled Studies for Early Parkinson's Disease (Early Controlled Studies: 1, 4, & 21)

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
Total Patients (N)	388			235				
All Body Systems	344	88.7	(85.0, 91.6)	202	86.0	(80.7, 90.0)	2.7	(-3.1, 8.5)
BODY AS A WHOLE	205	52.8	(47.7, 57.8)	150	63.8	(57.3, 69.9)	-11.0	(-19.2, -2.8)
...INFECT	59	15.2	(11.9, 19.3)	52	22.1	(17.1, 28.1)	-6.9	(-13.6, -0.2)
...HEADACHE	55	14.2	(11.0, 18.2)	37	15.7	(11.4, 21.1)	-1.5	(-7.6, 4.6)
...ASTHENIA	54	13.9	(10.7, 17.8)	27	11.5	(7.8, 16.5)	2.4	(-3.3, 8.1)
...PAIN	51	13.1	(10.0, 17.0)	45	19.1	(14.4, 24.8)	-6.0	(-12.4, 0.4)
...INJURY ACCID	34	8.8	(6.3, 12.2)	20	8.5	(5.4, 13.0)	0.3	(-4.6, 5.2)
...PAIN BACK	31	8.0	(5.6, 11.3)	20	8.5	(5.4, 13.0)	-0.5	(-5.3, 4.3)
...PAIN ABDO	20	5.2	(3.3, 8.0)	15	6.4	(3.8, 10.5)	-1.2	(-5.4, 3.0)
...EDEMA GENERAL	19	4.9	(3.1, 7.7)	7	3.0	(1.3, 6.3)	1.9	(-1.5, 5.3)
...FLU SYND	10	2.6	(1.3, 4.9)	6	2.6	(1.1, 5.8)	0.0	(-2.9, 2.9)
...MALAISE	7	1.8	(0.8, 3.8)	2	0.9	(0.2, 3.4)	0.9	(-1.2, 3.0)
...ALLERG REACT	6	1.5	(0.6, 3.4)	4	1.7	(0.5, 4.6)	-0.2	(-2.6, 2.2)
...REACT UNEVAL	6	1.5	(0.6, 3.4)	2	0.9	(0.2, 3.4)	0.6	(-1.5, 2.7)
...PAIN CHEST	5	1.3	(0.5, 3.2)	11	4.7	(2.5, 8.5)	-3.4	(-6.7, -0.1)
...PAIN NECK	5	1.3	(0.5, 3.2)	5	2.1	(0.8, 5.1)	-0.8	(-3.3, 1.7)
...FEVER	4	1.0	(0.3, 2.8)	1	0.4	(0.0, 2.7)	0.6	(-1.0, 2.2)
CARDIOVASCULAR SYSTEM	50	12.9	(9.8, 16.7)	38	16.2	(11.9, 21.7)	-3.3	(-9.4, 2.8)
...HYPOTENS POST	30	7.7	(5.3, 10.9)	21	8.9	(5.7, 13.5)	-1.2	(-6.0, 3.6)
...VASODILAT	11	2.8	(1.5, 5.1)	10	4.3	(2.2, 8.0)	-1.5	(-4.9, 1.9)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
 N = Intent-to-treat population
 Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						‡ difference	95% C.I. for ‡ difference
	Pramipexole			Placebo				
	n	‡	95% C.I.	n	‡	95% C.I.		
...HYPERTENS	6	1.5	(0.6, 3.4)	4	1.7	(0.5, 4.6)	-0.2	(-2.6, 2.2)
...SYNCOPE	5	1.3	(0.5, 3.2)	2	0.9	(0.2, 3.4)	0.4	(-1.6, 2.4)
...TACHYCARDIA	5	1.3	(0.5, 3.2)	3	1.3	(0.3, 4.0)	0.0	(-2.2, 2.2)
DIGESTIVE SYSTEM	181	46.6	(41.6, 51.7)	94	40.0	(33.7, 46.6)	6.6	(-1.7, 14.9)
...NAUSEA	107	27.6	(23.3, 32.4)	42	17.9	(13.3, 23.5)	9.7	(2.7, 16.7)
...CONSTIP	53	13.7	(10.5, 17.6)	14	6.0	(3.5, 10.1)	7.7	(2.8, 12.6)
...DYSPEPSIA	28	7.2	(4.9, 10.4)	16	6.8	(4.1, 11.0)	0.4	(-4.1, 4.9)
...ANOREXIA	17	4.4	(2.7, 7.1)	5	2.1	(0.8, 5.1)	2.3	(-0.8, 5.4)
...DIARRHEA	17	4.4	(2.7, 7.1)	18	7.7	(4.8, 12.1)	-3.3	(-7.6, 1.0)
...DRY MOUTH	13	3.4	(1.9, 5.9)	16	6.8	(4.1, 11.0)	-3.4	(-7.4, 0.6)
...SALIVA INC	10	2.6	(1.3, 4.9)	7	3.0	(1.3, 6.3)	-0.4	(-3.4, 2.6)
...DYSPHAGIA	7	1.8	(0.8, 3.8)	1	0.4	(0.0, 2.7)	1.4	(-0.5, 3.3)
...FLATUL	7	1.8	(0.8, 3.8)	4	1.7	(0.5, 4.6)	0.1	(-2.4, 2.6)
...TOOTH DIS	7	1.8	(0.8, 3.8)	4	1.7	(0.5, 4.6)	0.1	(-2.4, 2.6)
...VOMIT	7	1.8	(0.8, 3.8)	8	3.4	(1.6, 6.8)	-1.6	(-4.6, 1.4)
METABOLIC & NUTRITIONAL SYSTEM	31	8.0	(5.6, 11.3)	14	6.0	(3.5, 10.1)	2.0	(-2.4, 6.4)
...EDEMA PERIPH	19	4.9	(3.1, 7.7)	10	4.3	(2.2, 8.0)	0.6	(-3.1, 4.3)
...WEIGHT DEC	7	1.8	(0.8, 3.8)	1	0.4	(0.0, 2.7)	1.4	(-0.5, 3.3)
...CREATINE PK INC	5	1.3	(0.5, 3.2)	3	1.3	(0.3, 4.0)	0.0	(-2.2, 2.2)
MUSCULO SKELETAL SYSTEM	22	5.7	(3.7, 8.6)	12	5.1	(2.8, 9.0)	0.6	(-3.4, 4.6)
...CRAMPS LEG	17	4.4	(2.7, 7.1)	9	3.8	(1.9, 7.3)	0.6	(-2.9, 4.1)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...TWITCH	6	1.5	(0.6, 3.4)	3	1.3	(0.3, 4.0)	0.2	(-2.0, 2.4)
NERVOUS SYSTEM	258	66.5	(61.5, 71.1)	138	58.7	(52.1, 65.0)	7.8	(-0.4, 16.0)
...DIZZINESS	97	25.0	(20.8, 29.7)	57	24.3	(19.1, 30.4)	0.7	(-6.6, 8.0)
...SOMNOLENCE	85	21.9	(18.0, 26.4)	21	8.9	(5.7, 13.5)	13.0	(7.2, 18.8)
...INSOMNIA	66	17.0	(13.5, 21.2)	27	11.5	(7.8, 16.5)	5.5	(-0.4, 11.4)
...TREMOR	37	9.5	(6.9, 13.0)	39	16.6	(12.2, 22.1)	-7.1	(-13.0, -1.2)
...HALLUCIN	35	9.0	(6.4, 12.4)	6	2.6	(1.1, 5.8)	6.4	(2.6, 10.2)
...HYPERTONIA	23	5.9	(3.9, 8.9)	18	7.7	(4.8, 12.1)	-1.8	(-6.3, 2.7)
...DEPRESSION	22	5.7	(3.7, 8.6)	17	7.2	(4.4, 11.5)	-1.5	(-5.9, 2.9)
...ANXIETY	18	4.6	(2.8, 7.3)	11	4.7	(2.5, 8.5)	-0.1	(-3.9, 3.7)
...DREAM ABNORM	17	4.4	(2.7, 7.1)	10	4.3	(2.2, 8.0)	0.1	(-3.5, 3.7)
...CONFUS	16	4.1	(2.4, 6.7)	3	1.3	(0.3, 4.0)	2.8	(0.0, 5.6)
...AMNESIA	14	3.6	(2.1, 6.1)	4	1.7	(0.5, 4.6)	1.9	(-0.9, 4.7)
...ATAXIA	13	3.4	(1.9, 5.9)	19	8.1	(5.1, 12.5)	-4.7	(-9.0, -0.4)
...EXTRAPYR SYND	13	3.4	(1.9, 5.9)	24	10.2	(6.8, 15.0)	-6.8	(-11.4, -2.2)
...HYPESTHESIA	11	2.8	(1.5, 5.1)	2	0.9	(0.2, 3.4)	1.9	(-0.5, 4.3)
...GAIT ABNORM	8	2.1	(1.0, 4.2)	6	2.6	(1.1, 5.8)	-0.5	(-3.3, 2.3)
...DYSTONIA	7	1.8	(0.8, 3.8)	3	1.3	(0.3, 4.0)	0.5	(-1.8, 2.8)
...AKATHISIA	6	1.5	(0.6, 3.4)	0	0.0	(0.0, 2.0)	1.5	(-0.1, 3.1)
...HYPOKINESIA	6	1.5	(0.6, 3.4)	12	5.1	(2.8, 9.0)	-3.6	(-7.0, -0.2)
...THINKING ABNORM	6	1.5	(0.6, 3.4)	1	0.4	(0.0, 2.7)	1.1	(-0.7, 2.9)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment

N = Intent-to-treat population

Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...LIBIDO DEC	5	1.3	(0.5, 3.2)	0	0.0	(0.0, 2.0)	1.3	(-0.2, 2.8)
...MYOCLONUS	5	1.3	(0.5, 3.2)	1	0.4	(0.0, 2.7)	0.9	(-0.8, 2.6)
...NERVOUSNESS	5	1.3	(0.5, 3.2)	5	2.1	(0.8, 5.1)	-0.8	(-3.3, 1.7)
...PARESTHESIA	5	1.3	(0.5, 3.2)	7	3.0	(1.3, 6.3)	-1.7	(-4.5, 1.1)
...VERTIGO	5	1.3	(0.5, 3.2)	13	5.5	(3.1, 9.5)	-4.2	(-7.7, -0.7)
...PARALYSIS	4	1.0	(0.3, 2.8)	4	1.7	(0.5, 4.6)	-0.7	(-3.0, 1.6)
RESPIRATORY SYSTEM	48	12.4	(9.4, 16.2)	37	15.7	(11.4, 21.1)	-3.3	(-9.3, 2.7)
...PHARYNGITIS	13	3.4	(1.9, 5.9)	8	3.4	(1.6, 6.8)	0.0	(-3.3, 3.3)
...SINUSITIS	13	3.4	(1.9, 5.9)	9	3.8	(1.9, 7.3)	-0.4	(-3.8, 3.0)
...RHINITIS	12	3.1	(1.7, 5.5)	8	3.4	(1.6, 6.8)	-0.3	(-3.5, 2.9)
...DYSPNEA	9	2.3	(1.1, 4.5)	6	2.6	(1.1, 5.8)	-0.3	(-3.2, 2.6)
...COUGH INC	8	2.1	(1.0, 4.2)	7	3.0	(1.3, 6.3)	-0.9	(-3.8, 2.0)
...VOICE ALTERAT	5	1.3	(0.5, 3.2)	7	3.0	(1.3, 6.3)	-1.7	(-4.5, 1.1)
SKIN & APPENDAGES	30	7.7	(5.3, 10.9)	27	11.5	(7.8, 16.5)	-3.8	(-9.0, 1.4)
...RASH	15	3.9	(2.3, 6.5)	12	5.1	(2.8, 9.0)	-1.2	(-5.0, 2.6)
...SWEAT	13	3.4	(1.9, 5.9)	14	6.0	(3.5, 10.1)	-2.6	(-6.5, 1.3)
...PRURITUS	5	1.3	(0.5, 3.2)	2	0.9	(0.2, 3.4)	0.4	(-1.6, 2.4)
SPECIAL SENSES	37	9.5	(6.9, 13.0)	14	6.0	(3.5, 10.1)	3.5	(-1.1, 8.1)
...ACCOMMODATION ABNORM	11	2.8	(1.5, 5.1)	6	2.6	(1.1, 5.8)	0.2	(-2.8, 3.2)
...VISION ABNORM	10	2.6	(1.3, 4.9)	0	0.0	(0.0, 2.0)	2.6	(0.7, 4.5)
...TINNITUS	5	1.3	(0.5, 3.2)	2	0.9	(0.2, 3.4)	0.4	(-1.6, 2.4)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment

N = Intent-to-treat population

Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...CONJUNCTIVITIS	4	1.0	(0.3, 2.8)	3	1.3	(0.3, 4.0)	-0.3	(-2.4, 1.8)
...DIPLOPIA	4	1.0	(0.3, 2.8)	2	0.9	(0.2, 3.4)	0.1	(-1.8, 2.0)
...TASTE PERVERS	4	1.0	(0.3, 2.8)	2	0.9	(0.2, 3.4)	0.1	(-1.8, 2.0)
UROGENITAL SYSTEM	24	6.2	(4.1, 9.2)	24	10.2	(6.8, 15.0)	-4.0	(-8.9, 0.9)
...INFECT URIN TRACT	11	2.8	(1.5, 5.1)	12	5.1	(2.8, 9.0)	-2.3	(-5.9, 1.3)
...URIN FREQUENCY	8	2.1	(1.0, 4.2)	10	4.3	(2.2, 8.0)	-2.2	(-5.5, 1.1)
...IMPOTENCE	7	1.8	(0.8, 3.8)	3	1.3	(0.3, 4.0)	0.5	(-1.8, 2.8)

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ON ORIGINAL

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Appendix 4.13.1.2.1

% and 95% C.I. of Patients with Adverse Events (TES Reported in $\geq 1\%$ of the Patients in the Pramipexole Group)
 Group: All Double-Blind Placebo Controlled Studies for Advanced Parkinson's Disease (Advanced Controlled Studies: 10, 19, 20 & 22)

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
Total Patients (N)	260			264				
All Body Systems	245	94.2	(90.4, 96.6)	237	89.8	(85.3, 93.1)	4.4	(-0.6, 9.4)
BODY AS A WHOLE	137	52.7	(46.4, 58.9)	133	50.4	(44.2, 56.6)	2.3	(-6.6, 11.2)
...INJURY ACCID	43	16.5	(12.3, 21.7)	39	14.8	(10.9, 19.8)	1.7	(-4.9, 8.3)
...PAIN	31	11.9	(8.3, 16.6)	43	16.3	(12.2, 21.4)	-4.4	(-10.7, 1.9)
...ASTHENIA	26	10.0	(6.8, 14.5)	21	8.0	(5.1, 12.1)	2.0	(-3.3, 7.3)
...INFECT	26	10.0	(6.8, 14.5)	36	13.6	(9.8, 18.5)	-3.6	(-9.5, 2.3)
...HEADACHE	23	8.8	(5.8, 13.1)	38	14.4	(10.5, 19.4)	-5.6	(-11.4, 0.2)
...PAIN BACK	14	5.4	(3.1, 9.1)	18	6.8	(4.2, 10.7)	-1.4	(-5.9, 3.1)
...FLU SYND	12	4.6	(2.5, 8.1)	18	6.8	(4.2, 10.7)	-2.2	(-6.5, 2.1)
...EDEMA GENERAL	10	3.8	(1.9, 7.1)	7	2.7	(1.2, 5.7)	1.1	(-2.3, 4.5)
...PAIN ABDO	10	3.8	(1.9, 7.1)	10	3.8	(1.9, 7.1)	0.0	(-3.7, 3.7)
...PAIN CHEST	8	3.1	(1.5, 6.2)	4	1.5	(0.5, 4.1)	1.6	(-1.3, 4.5)
...MALAISE	7	2.7	(1.2, 5.7)	5	1.9	(0.7, 4.6)	0.8	(-2.1, 3.7)
...PAIN NECK	4	1.5	(0.5, 4.1)	4	1.5	(0.5, 4.1)	0.0	(-2.5, 2.5)
CARDIOVASCULAR SYSTEM	148	56.9	(50.6, 63.0)	144	54.5	(48.3, 60.6)	2.4	(-6.5, 11.3)
...HYPOTENS POST	137	52.7	(46.4, 58.9)	127	48.1	(42.0, 54.3)	4.6	(-4.3, 13.5)
...HYPERTENS	7	2.7	(1.2, 5.7)	7	2.7	(1.2, 5.7)	0.0	(-3.2, 3.2)
...HYPOTENS	6	2.3	(0.9, 5.2)	8	3.0	(1.4, 6.1)	-0.7	(-3.8, 2.4)
...VASODILAT	5	1.9	(0.7, 4.7)	7	2.7	(1.2, 5.7)	-0.8	(-3.7, 2.1)
...SYNCOPE	4	1.5	(0.5, 4.1)	7	2.7	(1.2, 5.7)	-1.2	(-4.0, 1.6)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
 N = Intent-to-treat population
 Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...PALPITAT	3	1.2	(0.3, 3.7)	4	1.5	(0.5, 4.1)	-0.3	(-2.7, 2.1)
DIGESTIVE SYSTEM	110	42.3	(36.3, 48.6)	110	41.7	(35.7, 47.9)	0.6	(-8.2, 9.4)
...NAUSEA	58	22.3	(17.5, 27.9)	61	23.1	(18.3, 28.7)	-0.8	(-8.4, 6.8)
...CONSTIP	26	10.0	(6.8, 14.5)	23	8.7	(5.7, 12.9)	1.3	(-4.1, 6.7)
...DRY MOUTH	17	6.5	(3.9, 10.4)	7	2.7	(1.2, 5.7)	3.8	(-0.2, 7.8)
...ANOREXIA	14	5.4	(3.1, 9.1)	18	6.8	(4.2, 10.7)	-1.4	(-5.9, 3.1)
...DYSPEPSIA	13	5.0	(2.8, 8.6)	17	6.4	(3.9, 10.2)	-1.4	(-5.7, 2.9)
...DIARRHEA	10	3.8	(1.9, 7.1)	11	4.2	(2.2, 7.6)	-0.4	(-4.1, 3.3)
...SALIVA INC	7	2.7	(1.2, 5.7)	11	4.2	(2.2, 7.6)	-1.5	(-5.0, 2.0)
...TOOTH DIS	7	2.7	(1.2, 5.7)	8	3.0	(1.4, 6.1)	-0.3	(-3.5, 2.9)
...VOMIT	5	1.9	(0.7, 4.7)	12	4.5	(2.4, 8.0)	-2.6	(-6.0, 0.8)
...DYSPHAGIA	3	1.2	(0.3, 3.7)	5	1.9	(0.7, 4.6)	-0.7	(-3.2, 1.8)
...FLATUL	3	1.2	(0.3, 3.7)	2	0.8	(0.1, 3.1)	0.4	(-1.7, 2.5)
METABOLIC & NUTRITIONAL SYSTEM	9	3.5	(1.7, 6.7)	3	1.1	(0.3, 3.5)	2.4	(-0.5, 5.3)
...EDEMA PERIPH	6	2.3	(0.9, 5.2)	2	0.8	(0.1, 3.1)	1.5	(-1.0, 4.0)
...CREATINE PK INC	3	1.2	(0.3, 3.7)	1	0.4	(0.0, 2.5)	0.8	(-1.1, 2.7)
MUSCULO SKELETAL SYSTEM	43	16.5	(12.3, 21.7)	28	10.6	(7.3, 15.1)	5.9	(-0.3, 12.1)
...CRAMPS LEG	14	5.4	(3.1, 9.1)	12	4.5	(2.4, 8.0)	0.9	(-3.2, 5.0)
...MYALGIA	10	3.8	(1.9, 7.1)	13	4.9	(2.7, 8.4)	-1.1	(-5.0, 2.8)
...ARTHRITIS	7	2.7	(1.2, 5.7)	3	1.1	(0.3, 3.5)	1.6	(-1.1, 4.3)
...TWITCH	6	2.3	(0.9, 5.2)	0	0.0	(0.0, 1.8)	2.3	(0.1, 4.5)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

BEST POSSIBLE COPY

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...BURSITIS	4	1.5	(0.5, 4.1)	1	0.4	(0.0, 2.5)	1.1	(-0.9, 3.1)
...ARTHRALGIA	3	1.2	(0.3, 3.7)	5	1.9	(0.7, 4.6)	-0.7	(-3.2, 1.8)
...MYASTHENIA	3	1.2	(0.3, 3.7)	0	0.0	(0.0, 1.8)	1.2	(-0.5, 2.9)
NERVOUS SYSTEM	213	81.9	(76.6, 86.3)	199	75.4	(69.7, 80.4)	6.5	(-0.9, 13.9)
...DYSKINESIA	123	47.3	(41.1, 53.6)	83	31.4	(25.9, 37.4)	15.9	(7.3, 24.5)
...EXTRAPYR SYND	72	27.7	(22.4, 33.6)	68	25.8	(20.7, 31.6)	1.9	(-6.1, 9.9)
...INSOMNIA	70	26.9	(21.7, 32.8)	57	21.6	(16.9, 27.2)	5.3	(-2.4, 13.0)
...DIZZINESS	67	25.8	(20.7, 31.6)	66	25.0	(20.0, 30.8)	0.8	(-7.0, 8.6)
...HALLUCIN	43	16.5	(12.3, 21.7)	10	3.8	(1.9, 7.1)	12.7	(7.3, 18.1)
...DREAM ABNORM	28	10.8	(7.4, 15.4)	25	9.5	(6.4, 13.9)	1.3	(-4.3, 6.9)
...CONFUS	26	10.0	(6.8, 14.5)	19	7.2	(4.5, 11.2)	2.8	(-2.4, 8.0)
...SOMNOLENCE	23	8.8	(5.8, 13.1)	16	6.1	(3.6, 9.9)	2.7	(-2.2, 7.6)
...DEPRESSION	22	8.5	(5.5, 12.7)	44	16.7	(12.5, 21.9)	-8.2	(-14.2, -2.2)
...DYSTONIA	21	8.1	(5.2, 12.3)	19	7.2	(4.5, 11.2)	0.9	(-4.0, 5.8)
...TREMOR	19	7.3	(4.6, 11.3)	38	14.4	(10.5, 19.4)	-7.1	(-12.8, -1.4)
...GAIT ABNORM	18	6.9	(4.3, 10.9)	13	4.9	(2.7, 8.4)	2.0	(-2.4, 6.4)
...HYPERTONIA	17	6.5	(3.9, 10.4)	16	6.1	(3.6, 9.9)	0.4	(-4.1, 4.9)
...AMNESIA	15	5.8	(3.4, 9.6)	11	4.2	(2.2, 7.6)	1.6	(-2.5, 5.7)
...HYPOKINESIA	15	5.8	(3.4, 9.6)	22	8.3	(5.4, 12.5)	-2.5	(-7.3, 2.3)
...ATAXIA	12	4.6	(2.5, 8.1)	13	4.9	(2.7, 8.4)	-0.3	(-4.3, 3.7)
...ANXIETY	9	3.5	(1.7, 6.7)	12	4.5	(2.4, 8.0)	-1.0	(-4.7, 2.7)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...PARESTHESIA	8	3.1	(1.5, 6.2)	9	3.4	(1.7, 6.6)	-0.3	(-3.7, 3.1)
...AKATHISIA	7	2.7	(1.2, 5.7)	6	2.3	(0.9, 5.2)	0.4	(-2.7, 3.5)
...THINKING ABNORM	7	2.7	(1.2, 5.7)	4	1.5	(0.5, 4.1)	1.2	(-1.6, 4.0)
...APATHY	6	2.3	(0.9, 5.2)	12	4.5	(2.4, 8.0)	-2.2	(-5.7, 1.3)
...HYPESTHESIA	5	1.9	(0.7, 4.7)	4	1.5	(0.5, 4.1)	0.4	(-2.2, 3.0)
...PARANOID REACT	5	1.9	(0.7, 4.7)	1	0.4	(0.0, 2.5)	1.5	(-0.7, 3.7)
...NERVOUSNESS	4	1.5	(0.5, 4.1)	7	2.7	(1.2, 5.7)	-1.2	(-4.0, 1.6)
...DELUSIONS	3	1.2	(0.3, 3.7)	1	0.4	(0.0, 2.5)	0.8	(-1.1, 2.7)
...SLEEP DIS	3	1.2	(0.3, 3.7)	0	0.0	(0.0, 1.8)	1.2	(-0.5, 2.9)
...VERTIGO	3	1.2	(0.3, 3.7)	4	1.5	(0.5, 4.1)	-0.3	(-2.7, 2.1)
RESPIRATORY SYSTEM	29	11.2	(7.8, 15.8)	19	7.2	(4.5, 11.2)	4.0	(-1.3, 9.3)
...DYSPNEA	10	3.8	(1.9, 7.1)	8	3.0	(1.4, 6.1)	0.8	(-2.7, 4.3)
...RHINITIS	7	2.7	(1.2, 5.7)	3	1.1	(0.3, 3.5)	1.6	(-1.1, 4.3)
...SINUSITIS	6	2.3	(0.9, 5.2)	4	1.5	(0.5, 4.1)	0.8	(-1.9, 3.5)
...PNEUMONIA	5	1.9	(0.7, 4.7)	0	0.0	(0.0, 1.8)	1.9	(-0.1, 3.9)
...COUGH INC	4	1.5	(0.5, 4.1)	4	1.5	(0.5, 4.1)	0.0	(-2.5, 2.5)
...PHARYNGITIS	3	1.2	(0.3, 3.7)	5	1.9	(0.7, 4.6)	-0.7	(-3.2, 1.8)
SKIN & APPENDAGES	24	9.2	(6.1, 13.6)	22	8.3	(5.4, 12.5)	0.9	(-4.3, 6.1)
...RASH	9	3.5	(1.7, 6.7)	10	3.8	(1.9, 7.1)	-0.3	(-3.9, 3.3)
...SWEAT	9	3.5	(1.7, 6.7)	9	3.4	(1.7, 6.6)	0.1	(-3.4, 3.6)
...SKIN DIS	5	1.9	(0.7, 4.7)	3	1.1	(0.3, 3.5)	0.8	(-1.7, 3.3)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment

N = Intent-to-treat population

Note: Difference refers to p(Pramipexole) - p(Placebo).

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Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
... PRURITUS	3	1.2	(0.3, 3.7)	2	0.8	(0.1, 3.1)	0.4	(-1.7, 2.5)
SPECIAL SENSES	24	9.2	(6.1, 13.6)	12	4.5	(2.4, 8.0)	4.7	(0.0, 9.4)
... ACCOMMODATION ABNORM	10	3.8	(1.9, 7.1)	6	2.3	(0.9, 5.2)	1.5	(-1.8, 4.8)
... VISION ABNORM	8	3.1	(1.5, 6.2)	2	0.8	(0.1, 3.1)	2.3	(-0.4, 5.0)
... CONJUNCTIVITIS	3	1.2	(0.3, 3.7)	3	1.1	(0.3, 3.5)	0.1	(-2.1, 2.3)
... DIPLOPIA	3	1.2	(0.3, 3.7)	0	0.0	(0.0, 1.8)	1.2	(-0.5, 2.9)
... LACRIMATION DIS	3	1.2	(0.3, 3.7)	2	0.8	(0.1, 3.1)	0.4	(-1.7, 2.5)
UROGENITAL SYSTEM	25	9.6	(6.4, 14.0)	17	6.4	(3.9, 10.2)	3.2	(-1.8, 8.2)
... URIN FREQUENCY	15	5.8	(3.4, 9.6)	7	2.7	(1.2, 5.7)	3.1	(-0.7, 6.9)
... INFECT URIN TRACT	10	3.8	(1.9, 7.1)	9	3.4	(1.7, 6.6)	0.4	(-3.2, 4.0)
... INCONTIN URIN	5	1.9	(0.7, 4.7)	3	1.1	(0.3, 3.5)	0.8	(-1.7, 3.3)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

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Appendix 4.13.2.1.1
 ET Patients In Completed Adequate And Well-Controlled Studies:
 Adverse Events Occurring With Frequency Greater Than Or Equal to 10%
 By Study Phase Where Event Was First Reported
 Date Produced: 10/30/96

Body System	Costart	Pramipexole				Placebo			
		Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)	Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)
Total Patients		377(100.00)	346(100.00)	332(100.00)	377(100.00)	222(100.00)	212(100.00)	200(100.00)	222(100.00)
BODY AS A WHOLE	ASTHENIA	36(9.55)	11(3.18)	6(1.81)	53(14.06)	16(7.21)	7(3.30)	4(2.00)	27(12.16)
	HEADACHE	43(11.41)	9(2.60)	1(0.30)	53(14.06)	24(10.81)	12(5.66)		36(16.22)
	INFECT	20(5.31)	34(9.83)	4(1.20)	58(15.38)	20(9.01)	27(12.74)	3(1.50)	50(22.52)
	PAIN	21(5.57)	27(7.80)	3(0.90)	51(13.53)	25(11.26)	18(8.49)	2(1.00)	45(20.27)
DIGESTIVE SYSTEM	CONSTIP	42(11.14)	9(2.60)	2(0.60)	53(14.06)	8(3.60)	6(2.83)		14(6.31)
	NAUSEA	88(23.34)	17(4.91)	1(0.30)	106(28.12)	25(11.26)	15(7.08)	1(0.50)	41(18.47)
NERVOUS SYSTEM	DIZZINESS	69(18.30)	25(7.23)	2(0.60)	96(25.46)	44(19.82)	12(5.66)		56(25.23)
	INSOMNIA	42(11.14)	13(3.76)	10(3.01)	65(17.24)	21(9.46)	6(2.83)		27(12.16)
	SOMNOLENCE	70(18.57)	15(4.34)		85(22.55)	18(8.11)	2(0.94)	1(0.50)	21(9.46)

Includes Studies M/2730/0001 and M/2730/0004

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Appendix 4.13.2.2.1

AT Patients In Completed Adequate And Well-Controlled Studies:
Adverse Events Occurring With Frequency Greater Than Or Equal to 10%
By Study Phase Where Event Was First Reported

Body System	Costart	Pramipexole				Placebo			
		Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)	Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)
Total Patients		181(100.00)	169(100.00)	177(100.00)	181(100.00)	178(100.00)	157(100.00)	165(100.00)	178(100.00)
BODY AS A WHOLE	INFECT	8(4.42)	15(8.88)		23(12.71)	12(6.74)	19(12.10)	2(1.21)	33(18.54)
	INJURY ACCID	16(8.84)	24(14.20)	2(1.13)	42(23.20)	17(9.55)	18(11.46)	3(1.82)	39(21.91)
	PAIN	9(4.97)	15(8.88)	1(0.56)	25(13.81)	10(5.62)	20(12.74)	3(1.82)	33(18.54)
CARDIOVASCULAR SYSTEM	HYPOTENS POST	92(50.83)	26(15.38)	5(2.82)	123(67.96)	93(52.25)	16(10.19)	9(5.45)	118(66.29)
DIGESTIVE SYSTEM	CONSTIP	11(6.08)	12(7.10)		23(12.71)	12(6.74)	9(5.73)	1(0.61)	22(12.36)
	NAUSEA	35(19.34)	7(4.14)	2(1.13)	44(24.31)	35(19.66)	13(8.28)	2(1.21)	50(28.09)
NERVOUS SYSTEM	CONFUS	14(7.73)	8(4.73)	1(0.56)	23(12.71)	10(5.62)	6(3.82)	2(1.21)	18(10.11)
	DIZZINESS	43(23.76)	8(4.73)	3(1.69)	54(29.83)	33(18.54)	16(10.19)	2(1.21)	51(28.65)
	DREAM ABNORM	14(7.73)	6(3.55)	1(0.56)	21(11.60)	15(8.43)	5(3.18)		20(11.24)
	DYSKINESIA	99(54.70)	12(7.10)	2(1.13)	113(62.43)	59(33.15)	17(10.83)	1(0.61)	77(43.26)
	EXTRAPYR SYND	12(6.63)	39(23.08)	14(7.91)	65(35.91)	26(14.61)	29(18.47)	6(3.64)	61(34.27)
	HALLUCIN	28(15.47)	6(3.55)	4(2.26)	38(20.99)	6(3.37)	3(1.91)	1(0.61)	10(5.62)
	INSOMNIA	27(14.92)	17(10.06)	7(3.95)	51(28.18)	32(17.98)	16(10.19)	1(0.61)	49(27.53)

Includes Study M/2730/0010

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Appendix 4.13.4.1
Adverse Events By Dose At First Occurrence
ET Patients; Studies 1, 4, & 21

	Dose at First Occurrence									
	0 - 0.75		>0.75 - 1.5		>1.5 - 3.0		>3.0 - 4.5		>4.5	
	n	%	n	%	n	%	n	%	n	%
Total Patients (N)	387		372		308		234		45	
ASTHENIA	21	5.43	7	1.88	7	2.27	9	3.85	2	4.44
CONSTIP	18	4.65	10	2.69	9	2.92	12	5.13	2	4.44
DIZZINESS	30	7.75	16	4.30	19	6.17	28	11.97	1	2.22
HEADACHE	33	8.53	5	1.34	7	2.27	7	2.99	1	2.22
INFECT	6	1.55	8	2.15	8	2.60	30	12.82	1	2.22
INSOMNIA	21	5.43	15	4.03	8	2.60	11	4.70	0	0.00
NAUSEA	42	10.85	21	5.65	22	7.17	21	8.97	0	0.00
PAIN	11	2.84	4	1.08	9	2.92	21	8.97	3	6.67
SOMNOLENCE	29	7.49	17	4.57	16	5.19	23	9.83	0	0.00

Events with first occurrence during the dose reduction phase have been excluded

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Appendix 4.13.4.2
Adverse Events By Dose At First Occurrence
AT Patients; Studies 10, 19, 20, & 22

	Dose at First Occurrence									
	0 - 0.75		>0.75 - 1.5		>1.5 - 3.0		>3.0 - 4.5		>4.5	
	n	%	n	%	n	%	n	%	n	%
Total Patients (N)	260		246		226		183		45	
DIZZINESS	26	10.00	7	2.85	14	6.19	15	3.54	1	2.22
DREAM ABNORM	12	4.62	6	2.44	4	1.77	5	2.73	0	0.00
DYSKINESIA	41	15.77	35	14.23	27	11.95	18	9.84	0	0.00
EXTRAPYR SYND	5	1.92	5	2.03	11	4.87	30	16.39	0	0.00
HALLUCIN	8	3.08	6	2.44	13	5.75	8	4.37	3	6.67
HYPOTENS POST	57	21.92	18	7.32	26	11.50	27	14.75	4	8.89
INJURY ACCID	8	3.08	5	2.03	10	4.42	18	9.84	0	0.00
INSOMNIA	20	7.69	7	2.85	11	4.87	23	12.57	1	2.22
NAUSEA	26	10.00	14	5.69	9	3.98	6	3.28	1	2.22
PAIN	3	1.15	5	2.03	8	3.54	12	6.56	0	0.00

Events with first occurrence during the dose reduction phase have been excluded

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Appendix 4.13.6.1
 ET Patients Studies 1, 4, & 21
 Adverse Events By Age

Age	Costart	Framipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
<= 45	ASTHENIA	8	30	0.267	4	23	0.174	1.53	0.53	4.47
	CONSTIP	3	30	0.100	1	23	0.043	2.30	0.26	20.70
	DEPRESSION	4	30	0.133	3	23	0.130	1.02	0.25	4.12
	DIZZINESS	5	30	0.167	5	23	0.217	0.77	0.25	2.34
	DYSPEPSIA	3	30	0.100	1	23	0.043	2.30	0.26	20.70
	HALLUCIN	3	30	0.100	.	.	.	.	.	.
	HEADACHE	6	30	0.200	3	23	0.130	1.53	0.43	5.49
	HYPERTONIA	1	30	0.033	5	23	0.217	0.15	0.02	1.22
	HYPOTENS POST	3	30	0.100	.	.	.	.	.	.
	INFECT	.	.	.	9	23	0.391	.	.	.
	INJURY ACCID	2	30	0.067	2	23	0.087	0.77	0.12	5.04
	INSOMNIA	10	30	0.333	2	23	0.087	3.83	0.93	15.82
	NAUSEA	6	30	0.200	5	23	0.217	0.92	0.32	2.64
	PAIN	6	30	0.200	1	23	0.043	4.60	0.59	35.60
	PAIN ABDO	.	.	.	2	23	0.087	.	.	.
	PAIN BACK	1	30	0.033	.	.	.	.	.	.
	SOMNOLENCE	7	30	0.233	1	23	0.043	5.37	0.71	40.61
	TREMOR	4	30	0.133	4	23	0.174	0.77	0.21	2.74
45-55	ASTHENIA	8	63	0.127	2	41	0.049	2.60	0.58	11.65
	CONSTIP	9	63	0.143	3	41	0.073	1.95	0.56	6.79

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021
 * N is the number of patients in each age group
 ** Relative risk computed as rate of PPX / rate of Placebo

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Age	Costart	Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
45-55	DEPRESSION	4	63	0.063	1	41	0.024	2.60	0.30	22.48
	DIZZINESS	11	63	0.175	7	41	0.171	1.02	0.43	2.42
	DYSPEPSIA	5	63	0.079	1	41	0.024	3.25	0.39	26.86
	HALLUCIN	2	63	0.032	1	41	0.024	1.30	0.12	13.90
	HEADACHE	12	63	0.190	9	41	0.220	0.87	0.40	1.87
	HYPERTONIA	4	63	0.063	3	41	0.073	0.87	0.20	3.68
	HYPOTENS POST	3	63	0.048	2	41	0.049	0.98	0.17	5.59
	INFECT	8	63	0.127	6	41	0.146	0.87	0.32	2.32
	INJURY ACCID	4	63	0.063	2	41	0.049	1.30	0.25	6.79
	INSOMNIA	13	63	0.206	4	41	0.098	2.12	0.74	6.04
	NAUSEA	15	63	0.238	10	41	0.244	0.98	0.49	1.96
	PAIN	8	63	0.127	11	41	0.268	0.47	0.21	1.06
	PAIN ABDO	3	63	0.048	1	41	0.024	1.95	0.21	18.13
	PAIN BACK	4	63	0.063	4	41	0.098	0.65	0.17	2.46
	SOMNOLENCE	10	63	0.159	1	41	0.024	6.51	0.87	48.95
	TREMOR	7	63	0.111	5	41	0.122	0.91	0.31	2.68
56-65	ASTHENIA	19	120	0.158	9	68	0.132	1.20	0.57	2.50
	CONSTIP	16	120	0.133	6	68	0.088	1.51	0.62	3.68
	DEPRESSION	9	120	0.075	7	68	0.103	0.73	0.28	1.87
	DIZZINESS	26	120	0.217	20	68	0.294	0.74	0.45	1.22

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021

* N is the number of patients in each age group

** Relative risk computed as rate of PPX / rate of Placebo

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		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Age	Costart									
56-65	DYSPEPSIA	13	120	0.108	4	68	0.059	1.84	0.63	5.43
	HALLUCIN	7	120	0.058	3	68	0.044	1.32	0.35	4.95
	HEADACHE	20	120	0.167	10	68	0.147	1.13	0.56	2.28
	HYPERTONIA	9	120	0.075	6	68	0.088	0.85	0.32	2.29
	HYPOTENS POST	8	120	0.067	9	68	0.132	0.50	0.20	1.24
	INFECT	23	120	0.192	15	68	0.221	0.87	0.49	1.55
	INJURY ACCID	11	120	0.092	6	68	0.088	1.04	0.40	2.68
	INSOMNIA	22	120	0.183	10	68	0.147	1.25	0.63	2.47
	NAUSEA	33	120	0.275	12	68	0.176	1.56	0.86	2.81
	PAIN	12	120	0.100	15	68	0.221	0.45	0.23	0.91
	PAIN ABDO	8	120	0.067	4	68	0.059	1.13	0.35	3.63
	PAIN BACK	14	120	0.117	4	68	0.059	1.98	0.68	5.79
	SOMNOLENCE	24	120	0.200	7	68	0.103	1.94	0.88	4.27
	TREMOR	19	120	0.158	13	68	0.191	0.83	0.44	1.57
66-75	ASTHENIA	11	144	0.076	11	83	0.133	0.58	0.26	1.27
	CONSTIP	21	144	0.146	3	83	0.036	4.03	1.24	13.12
	DEPRESSION	4	144	0.028	4	83	0.048	0.58	0.15	2.24
	DIZZINESS	46	144	0.319	19	83	0.229	1.40	0.88	2.21
	DYSPEPSIA	6	144	0.042	8	83	0.096	0.43	0.16	1.20
	HALLUCIN	16	144	0.111	2	83	0.024	4.61	1.09	19.56

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021

* N is the number of patients in each age group

** Relative risk computed as rate of PPX / rate of Placebo

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Age	Costart	Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
66-75	HEADACHE	17	144	0.118	13	83	0.157	0.75	0.39	1.47
	HYPERTONIA	7	144	0.049	3	83	0.036	1.34	0.36	5.06
	HYPOTENS POST	15	144	0.104	9	83	0.108	0.96	0.44	2.10
	INFECT	25	144	0.174	18	83	0.217	0.80	0.47	1.38
	INJURY ACCID	14	144	0.097	8	83	0.096	1.01	0.44	2.30
	INSOMNIA	20	144	0.139	9	83	0.108	1.28	0.61	2.68
	NAUSEA	43	144	0.299	12	83	0.145	2.07	1.16	3.69
	PAIN	21	144	0.146	16	83	0.193	0.76	0.42	1.37
	PAIN ABDO	9	144	0.063	5	83	0.060	1.04	0.36	2.99
	PAIN BACK	7	144	0.049	10	83	0.120	0.40	0.16	1.02
	SOMNOLENCE	38	144	0.264	10	83	0.120	2.19	1.15	4.16
	TREMOR	6	144	0.042	15	83	0.181	0.23	0.09	0.57
> 75	ASTHENIA	8	31	0.258	1	20	0.050	5.16	0.70	38.19
	CONSTIP	4	31	0.129	1	20	0.050	2.58	0.31	21.46
	DEPRESSION	1	31	0.032	2	20	0.100	0.32	0.03	3.33
	DIZZINESS	9	31	0.290	6	20	0.300	0.97	0.41	2.30
	DYSPEPSIA	1	31	0.032	2	20	0.100	0.32	0.03	3.33
	HALLUCIN	7	31	0.226	.	.	.	.	.	.
	HEADACHE	.	.	.	2	20	0.100	.	.	.
	HYPERTONIA	2	31	0.065	1	20	0.050	1.29	0.13	13.31

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021

* N is the number of patients in each age group

** Relative risk computed as rate of PPX / rate of Placebo

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Age	Costart	Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
> 75	HYPOTENS POST	1	31	0.032	1	20	0.050	0.65	0.04	9.74
	INFECT	3	31	0.097	4	20	0.200	0.48	0.12	1.94
	INJURY ACCID	3	31	0.097	2	20	0.100	0.97	0.18	5.29
	INSOMNIA	1	31	0.032	2	20	0.100	0.32	0.03	3.33
	NAUSEA	10	31	0.323	3	20	0.150	2.15	0.67	6.87
	PAIN	4	31	0.129	2	20	0.100	1.29	0.26	6.40
	PAIN ABDO	.	.	.	3	20	0.150	.	.	.
	PAIN BACK	5	31	0.161	2	20	0.100	1.61	0.35	7.53
	SOMNOLENCE	6	31	0.194	2	20	0.100	1.94	0.43	8.66
	TREMOR	1	31	0.032	2	20	0.100	0.32	0.03	3.33

* N is the number of patients in each age group

** Relative risk computed as rate of PPX / rate of Placebo

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Appendix 4.13.6.2
AT Patients Studies 10, 19, 20, & 22
Adverse Events By Age

Age	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
< = 45	AMNESIA	.	.	.	1	11	0.091	.	.	.
	ANOREXIA	.	.	.	2	11	0.182	.	.	.
	ASTHENIA	1	10	0.100	1	11	0.091	1.10	0.08	15.36
	CONFUS	1	10	0.100	.	.	.	.	.	.
	CONSTIP	1	10	0.100	.	.	.	.	.	.
	CRAMPS LEG	1	10	0.100	.	.	.	.	.	.
	DEPRESSION	2	10	0.200	5	11	0.455	0.44	0.11	1.78
	DIZZINESS	3	10	0.300	3	11	0.273	1.10	0.28	4.25
	DREAM ABNORM	1	10	0.100	2	11	0.182	0.55	0.06	5.18
	DRY MOUTH	.	.	.	1	11	0.091	.	.	.
	DYSKINESIA	8	10	0.800	5	11	0.455	1.76	0.86	3.61
	DYSPEPSIA	1	10	0.100	1	11	0.091	1.10	0.08	15.36
	DYSTONIA	.	.	.	1	11	0.091	.	.	.
	EXTRAPYR SYND	3	10	0.300	4	11	0.364	0.82	0.24	2.82
	HEADACHE	.	.	.	2	11	0.182	.	.	.
	HYPERTONIA	.	.	.	1	11	0.091	.	.	.
	HYPOKINESIA	2	10	0.200	1	11	0.091	2.20	0.23	20.72
	HYPOTENS POST	6	10	0.600	3	11	0.273	2.20	0.74	6.54
	INFECT	2	10	0.200	2	11	0.182	1.10	0.19	6.41
	INJURY ACCID	1	10	0.100	1	11	0.091	1.10	0.08	15.36

(CONTINUED)

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		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Age	Costart									
< = 45	INSOMNIA	2	10	0.200	5	11	0.455	0.44	0.11	1.78
	NAUSEA	3	10	0.300	3	11	0.273	1.10	0.28	4.25
	PAIN	2	10	0.200	1	11	0.091	2.20	0.23	20.72
	PAIN BACK	.	.	.	1	11	0.091	.	.	.
	SOMNOLENCE	1	10	0.100	1	11	0.091	1.10	0.08	15.36
	TREMOR	1	10	0.100	2	11	0.182	0.55	0.06	5.18
45-55	AMNESIA	4	48	0.083	4	51	0.078	1.06	0.28	4.01
	ANOREXIA	4	48	0.083	2	51	0.039	2.12	0.41	11.08
	ASTHENIA	7	48	0.146	2	51	0.039	3.72	0.81	17.02
	CONFUS	5	48	0.104	3	51	0.059	1.77	0.45	7.01
	CONSTIP	5	48	0.104	1	51	0.020	5.31	0.64	43.84
	CRAMPS LEG	4	48	0.083	3	51	0.059	1.42	0.33	6.00
	DEPRESSION	6	48	0.125	6	51	0.118	1.06	0.37	3.07
	DIZZINESS	8	48	0.167	10	51	0.196	0.85	0.37	1.97
	DREAM ABNORM	4	48	0.083	3	51	0.059	1.42	0.33	6.00
	DRY MOUTH	5	48	0.104	.	.	.	.	.	.
	DYSKINESIA	25	48	0.521	22	51	0.431	1.21	0.80	1.83
	DYSPEPSIA	2	48	0.042	3	51	0.059	0.71	0.12	4.06
	DYSTONIA	4	48	0.083	4	51	0.078	1.06	0.28	4.01
	EXTRAPYR SYND	21	48	0.438	13	51	0.255	1.72	0.97	3.03

(CONTINUED)

APPEARS THIS WAY
ON ORIGINAL

Age	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
45-55	GAIT ABNORM	2	48	0.042	2	51	0.039	1.06	0.16	7.25
	HALLUCIN	2	48	0.042	1	51	0.020	2.13	0.20	22.68
	HEADACHE	5	48	0.104	10	51	0.196	0.53	0.20	1.44
	HYPERTONIA	3	48	0.063	4	51	0.078	0.80	0.19	3.38
	HYPOKINESIA	5	48	0.104	5	51	0.098	1.06	0.33	3.44
	HYPOTENS POST	20	48	0.417	23	51	0.451	0.92	0.59	1.45
	INFECT	5	48	0.104	14	51	0.275	0.38	0.15	0.97
	INJURY ACCID	5	48	0.104	8	51	0.157	0.66	0.23	1.89
	INSOMNIA	19	48	0.396	12	51	0.235	1.68	0.92	3.08
	NAUSEA	11	48	0.229	14	51	0.275	0.83	0.42	1.65
	PAIN	4	48	0.083	7	51	0.137	0.61	0.19	1.94
	PAIN BACK	4	48	0.083	6	51	0.118	0.71	0.21	2.36
	SOMNOLENCE	4	48	0.083	3	51	0.059	1.42	0.33	6.00
	TREMOR	1	48	0.021	5	51	0.098	0.21	0.03	1.75
URIN FREQUENCY	3	48	0.063	2	51	0.039	1.59	0.28	9.13	
56-65	AMNESIA	3	91	0.033	4	90	0.044	0.74	0.17	3.22
	ANOREXIA	3	91	0.033	8	90	0.089	0.37	0.10	1.35
	ASTHENIA	12	91	0.132	10	90	0.111	1.19	0.54	2.61
	CONFUS	3	91	0.033	7	90	0.078	0.42	0.11	1.59
	CONSTIP	8	91	0.088	10	90	0.111	0.79	0.33	1.91

(CONTINUED)

APPEARS THIS WAY
ON ORIGINAL

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Age	Costart									
56-65	CRAMPS LEG	4	91	0.044	6	90	0.067	0.66	0.19	2.26
	DEPRESSION	9	91	0.099	17	90	0.189	0.52	0.25	1.11
	DIZZINESS	22	91	0.242	23	90	0.256	0.95	0.57	1.57
	DREAM ABNORM	12	91	0.132	12	90	0.133	0.99	0.47	2.08
	DRY MOUTH	6	91	0.066	2	90	0.022	2.97	0.62	14.31
	DYSKINESIA	43	91	0.473	33	90	0.367	1.29	0.91	1.82
	DYSPEPSIA	4	91	0.044	8	90	0.089	0.49	0.15	1.58
	DYSTONIA	8	91	0.088	8	90	0.089	0.99	0.39	2.52
	EXTRAPYR SYND	19	91	0.209	22	90	0.244	0.85	0.50	1.47
	GAIT ABNORM	7	91	0.077	5	90	0.056	1.38	0.46	4.20
	HALLUCIN	15	91	0.165	4	90	0.044	3.71	1.28	10.75
	HEADACHE	10	91	0.110	16	90	0.178	0.62	0.30	1.29
	HYPERTONIA	7	91	0.077	8	90	0.089	0.87	0.33	2.29
	HYPOKINESIA	5	91	0.055	8	90	0.089	0.62	0.21	1.82
	HYPOTENS POST	47	91	0.516	45	90	0.500	1.03	0.78	1.38
	INFECT	10	91	0.110	7	90	0.078	1.41	0.56	3.55
	INJURY ACCID	14	91	0.154	17	90	0.189	0.81	0.43	1.55
	INSOMNIA	21	91	0.231	25	90	0.278	0.83	0.50	1.37
	NAUSEA	23	91	0.253	21	90	0.233	1.08	0.65	1.81
	PAIN	10	91	0.110	19	90	0.211	0.52	0.26	1.06

(CONTINUED)

APPEARS THIS WAY
ON ORIGINAL

Age	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
56-65	PAIN BACK	1	91	0.011	6	90	0.067	0.16	0.02	1.34
	SOMNOLENCE	8	91	0.088	5	90	0.056	1.58	0.54	4.65
	TREMOR	8	91	0.088	20	90	0.222	0.40	0.18	0.85
	URIN FREQUENCY	3	91	0.033	3	90	0.033	0.99	0.21	4.77
66-75	AMNESIA	7	96	0.073	2	98	0.020	3.57	0.76	16.77
	ANOREXIA	6	96	0.063	2	98	0.020	3.06	0.63	14.80
	ASTHENIA	5	96	0.052	6	98	0.061	0.85	0.27	2.69
	CONFUS	13	96	0.135	7	98	0.071	1.90	0.79	4.55
	CONSTIP	11	96	0.115	10	98	0.102	1.12	0.50	2.52
	CRAMPS LEG	4	96	0.042	3	98	0.031	1.36	0.31	5.92
	DEPRESSION	4	96	0.042	14	98	0.143	0.29	0.10	0.85
	DIZZINESS	28	96	0.292	25	98	0.255	1.14	0.72	1.81
	DREAM ABNORM	9	96	0.094	8	98	0.082	1.15	0.46	2.85
	DRY MOUTH	6	96	0.063	4	98	0.041	1.53	0.45	5.26
	DYSKINESIA	41	96	0.427	19	98	0.194	2.20	1.38	3.51
	DYSPEPSIA	5	96	0.052	5	98	0.051	1.02	0.31	3.41
	DYSTONIA	6	96	0.063	5	98	0.051	1.23	0.39	3.88
	EXTRAPYR SYND	23	96	0.240	23	98	0.235	1.02	0.62	1.69
	GAIT ABNORM	7	96	0.073	6	98	0.061	1.19	0.42	3.42
	HALLUCIN	22	96	0.229	4	98	0.041	5.61	2.01	15.69

(CONTINUED)

APPEARS THIS WAY
ON ORIGINAL

Age	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
66-75	HEADACHE	7	96	0.073	9	98	0.092	0.79	0.31	2.05
	HYPERTONIA	6	96	0.063	3	98	0.031	2.04	0.53	7.93
	HYPOKINESIA	3	96	0.031	7	98	0.071	0.44	0.12	1.64
	HYPOTENS POST	52	96	0.542	48	98	0.490	1.11	0.84	1.45
	INFECT	7	96	0.073	12	98	0.122	0.60	0.24	1.45
	INJURY ACCID	17	96	0.177	11	98	0.112	1.58	0.78	3.19
	INSOMNIA	24	96	0.250	13	98	0.133	1.88	1.02	3.48
	NAUSEA	19	96	0.198	20	98	0.204	0.97	0.55	1.70
	PAIN	11	96	0.115	14	98	0.143	0.80	0.38	1.68
	PAIN BACK	6	96	0.063	4	98	0.041	1.53	0.45	5.26
	SOMNOLENCE	10	96	0.104	6	98	0.061	1.70	0.64	4.50
	TREMOR	8	96	0.083	9	98	0.092	0.91	0.37	2.25
	URIN FREQUENCY	9	96	0.094	1	98	0.010	9.19	1.19	71.14
	> 75	AMNESIA	1	15	0.067	.	.	.	.	.
ANOREXIA		1	15	0.067	4	14	0.286	0.23	0.03	1.84
ASTHENIA		1	15	0.067	2	14	0.143	0.47	0.05	4.60
CONFUS		4	15	0.267	2	14	0.143	1.87	0.40	8.65
CONSTIP		1	15	0.067	2	14	0.143	0.47	0.05	4.60
CRAMPS LEG		1	15	0.067	.	.	.	.	.	.
DEPRESSION		1	15	0.067	2	14	0.143	0.47	0.05	4.60

(CONTINUED)

APPEARS THIS WAY
ON ORIGINAL

Age	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
> 75	DIZZINESS	6	15	0.400	5	14	0.357	1.12	0.44	2.86
	DREAM ABNORM	2	15	0.133	.	.	.	.	.	.
	DYSKINESIA	6	15	0.400	4	14	0.286	1.40	0.50	3.94
	DYSPEPSIA	1	15	0.067	.	.	.	.	.	.
	DYSTONIA	3	15	0.200	1	14	0.071	2.80	0.33	23.87
	EXTRAPYR SYND	6	15	0.400	6	14	0.429	0.93	0.39	2.22
	GAIT ABNORM	2	15	0.133	.	.	.	.	.	.
	HALLUCIN	4	15	0.267	1	14	0.071	3.73	0.47	29.49
	HEADACHE	1	15	0.067	1	14	0.071	0.93	0.06	13.54
	HYPERTONIA	1	15	0.067	.	.	.	.	.	.
	HYPOKINESIA	.	.	.	1	14	0.071	.	.	.
	HYPOTENS POST	12	15	0.800	8	14	0.571	1.40	0.83	2.35
	INFECT	2	15	0.133	1	14	0.071	1.87	0.19	18.38
	INJURY ACCID	6	15	0.400	2	14	0.143	2.80	0.67	11.64
	INSOMNIA	4	15	0.267	2	14	0.143	1.87	0.40	8.65
	NAUSEA	2	15	0.133	3	14	0.214	0.62	0.12	3.19
	PAIN	4	15	0.267	2	14	0.143	1.87	0.40	8.65
	PAIN BACK	3	15	0.200	1	14	0.071	2.80	0.33	23.87
	SOMNOLENCE	.	.	.	1	14	0.071	.	.	.
	TREMOR	1	15	0.067	2	14	0.143	0.47	0.05	4.60
URIN FREQUENCY	.	.	.	1	14	0.071	.	.	.	

* N is the number of patients in each gender

** Relative risk computed as rate of PPX / rate of Placebo

APPEARS THIS WAY
ON ORIGINAL

Appendix 4.13.6.3
 ET Patients Studies 1, 4, & 21
 Adverse Events By Gender

Sex	Cstart	Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Male	ASTHENIA	32	251	0.127	10	141	0.071	1.80	0.91	3.55
	CONSTIP	36	251	0.143	7	141	0.050	2.89	1.32	6.32
	DEPRESSION	17	251	0.068	5	141	0.035	1.91	0.72	5.07
	DIZZINESS	57	251	0.227	29	141	0.206	1.10	0.74	1.64
	DYSPEPSIA	18	251	0.072	11	141	0.078	0.92	0.45	1.89
	HALLUCIN	24	251	0.096	5	141	0.035	2.70	1.05	6.91
	HEADACHE	27	251	0.108	16	141	0.113	0.95	0.53	1.70
	HYPERTONIA	15	251	0.060	10	141	0.071	0.84	0.39	1.83
	HYPOTENS POST	19	251	0.076	12	141	0.085	0.89	0.44	1.78
	INFECT	39	251	0.155	33	141	0.234	0.66	0.44	1.01
	INJURY ACCID	25	251	0.100	9	141	0.064	1.56	0.75	3.25
	INSOMNIA	45	251	0.179	17	141	0.121	1.49	0.89	2.50
	NAUSEA	47	251	0.187	16	141	0.113	1.65	0.97	2.80
	PAIN	29	251	0.116	24	141	0.170	0.68	0.41	1.12
	PAIN ABDO	12	251	0.048	7	141	0.050	0.96	0.39	2.39
	PAIN BACK	16	251	0.064	10	141	0.071	0.90	0.42	1.93
	SOMNOLENCE	60	251	0.239	9	141	0.064	3.75	1.92	7.32
TREMOR	27	251	0.108	22	141	0.156	0.69	0.41	1.16	
Female	ASTHENIA	22	137	0.161	17	94	0.181	0.89	0.50	1.58
	CONSTIP	17	137	0.124	7	94	0.074	1.67	0.72	3.86

(CONTINUED)

APPEARS THIS WAY
 ON ORIGINAL

Sex	Costart	Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Female	DEPRESSION	5	137	0.036	12	94	0.128	0.29	0.10	0.78
	DIZZINESS	40	137	0.292	28	94	0.298	0.98	0.65	1.47
	DYSPEPSIA	10	137	0.073	5	94	0.053	1.37	0.48	3.89
	HALLUCIN	11	137	0.080	1	94	0.011	7.55	0.99	57.48
	HEADACHE	28	137	0.204	21	94	0.223	0.91	0.55	1.51
	HYPERTONIA	8	137	0.058	8	94	0.085	0.69	0.27	1.76
	HYPOTENS POST	11	137	0.080	9	94	0.096	0.84	0.36	1.94
	INFECT	20	137	0.146	19	94	0.202	0.72	0.41	1.28
	INJURY ACCID	9	137	0.066	11	94	0.117	0.56	0.24	1.30
	INSOMNIA	21	137	0.153	10	94	0.106	1.44	0.71	2.92
	NAUSEA	60	137	0.438	26	94	0.277	1.58	1.08	2.31
	PAIN	22	137	0.161	21	94	0.223	0.72	0.42	1.23
	PAIN ABDO	8	137	0.058	8	94	0.085	0.69	0.27	1.76
	PAIN BACK	15	137	0.109	10	94	0.106	1.03	0.48	2.19
	SOMNOLENCE	25	137	0.182	12	94	0.128	1.43	0.76	2.70
TREMOR	10	137	0.073	17	94	0.181	0.40	0.19	0.84	

* N is the number of patients in each gender

** Relative risk computed as rate of PPX / rate of Placebo

APPEARS THIS WAY
ON ORIGINAL

Appendix 4.13.6.4
AT Patients Studies 10, 19, 20, & 22
Adverse Events By Gender

Sex	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Male	AMNESIA	9	164	0.055	8	173	0.046	1.19	0.47	3.00
	ANOREXIA	9	164	0.055	9	173	0.052	1.05	0.43	2.59
	ASTHENIA	17	164	0.104	11	173	0.064	1.63	0.79	3.38
	CONFUS	19	164	0.116	13	173	0.075	1.54	0.79	3.02
	CONSTIP	20	164	0.122	14	173	0.081	1.51	0.79	2.88
	CRAMPS LEG	6	164	0.037	9	173	0.052	0.70	0.26	1.93
	DEPRESSION	10	164	0.061	24	173	0.139	0.44	0.22	0.89
	DIZZINESS	42	164	0.256	34	173	0.197	1.30	0.87	1.94
	DREAM ABNORM	16	164	0.098	18	173	0.104	0.94	0.50	1.78
	DRY MOUTH	11	164	0.067	4	173	0.023	2.90	0.94	8.93
	DYSKINESIA	73	164	0.445	52	173	0.301	1.48	1.11	1.97
	DYSPEPSIA	10	164	0.061	8	173	0.046	1.32	0.53	3.26
	DYSTONIA	13	164	0.079	13	173	0.075	1.05	0.50	2.21
	EXTRAPYR SYND	44	164	0.268	40	173	0.231	1.16	0.80	1.68
	GAIT ABNORM	12	164	0.073	9	173	0.052	1.41	0.61	3.25
	HALLUCIN	31	164	0.189	9	173	0.052	3.63	1.79	7.40
	HEADACHE	10	164	0.061	22	173	0.127	0.48	0.23	0.98
	HYPERTONIA	11	164	0.067	8	173	0.046	1.45	0.60	3.52
	HYPOKINESIA	7	164	0.043	15	173	0.087	0.49	0.21	1.18
	HYPOTENS POST	86	164	0.524	78	173	0.451	1.16	0.93	1.45

(CONTINUED)

**APPEARS THIS WAY
ON ORIGINAL**

Sex	Costart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Male	INFECT	18	164	0.110	25	173	0.145	0.76	0.43	1.34
	INJURY ACCID	29	164	0.177	19	173	0.110	1.61	0.94	2.76
	INSOMNIA	41	164	0.250	35	173	0.202	1.24	0.83	1.84
	NAUSEA	34	164	0.207	34	173	0.197	1.05	0.69	1.61
	PAIN	19	164	0.116	27	173	0.156	0.74	0.43	1.28
	PAIN BACK	10	164	0.061	16	173	0.092	0.66	0.31	1.41
	SOMNOLENCE	17	164	0.104	11	173	0.064	1.63	0.79	3.38
	TREMOR	13	164	0.079	21	173	0.121	0.65	0.34	1.26
	URIN FREQUENCY	8	164	0.049	5	173	0.029	1.69	0.56	5.05
Female	AMNESIA	6	96	0.063	3	91	0.033	1.90	0.49	7.36
	ANOREXIA	5	96	0.052	9	91	0.099	0.53	0.18	1.51
	ASTHENIA	9	96	0.094	10	91	0.110	0.85	0.36	2.00
	CONFUS	7	96	0.073	6	91	0.066	1.11	0.39	3.17
	CONSTIP	6	96	0.063	9	91	0.099	0.63	0.23	1.70
	CRAMPS LEG	8	96	0.083	3	91	0.033	2.53	0.69	9.23
	DEPRESSION	12	96	0.125	20	91	0.220	0.57	0.30	1.10
	DIZZINESS	25	96	0.260	32	91	0.352	0.74	0.48	1.15
	DREAM ABNORM	12	96	0.125	7	91	0.077	1.63	0.67	3.95
	DRY MOUTH	6	96	0.063	3	91	0.033	1.90	0.49	7.36
	DYSKINESIA	50	96	0.521	31	91	0.341	1.53	1.08	2.16

(CONTINUED)

APPEARS THIS WAY
ON ORIGINAL

Sex	Cosstart	Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Female	DYSPEPSIA	3	96	0.031	9	91	0.099	0.32	0.09	1.13
	DYSTONIA	8	96	0.083	6	91	0.066	1.26	0.46	3.50
	EXTRAPYR SYND	28	96	0.292	28	91	0.308	0.95	0.61	1.47
	GAIT ABNORM	6	96	0.063	4	91	0.044	1.42	0.41	4.88
	HALLUCIN	12	96	0.125	1	91	0.011	11.38	1.51	85.73
	HEADACHE	13	96	0.135	16	91	0.176	0.77	0.39	1.51
	HYPERTONIA	6	96	0.063	8	91	0.088	0.71	0.26	1.97
	HYPOKINESIA	8	96	0.083	7	91	0.077	1.08	0.41	2.87
	HYPOTENS POST	51	96	0.531	49	91	0.538	0.99	0.76	1.29
	INFECT	8	96	0.083	11	91	0.121	0.69	0.29	1.64
	INJURY ACCID	14	96	0.146	20	91	0.220	0.66	0.36	1.23
	INSOMNIA	29	96	0.302	22	91	0.242	1.25	0.78	2.01
	NAUSEA	24	96	0.250	27	91	0.297	0.84	0.53	1.35
	PAIN	12	96	0.125	16	91	0.176	0.71	0.36	1.42
	PAIN BACK	4	96	0.042	2	91	0.022	1.90	0.36	10.10
	SOMNOLENCE	6	96	0.063	5	91	0.055	1.14	0.36	3.60
	TREMOR	6	96	0.063	17	91	0.187	0.33	0.14	0.81
	URIN FREQUENCY	7	96	0.073	2	91	0.022	3.32	0.71	15.56

* N is the number of patients in each gender
** Relative risk computed as rate of PPX / rate of Placebo

APPEARS THIS WAY
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Predefined Limits for Laboratory Assays

<u>Assay</u>	<u>Unit of Measure</u>	<u>Sex</u>	<u>Criterion Value</u>
Hemoglobin	g/dL	M	<10, >18
		F	<9, >17
Hematocrit	%	M	<30, >54
		F	<27, >51
RBC	10 ⁶ /uL	M	<3, >7
		F	<2.5, >6.5
MCV	fL		<75, >110
MCH	pg		<24, >36
MCHC	%		<30, >38
Platelet Count	cells/mm ³		<80,000 >600,000
WBC Count	10 ³ /uL		<3, >13
Neutrophils	%		<=15
Lymphocytes	%		<=10, >=80
Monocytes	%		>=20
Eosinophil	%		>=10
Basophil	%		>=10
Bands	%		>=10
Glucose	mg/dL		<60, >200
BUN	mg/dL		>40
Creatinine	mg/dL		>2.5
Uric Acid	mg/dL		>10
Total Cholesterol	mg/dL		>50
Total Bilirubin	mg/dL		>2.5
Alkaline Phosphatase	U/L		2.5 x ULN*
LDH	U/L		2.5 x ULN
SGOT (AST)	U/L		2.5 x ULN
SGPT (ALT)	U/L		2.5 x ULN
Creatine Kinase	U/L		2.5 x ULN
Gamma-Glutamyl Transpeptidase (GGT)	U/L		2.5 x ULN
Total Protein	g/dL		<4.5, >9
Calcium	mg/dL		<=8, >=12
Chloride	mEq/L		<=90, >=115
Protein Globulin	G/DL		<=1.0, >=4.0

(Continued)

Predefined Limits for Laboratory Assays

<u>Assay</u>	<u>Unit of Measure</u>	<u>Sex</u>	<u>Criterion Value</u>
Potassium	mEq/L		≤3.0, ≥6.0
Sodium	mEq/L		≤125, ≥160
Specific Gravity			≤1.005, ≥1.028
pH			≤4.0, ≥9.0
Urine Protein			> 1+
Urine Glucose			> 1+
Urine Ketone			> 2+
Urine RBC			> 5
Urine WBC	HPF	M	> 10
	HPF	F	> 20
Urine Casts			Present
Culture			Positive

* ULN = Upper Limit of Normal Range

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**Summary of All patients With Laboratory Values
Exceeding Predefined Limits
Group: Adequate and Well-Controlled Studies# for Parkinson's Disease**

Laboratory Test		Medication					
		Pramipexole			Placebo		
		n	N	%	n	N	%
Hematology	Hemoglobin	5	547	0.91	5	394	1.27
	Hematocrit	4	547	0.73	5	394	1.27
	RBC Count	1	547	0.18	1	394	0.25
	MCV	3	547	0.55	2	394	0.51
	MCH	5	547	0.91	4	394	1.02
	MCHC	4	547	0.73	3	394	0.76
	WBC Count	13	547	2.38	15	394	3.81
	Neutrophils Segs	0	339	0	0	343	0
	Bands	0	209	0	0	51	0
	Lymphocytes	16	547	2.93	7	394	1.78
	Monocytes	0	547	0	0	394	0
	Eosinophils	19	547	3.47	24	394	6.09
	Basophils	0	547	0	0	394	0
	Platelet Count	3	546	0.55	1	394	0.25
	Blood Chemistry	Glucose	30	547	5.48	25	394
BUN		1	547	0.18	2	394	0.51
Creatinine		1	547	0.18	0	394	0
Uric Acid		3	547	0.55	4	394	1.02
Cholesterol, Total		16	547	2.93	14	394	3.55
Bilirubin, Total		0	547	0	1	394	0.25
Alkaline Phosphatase		2	547	0.37	0	394	0
LDH		1	547	0.18	0	394	0
SGOT		4	547	0.73	0	394	0
SGPT		4	547	0.73	2	394	0.51
CPK		19	544	3.49	9	392	2.30
GGT		11	547	2.01	4	394	1.02
Protein, Total		1	547	0.18	0	394	0
Urinalysis		Urine Protein	8	364	2.20	2	219
	Urine Glucose	6	364	1.65	5	219	2.28
	Urine Micro WBC	12	364	3.30	14	219	6.39
	Urine Micro RBC	13	364	3.57	18	219	8.22
	Urine Ketone	0	364	0	0	219	0
	Urine Micro Casts	6	161	3.73	8	169	4.73
	Urine Culture	0	0	0	1	1	100.00

Source: Appendix C, Table 30.1
Protocols M/2730/0001, M/2730/0004, and M/2730/0010

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Appendix 4.15.3

1

PLACEBO Protocol: M/2730				Laboratory Test: CPK (Pt's who had elevated CPK's at endpoint*).			
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Burch	46/F/W	-12 25 53 106 169 232 239		Angina - 1988; Hypertension; Bypass surgery (for weight control) - 1975; Hypothyroidism - 1968; Prostatism; Osteoarthritis; Back pain; Obesity; ECG NSR; Prominent anterior forces; may be artifact	Artane Eldepryl Flagyl Sulfamethoxazole Naproxen Tylenol with codeine Relafen Voltaren Amitriptyline Steroid injection	Increase fall or injury was not noted. All CPK were 100% CK-MM. Investigator judged elevations as not clinically significant.
0001	Paulson	46/F/W	-14 28 71 136 196 260 267		Inferior Infarct - ?; Increased cholesterol; Increased CPK; Increased eosinophils; kidney stones ?; L. knee surgery - 1987 H/A; Tight muscle - scalp; ECG NSR; Inferior infarct age undet.	Kemidrin Benadryl ASA Eldepryl	The CPK was already slightly increased at baseline. On Day 71, the patient complained of chest pains for which stress test was ordered. All CPK fractionizations showed $\geq$ 98% CK-MM. Though not clinically significant patient was referred to cardiologist.

*Endpoint = end of study or dropout.

2

PLACEBO Protocol: M/2730				Laboratory Test: CPK (Pt's who had elevated CPK's at endpoint*).			
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Weiner	71/F/W	-7 22 64 120 183 239 253		Ing hernia - 1983; Spinal fusion - 1970; R. Carpel tunnel Sx - 1993; Blood in semen - 1993; Increased CPK - etiology unknown; arthritis R. knee; ECG Abnormal R. Waves Q II III, F; old I WMI; ST-T changes I, AV, V6	Deprenyl-PD Naproxen Corticosteroid injection Tetracycline Dyazide	The patient's CPK was increased at baseline and remained elevated till end of study. Investigator's opinion: no evidence of skeletal muscle damage and elevation judged to be NCS. Fractionation showed $\geq 95\%$ CK3=MM.
0010	Lieberman	59/M/W	-7 25 37 67		Gastric reaction - 1966; Vagotomy-partial- 1966; Periodic back pain; ECG = NSR	Pergolide Selegiline Norazepam Amantadine Trihexy- pheridil Sinemet	Patient had increasing dyskinesia. Investiga- tor felt the elevated CPK was secondary to severe dyskinesia which necessitated visit to ER.

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*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730		Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)					
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Bennett	63/F/W	-11 25 32 53 109 170 221 228		Hypertension - 1992; Spinal stenosis surgery - 1992; L. Carpel tunnel syndrome surgery - 1992; ECG-NSR, LVH by voltage	terazosin	Day 25 CPK 511; CPK fractionated showed CK-MM - Contused R. wrist 3 days prior to CPK; Day 221 CPK fractionated showed CK-MM investigator comment "physical exertion"

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*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Fazzini	65/F/W	-12 24 52 115 175 233 245		Angina - ASHD-63 HTN - 91; Renal calculi 1963 (nephrolithiasis); L. Knee surgery - 1990; R. Ing. hernia - 1941; Tonsillectomy - 30's; Ganglion cyst R. gr. toe - 1978; Skin cyst - neck - 1978; CXR - Screen; linear scarring in R. lung field; diaphragm flattened; Aorta elongated & tortuous. Heart size enlarged - some degree of COPD & old fibrosis @ R. base ASHD suggested. ECG - Sinus bradycardia; Early R. Wave progression; 1st degree AV block.	Eldynyl Cardizem Tenormin ASA - nitro- glycerin	Day 24 CPK fractionated; CK-MM ; Investigator comment: NCS

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	Eidelman	46/M/W	-23 22 52 106 162 218 224		Diverticulitis - 1993; Back pain - 1973; Subarachnoid Cyst - 1990; ECG = NSR	Sinemet CR	1st elevation was said to be due to prolonged tourniquet time; 2nd elevation was due to patient shoveling driveway for 5 hours. Both fractionated CKB-
0010	Perimutter	55/M/W	-7 29 43 99 155 213 218		Migraine - 1988; Tunnel Vision - 1990; Generalized choreiform movements (bradykinesia R>L) ECG=NSR; L. anterior fascicular block	Persantine Amantadine Diphenhydramine Sinemet CR	Patient developed severe esophageal spasm for which he was hospitalized. He also experienced increased dyskinesia & nocturnal myoclonus. The patient had multiple needle sticks prior to this blood draw accounting for elevated CPK fractionation:

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730		Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)					
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	Richter	81/M/W	-12 20 106 175 234 241		Hypertension - 1991; L. Inguinal hernia - 1993; Back muscle spasm; Osgood-Schlatter Disease - 1993; ECG-NSR; Slight cardiomegaly on chest x-ray	Primivil Hydrochlorothiazide Toradol	Patient had elevated CPK 6 weeks prior to baseline which the investigator related to muscle trauma. Fractionation: CK3-MM = 0; Subsequently CPK came down and other fractionation also was CK3-MM :

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*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Fazzini	33/F/W	-7 22 53 92 148 162		ECG - Sinus bradycardia; R. bundle intraventricular conduction delay	Eldepryl Permax	Day 92 CPK fractionated showed ,PK , CK-MM, Investigator comment: NCS; Day 162 dropped from study due to adverse event (paranoia & auditory hallucinations).
0001	Friedman	60/F/W	-7 27 58 124 177 247 254		Hypertension, increased cholesterol; lobectomy (bronchiectasis), ulcer, IBS, hyperthyroidism; kidney stones; erectile dysfunction (due to hypertension meds); anxiety; ECG poor R Wave progression, L. axis-clockwise rotation - ST Wave Abnormality	Eldepryl Inderol Mevacor Zantac Imodium Allopurinol Klonopin	Day 177 CPK fractionated showed CPK CK-MM, Investigator comment: NCS

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Kurth	48/F/W	-16 22 50 101 154 224 230		Urinary urgency; head injury - 1984; ECG - NSR	Eldepryl Amantadine Elavil	Day 22 CPK PK fractionated showed Investigator comment: NCS

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*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
0001	Olanow	66/F/W	-2 22 50 106 160 218 225		Stroke L. - 1989; Arthritis - 1990; Intermittent constipation -1993; Back cyst removed; Mortons neuroma - 1992; Memory difficulties - 1991; Intermittent light-headedness - 1991; ECG - Rapid early transition. Non Sp. ST-T Wave changes; Sm. non-pathological Q waves lead III. Cannot R/O old inferior posterior MI; borderline abnormalities may not indicate heart disease	Cogentin Eldepryl	Prior to Day 106, Patient reported freezing; blurry vision; & increased forgetfulness; Day 106 - fractionated showed Investigator comment: NCS

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Richter	56/F/W	-5 51 107 170 247		Hematuria; erectile dysfunction; Rash - chest; ECG - Sinus bradycardia; L. possible Atrial enlargement - bigeminal PAC's with standing	No relevant concomitant medications.	Day 170 CPK CPK fractionated; Showf Muscle problem ongoing per investigator

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PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
0001	Watts	57/F/W	-13 27 58 111 125 169 220 232		PUD - 1972; occasional burning on urination - 1992; urinary frequency - 1992; partial amputation 5th digit R. hand - 1967; bilateral hip pain - 1992; head trauma - 1955; ECG sinus bradycardia L. axis deviation - old findings; T-abnormality - old findings	Selegiline trinekyph- nidyl non ASA analgesic ibuprofen Novacaine llysine	Day 111 CPK CPK fractionated; showed Investigator comment: "No chest pain, injury or flu, will recheck again with muscle specific enzyme"; Day 125 CPK CPK fractionated showed Investigator comment: "unknown clinical significant - asymptomatic; ? myositis; injury, without chest pain and fever; second high value will repeat and check aldolase and ESR at same time".

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0004	Grimes	59/M/W	-10 45 68		Impotence x 1; A-Fib x 15 yrs; hypertension (renal dysfunction); transient arthritis - wrists; gout - which was drug related in 1988; cholecystectomy in 1982; ECG Atrial Fibrillation.	Deprenyl Doxyclyne Digoxin, ASA Novahy-diazide Novasen Vasotec Verapamil HCL Selegeline Isoptin Enalapril Maleate	Day 45 CPK CPK not fractionated, investigator comment: "all known before".
0004	Sethi	70/M/W	-10 43 68		Hiatal hernia - 1991; strained muscle mid back; benign cyst R. kidney - 1987.	Ibuprofen Tums Standback powder amoxicillin L-Deprenyl Amantidine Nubain Fentanyl Dxycodone & propoxyphene	Day 43 CPK CPK not fractionated. R. hip fx - patient fell 8/2/94 @ Day 42 - hospitalized for surgery. Not walking at end of study;

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
0010	Guttman	52/M/O	-6 25 59 105 155 204 211		Kidney stone (1979) MVA back injury (1989) Knee effusion (1993) Slightly hypertensive intermittent (L) Knee pain Chronic sinus infection ECG: NSR Day 56: NSR with non-specific T-wave abnormality	Sinemet CR Naprosyn Steroid injection (for knee) on Visit 4 Amoxicillin (for sinus)	Per investigator, the elevated CPK (not fractionated) was skeletal, probably related to osteoarthropathy & was accompanied by slight ↑ LDH (not clinically significant level of CPK levels came down at subsequent visits

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
0010	Hubble	53/M/W	-8 21 49 105 162 218 225		Multiple fractures (1961, 1962, 199) ECG = NSR	Eldepryl Trazodine Restoril	Around Day 105, pt fell off a horse while riding. Investigator noted that pt. had rhabdomyolysis due to fall; fractionation was CPK subsequently returned to normal
0010	Jankovic	62/M/W	-7 24 43 65		Occasional dizzy spells. ECG = NSR	Sinemet	Pt. had complained of increasing early morning dystonia. CPK fractionation = Pt. was discontinued from study; no work-up or diagnosis available. The CPK returned to normal on Day 65

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*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Factor	76/F/W	-7 22 29 85 141 204 211		Sm. ventral hernia midline; angina since 1975; CABG 1975; Enlarged prostate 1993; Arthritis (neck) - 1993; increased serum glucose -1989; hiatrial hernia - 1992; gall stones - 1992-93; circumcision - 1974 ECG; Sinus Rythymn borderline; 1st degree AV block; baseline artifact; systolic ejection murmur	Nitro disc Ecotrin Proscar Eldepryl	Day 211 CPI CPK fractionated showed Investigator comment: NCS; No fall/injury reported.

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*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Olanow	73/F/W	-13 22 50 103 163 219 227		Arthritis shoulder & hip - 1983; hypertension - 1989; anxiety - 1973; Surgeries: Hernia - 1983; rhinoplasty - 1968; plastic surgery ears - 1958 ECG - marked sinus arrhythmia - premature supraventricular complexes - occasional PAC- freq. dropped beats	Ibuprofen Eldepryl Zestril Tranxene	Day 227 CPK fractionated; showed CPK Investigator comment: "minor injury?" No other information available.

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PRAMIPEXOLE Protocol: M/2730				Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).			
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	Richter	62/F/W	-14 22 55 110 172 242 249		Angioplasty - 1988; histoplasmosis - 1947; appendectomy; hiatal hernia; frequency urination; enlarged prostate - 1978; mild depression; Hyperlipidemia, hypertension - 1993; anxiety - 1991; ECG NSR; possible L. atrial enlargement; ventricular hypertrophy; ST-T Wave Abnormality; consider lateral Ischemia	Cardizen CD Hytrin Valium Buspar Benadryl Tagament Prozac Xanax Ativan	Day 249 CPK CPK fractionated showed Investigator comment: "muscle spasm ongoing". Minor fall - Day 249.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0004	Kurlan	60/M/W	-7 9		Borderline hypertension - 1992; Arthritis; anxiety x 3 months; mild depression; hyperflexia in legs L>R; ECG NSR movement artifact	Verapamil Tylenol Corimdin Nitro PRN Lopressor	On Day 7 patient was involved in a MVA; following syncope. While at clinic had ECG findings of ST-T wave elevations for which he was sent to ER. The diagnosis was myocardial infarction of anterior wall. Elevated CPK was not fractionated.
0004	Trosch	63/M/W	-9 43 71		COPD - 1990; PVC - 1990; Hypertension - 1992; Gout - 1992; Osteoarthritis - 1992; Asthma - childhood; ECG-NSR but possible left atrial enlargement & non-specific T-Wave Abnormality	Selegiline L-deprenyl Vasotec dilantin cyanoco- bala- min naproxen terazosin bumetanide	Day 9 - Hypertonia; Day 28 onset of bilateral pedal edema (removed from open-label study due to ongoing symptoms); Day 43 & 71 not fractionated. Investigator comment: NCS.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	Eidelman	63/F/W	-14 24 46		CABG (1990); AAA repair; Duodenal ulcer (1994); Fx - R shoulder (1992); knee replacement (1993); Obese; slightly hypertensive; ECG: Sinus tachycardia; L anterior fascicular block	Permax Parloqel Lasix Eldepryl K-Dor	Pt. fell several days prior to Day 46; CPK was not fractionated; pt. dropped from the study on Day 46 due to adverse event (visual hallucination)
0010	Paulson	64/M/W	-12 23 92 148		Dementia (1987); Hallucination (1990) Leg cramps (1989) Thrombosed hemorrhoids ECG: NSR	Sinemet CR Symmetrel Florinef (started on Day 90)	Around Day 148 - the ECG showed "old inferoposterior infarction". According to investigator, the patient had silent infarct & family doctor notified. Pt. died unexpectedly in his sleep.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	Tetrud	60/F/W	Baseline 20 51 107 163 191 212	Not done	Hypertension (1982) Hypothyroid (46 years) Arthritis (1982) Dystonia (foot, 1986) Depression (1993) ECG: NSR Chest X-ray: Mild scarring & atelectasis (Both bases - not clinically significant.)	Parlodel Triam/Hcz Synthroid Ecotrin Sinemet Flexeril (for dystonia)	Pt. had complained of increased shakiness, stiffness, tremor & worsening dystonia in spite of Flexeril; the dystonia was moderate to severe at times; CPK fractionated on Day 191 & 212. Showed

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*Endpoint = end of study or dropout.

Table 2 Placebo: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0001	Watts	58/F/W					-12 24 51 113 124 170 229 235		borderline hypertension, bilateral ankle edema, gallstone, kidney stone, L. pyelolithotomy, R. knee pain, insomnia, dry mouth, voice hoarseness, H/As, urinary hesitation urgency, EKG - NSR with sinus arrhythmia - R. ventricular conduction delay - old findings, asymptomatic - sinus bradycardia	l-deprenyl, Rolaids, nizoral, ibuprofen, bufferin, Maalox	bilirubin wnl thru out study, SGPT & GGT increased at visit 13, inv. comment "clinically significant - was mildly symptomatic x 1 day with midline abd. pain, ? gallstone passed - recheck lab next wk, has had history of gallstones in past". GGT increased at visit 14 - inv. comment "NCS - prob. gallstone effect again"
0001	Farmer	64/F/W					-7 23 51 107 163 219 226		old knee inj, L. traumatic pinoveal nerve (same as muscular), mild depression - occ. bouts, back surgery - disc, PX: L. foot drop, CXR - mild atherosclerotic CV changes, degenerative mid-thoracic spine changes, hilar promence is considered to be due to pulmonary vessels	Sinemet, sulfamethoxazde, doxycycline, Hytrin, urispas, Motrin	bilirubin wnl thru out study, GGT increased at screen - inv. comment "NCS - other LFT is OK - will f/u during trial" prostatitis at visit 10

*Patients with ≥ 2 increased LFT abnormalities.

Table 2 Placebo: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0004	Trosch	56/M/W					-9 43 71		bladder infections, osteoarthritis/hands, muscular H/A, transient vocal cord paralysis, abd. umbilical hernia, occasional insomnia, depression, chemical pneumonia due to epoxy paint, 1970 PX: umbilical hernia, high frequency hearing loss	l-deprenyl, Mylanta, fluoxetine, ibuprophen, diphenhydramine, pseudoephedrine, excedrin x 2 days for H/A (day 42)	bilirubin wnl thru out study, GGT elevated day inv. NCS
0010	Karp	72/M/W					5 37 59 115 173 236		post nasal drip (hayfever), appendectomy, CXR - mild COPD	Symmetrel, Sinemet, ASA, chlorthrimeton	bilirubin wnl thru out study, GGT increased at screen - labs repeated at visit 1, GGT increased - inv. comment "probably 2" to sinemet high-dose, visit 2 - hematuria - ref. to urologist & primary care phy., cystoscopy & IVP - mass R. kidney (no f/u req)

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Table 2 Placebo: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Guttman	62/M/W			-14 23 49 94 141 206 212				atrial fibrillation - intermittent, congestive heart failure, seasonal asthma, hayfever, cholecystectomy, inguinal hernia repair, abn. liver function tests, diabetic, back pain, prostate surgery, bladder volume small - surgical expansion, hydronephrosis - partial; PX: R. arm mole (no change at end of study), EKG non-specific ST-T, changes possible old inferior infarct - incomplete R. bundle branch block	symmetrel, flexeril, glyburide, lanoxin, lasix, asprocream, instantine, prolopa, psyllium, nitropatch	bilirubin wnl thru out study, SGOT, SGPT increased - inv. states "chronic elevation flucuating abnormaly in past" - NCS, EKG changed from baseline at visit 19 - possible ischemia noted, f/u with FMD next day - on O ₂ (1 liter) at noc for dyspnea, study drug D/C until cardiac evaluation is completed visit 19

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Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0001	Farmer	77/F/W					-9 22 50 79 89		hypertension, cholecystectomy, menopause, inguinal herniorrhaphy, multi infarct dementia with short term memory loss, cataract surgery, Px - mild thyroid enlargement, no mass, +1 ankle edema, occ. ecchymotic areas, EKG - marked sinus arrhythmia with sinus bradycardia, occ. supra-ventricular complexes	Trental, Norvasc, Keralone, Darvocet	NCS, bilirubin wnl thru out study, GGT increased - NCS/inv.
0001	Siemers	59/F/W					-14 22 43 92 148 204 211		peptic ulcer disease - melena approx. twice/year, cholecystectomy, intermittant H/A, mild L. ulnar neuropathy, bilateral foot pain/planter callouses, CXR abn. - calcified granuloma RUL,	l-deprenyl, Tagamet, Tylenol, v-cillin, Baclofen, mylanta, ASA - (Baby), gaviscon, Valium, Ex-lax, inderal, benadryl, Clariton	bilirubin wnl thru out study, SGPT & GGT increased at screen - inv. comment "prior common bile duct stint following transection during cholecystectomy, clinically asymptomatic for 20+ years NCS", onset of hypertension at visit 17

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Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0001	Siemers	67/F/W					-14 22 29 85 139 197 204		hypertension, CAD, allergy - voltarin, hayfever, colitis, bowel obstruction - surgery, diabetes, hypothyroidism, fibromyalgia, bursitis both shoulders, anxiety, idiopathic thrombocytopenic purpura, cataracts - bilateral, gastroesophageal reflex, CXR - abn. - area of atelectasis bi-apical pleural thickening, inv/NCS, EKG - L. atrial abn. NSR, PX: +1 pedal edema	l-deprenyl, premarin, Verelan, Provera, Xanax, Beconase AQ, Synthroid, Darvocet, Artane, Mylanta, titralac acid, carafate	bilirubin wnl thru out study, GGT increased - "Estrogen replacement" NCS per inv.
0004	Kurlan	60/M/W	-7 9	19 173					borderline hypertension, ragweed allergy, arthritis, anxiety x 3 months, mild depression, PX: hyper-reflexia in legs L>R, EKG - Abn Q waves V1 - V6 st. elevation V1 - V6, extensive acute anterior wall injury/MI	acetomenophen, Verapamil	bilirubin elevated day 70 but remained within predefined limits - pt. was having myocardial infarction - increased CPK at the time of lab draws day 70, pt. terminated from study week 10 (day 70)

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Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0004	Hurtig	50/F/B					-16 53 76		hypertension, diabetes, sciatica - left, hepatitis (comment: GGT levels as high as 660 per FMD)	l-deprenyl, ibuprophen, insulin	bilirubin values normal thru out study, GGT values elevated thru out study - investigator indicates not significant due to history of hepatitis, episodic headaches during study-relieved with Motrin
0004	Trosch	67/M/W					-14 43 71		systolic murmur, episodic pulmonary inf, allergy - pen, Ca Prostate - "93"/ Surgery 93, Fx R. wrist - 47; arthritis R & L shoulders, melanoma & surgery L. shoulder - 1991, head trauma - 1957, Fx L. ankle - 89, T&A, hemorrhoids & surgery, cataract & surgery - 1990, facial/plastic surgery, EKG - bradycardia - L. Axis deviation with occ PVC.	l-deprenyl, Tavist-D, clindamycin (prophylatic finger infection)	bilirubin wnl thru out study, GGTincreased - NCS by inv., URI - day 70

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Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Eidelman	67/F/W	-6 23 51 94 148 204 209		-6 23 51 94 148 204 209		-6 23 51 94 148 204 209		cardiac cath - 50% blockage of L. decending artery, hypertension, PVC's (normal EKG), allergy - pcn, sulfa, hiatal hernia with esophageal reflux, cholecystectomy, hypothyroid, hypercholestendemia, c-section, ruptured ectopic preg, arthritis, sciatica, stapedectomy L. ear, deaf L., anxiety	Symmetrel, Synthroid, Maalox, Bentyl, Cogentin, Zantac, Ascriptin, eldepryl, Xanax, Sinemet, Cardizen, Senokot, tetracycline	bilirubin wnl thru out study, Dx of common bile stenosis by internist at visit 14, increased LFTs - inv. "referred to internist for flu", numbness across upper lip visit 10, carotid & transcranial doppler were ordered

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*Patients with ≥ 2 increased LFT abnormalities.
+Patients with elevated LFT but returned to normal at endpoint.

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Golbe	74/F/W			-21 29 85 141 199 206				hypertension, hysterectomy, R. ankle pain, depression, insomnia, cataract removed - OD, Px - LUE numbness, loud S ₁ RSB, EKG: NSR L. Axis deviation - possible anterior infarct age undetermined, non-specific T wave abnormality, non-specific ST abnormality anterior leads, CXR - small nodule L. upper lung field, no change from old films	Diazepam, trazodone, Ambien, temazepam, chlorthalidone, Sinemet, Tylenol	SGOT, SGPT, GGT increased - inv. comment "will watch - chronic & recurrent", bilirubin wnl thru out study
0010	Factor	49/M/W	-7 22 29						valve disease (aortic) replacement, hypertension, asthma, peptic ulcer, ruptured appendix - bowel resection, osteoarthritis, depression, herniorrhaphy, vein stripping/varicose veins, EKG - sinus tachycardia, CXR cardiomegaly - NCS	Klonopin, Motrin, Sinemet, Baclofen, Colace, Benadryl, Prozac, Ventolin spray, Permax, chloralhydrate	visit 5 increased SGOT inv. comment "Dx with rhabdomyolysis", hospitalized visit 9 due to increased CK mm, bilirubin wnl thru out study

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+Patients with elevated LFT but returned to normal at endpoint.

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Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Paulson	64/M/W	-12 23 36 92 148						shingles, dementia, hallucinations, old thrombosed hemorrhoid L. lateral quadrant, leg cramps, light headed, PX: dementia & hallucinations, CXR - plaque-like disease probably related to asbestos, EKG - sinus arrhythmia & junctional ST depression old, inferoposterior infarction	Symmetrel, Florinef, Sinemet CR, thiamine, Zofran	bilirubin wnl thru out study, SGOT increased visit 16, inv. comment "He had, apparently, a heart attack". Pt. was asymptomatic - died unexpectedly at night.
0010	Friedman	72/F/W					-7 24 57 108 162 218 225		hypertension, congestive heart failure, allergy to some medications, gallbladder out, low back strain, clinical myelopathy, depression, R. mastectomy, CA colon - resection, insomnia, hypotonic bladder, Px - +2 pedal edema, EKG NSR - possible anteroseptal infarct non-specific, ST-T wave abnormalities	Ianaxin, Sinemet CR, Pamelor, Benadryl, Restoril, Valisone Cream, Tylenol, quinine, Lasix	GGT increased - NCS, bilirubin wnl thru out study, mod to severe bilateral leg pain visit 6 to end of study

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Jankovic	45/M/W			-7 24 78 136 194 204		-7 24 78 136 194 204		possible history of murmur, eczema, lumbar laminectomy, post traumatic stress inj, EKG L. axis deviation, early precordial R/S transition, sinus tachycardia, Px: eczema - face	e-ldepryl, Sinemet, amitriptyline, tums, Voltarin, Betametasone, Advil	bilirubin wnl thru out study, inv. made no comments re. increased LFTs
0010	Montgomery	65/F/W					-7 22 50 73		Pt. has had increased LFTs for many years, post-menopausal, R. mastectomy	Sinemet, Gyne Lotrimin Vaginal Cream	GGT increased - inv. "NCS - known for sometime", bilirubin wnl thru out study, pt. withdrawn from study due to paranoia visit 19

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*Patients with ≥ 2 increased LFT abnormalities.

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Richter	67/M/W			-7 22 50		-7 29 50		intermittent hypotensive episodes, constipation, kidney stones x 3 - surgery x 3 ultrasound x 2, impotence, skin cancers - removal, EKG - NSR with occ. premature supra-ventricular complexes, L. anterior fascicular block, CXR - small area discord atelectasis at L. base otherwise essentially normal chest	e-ldepryl, Donnatal, Sinemet, lortab	abn. hepatic function at visit 5 - hepatitis eval. I done for increased LFTs, pt. positive for A, AB, bilirubin remained wnl thru out study & pt. remained asymptomatic, study meds stopped due to abn hepatic function & pt. allowed into open label when LFT ret. to normal

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*Patients with ≥ 2 increased LFT abnormalities.

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	Stoessl	68/F/W					-14 23 52 105 161 217 224		hypertension, allergy - sulfa, appendectomy, cholecystectomy, Fx R. femur - internal fixation, arthritis, occasional nocturnal visual hallucinations, no frank psychosis, levodopa related, macular degeneration, sciatica, PX: GRII/VI murmur, osteoarthritic knees, CXR - cardiomegaly - questionable density, lingular lobe on the left - etiology unk, EKG NSR nondiagnostic inferior ST, depression - incomplete L. BBB, sinus tachycardia L. axis deviation, echo cardigram scheduled due to one episode of chest pain	Domperidone, Dulcolax, surgam, amitriptyline, calcium carbonate, Sinemet, Tylenol #2, fluviral	bilirubin wnl thru out study, increased GGT - inv. comment "repeated and judged not to be clinically significant"

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Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **December 6, 1996**

FROM: **Paul Leber, M.D.**
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: **NDA 20-667, Mirapex, [pramipexole]**

TO: **File NDA 20-667**
 &
 Robert Temple, M.D.
 Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that Pharmacia-Upjohn's NDA 20-667 for **Mirapex™** be declared **approvable**.

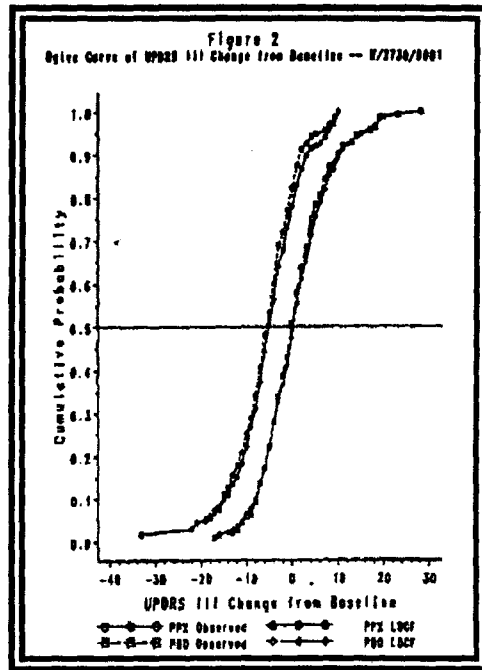
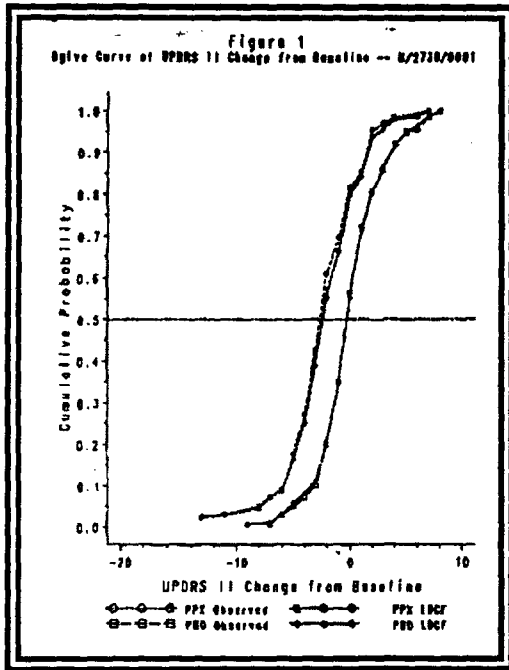
The sponsor's NDA provides results of 8 completed, adequate and well controlled, clinical investigations that speak to pramipexole's capacity to ameliorate the signs and symptoms of Parkinson's Disease. A review of the reports of these studies has led the team to conclude that the sponsor has provided substantial evidence of Mirapex's effectiveness as a treatment of the "signs and symptoms of idiopathic Parkinson's Disease." Specifically, reports to the NDA document the beneficial effects of Mirapex™ in patients with both early Parkinson's Disease (basically, in patients not receiving concomitant treatment with l-dopa and a decarboxylase inhibitor¹) and in those with advanced disease(i.e., those who had once, but were no longer responding satisfactorily, to treatment with maximally tolerable doses of l-dopa/carbidopa²).

¹ Among the 4 clinical trials (#'s 1,4,17 and 21), Studies 1 and 4 are deemed most persuasive and are the primary basis of our affirmative conclusions in this subpopulation.

² Among the 4 completed trials that apply to this subset of the population, Study 10 provides the most compelling results. Studies 19 and 22 are also sources of statistically significant findings supporting the sponsor's claims.

I will not review the effectiveness data here because, as the reviews conducted by Dr. Feeney (9/13/96) and Dr. Hoberman (10/24/96) comprehensively document, the results of the completed trials, including even those that we have not enumerated as sources of substantial evidence, provide robust support for the effectiveness of Mirapex™. The graphics that follow provide a visual insight into the consistency of the evidence of efficacy.

Study 1, Item 2 and 3 on UPDRS



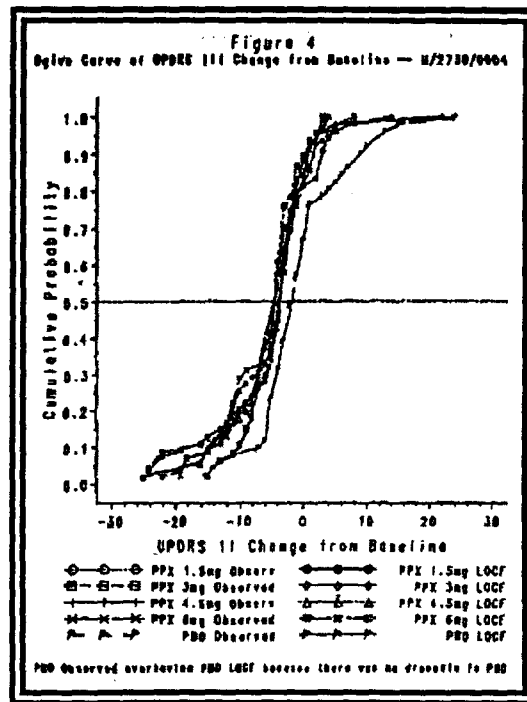
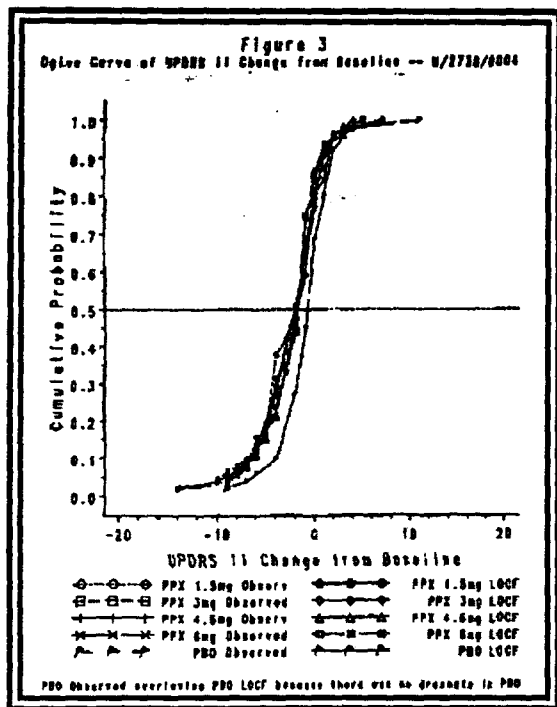
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The left shift of the ogive for improvement on UPDRS virtually says it all³. Exploratory analyses of the effect of age, sex and medication (other than l-dopa/carbidopa) did not find a treatment by concomitant treatment interaction. This is a strong positive study.

³ These are extracted verbatim from pages 22 and 25 of Dr. Feeney's review; the imported text on the figures is too small to read, but the consistent left shift of both the LOCF and OC data for pramipexole assigned patients (greater improvement from baseline for Mirapex™ assigned subjects) on both items of the UPDRS are obvious, a finding reflected in the very small 'p' value for the likelihood of the data given the null being true (no treatment effect).

To be clear, the evidence provided in the NDA is not without limitations. The results of Study 4, provided below, reveal, the sponsor has been unable to find a link between dose the magnitude of Mirapex's therapeutic effects.

Study 4, Fixed Dose comparison of 4 pramipexole vs. placebo (pages 45, 46 of Dr. Feeney's review.



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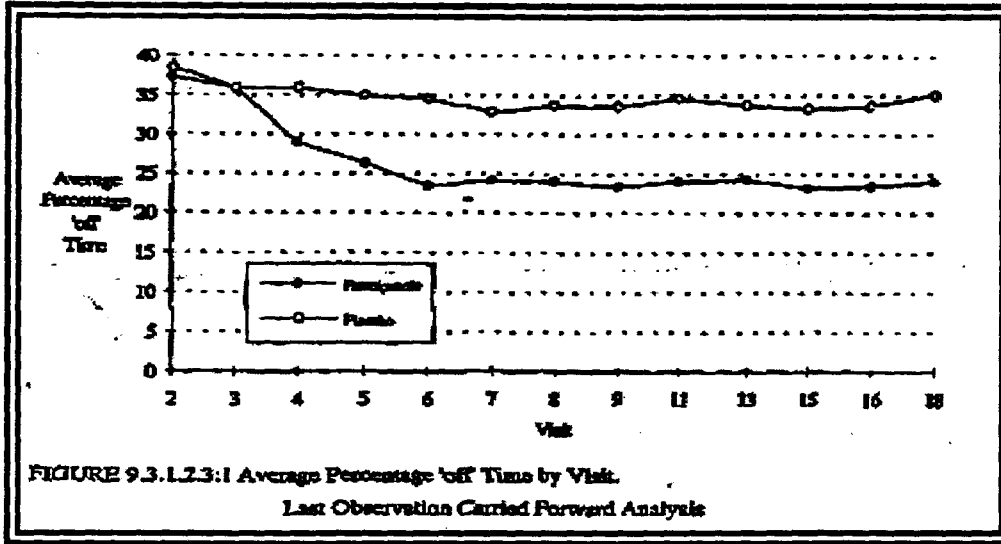
Among the 4 completed trials evaluating Mirapex as an adjunctive treatment, 3 can be deemed to provide support for its efficacy. Among the positive trials (i.e., Studies 10, 19 and 22), **Study 10** is critical to our affirmative conclusions regarding pramipexole's efficacy in this subpopulation.

Study 10

This is a strongly positive study. The graph that follows on the next page illustrates the clinical value of pramipexole in terms of the fraction of time awake that an advanced stage patient, being treated with maximally

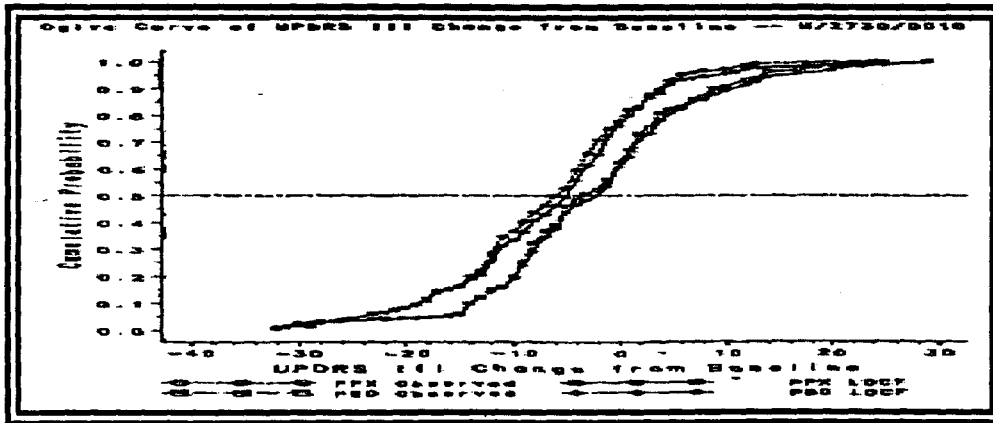
tolerated doses of l-dopa, spends in an 'off⁴' state.

Study 10, Average percent of time off by Visit⁵



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The changes on the UPDRS for both OC and LOCF data sets in this study are consistent as the cdf ogive for changes in its motor component document displayed below documents. (Feeney page 95).



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⁴ The "off" time refers to all time when an awake PD patient is immobilized and/or substantively impaired. Off is contrasted with "on" periods where the patient has some relief from the signs and symptoms of the disease.

⁵ taken from page 83 of Dr. Feeney's review

In sum, the NDA provides robust support for the sponsor's claim that Mirapex is an effective treatment for idiopathic Parkinson's Disease.

Safety in use

The evidence collected and reported to the NDA is sufficient to support a conclusion that Mirapex™ will be "safe for use" under the conditions of use enumerated and recommended in the draft product labeling developed by the Division. This conclusion is accompanied by a number of caveats, however.

To begin, a regulatory determination that a drug is "safe for use" is not a finding of fact, but an opinion. The opinion, importantly, is not really about safety, per se, but about the balance of risks and benefits associated with the use of the drug. Thus, when a regulator concludes that a drug has been shown to be safe for use, he is asserting only that the risks known to be associated with the use of the drug are, in his professional opinion, reasonably outweighed by the expected benefits of its use.

It should also be recognized that the basis for the opinion offered rests on imperfect knowledge. The measures of treatment effect obtained in clinical experiments that assess treatment effects on rating scales are, for example, not easily understood in terms of meaningful clinical benefit. Moreover, the risks associated with the use of a drug at the time a decision is made about its "safety for use," are invariably fewer than its actual risks because 1) too few patients are ordinarily exposed to a drug during its commercial development to capture adverse drug induced phenomena that occur at low incidence and 2) the typical clinical cohort in which a new drug is tested is not likely to be as vulnerable to the adverse effects/actions of the drug as is the population of patients for which the drug will be prescribed once marketed.

Both of these limitations affect our assessment of Mirapex's safety for use.

First, the total number of patients treated with pramipexole is small; as of the safety cutoff date (January 1995), only 1231 PD patients in toto

had been exposed to pramipexole. Among these, only 520 or so have been exposed to the maximum recommended dose of 4.5 mg/d for at least 12 weeks. While this number is probably sufficient to identify most of the common adverse events that are likely⁶ to be associated with pramipexole's use, the extent of exposure is clearly marginal insofar as its capacity to detect even one case of events that occur at a crude risk of 5 events/1000 patients exposed or less. While the later crude incidence may be deemed reasonably remote from the perspective of the individual patient, it is rather high from a societal viewpoint, especially if any of the risks not detected are serious ones⁷.

Also tending to undercut the basis for a conclusion that pramipexole is safe for use is the fact that the patients entered into the development cohort were selected so as to be free of the more serious illnesses (e.g., active heart disease) that are common among patients in the age range in which Parkinson's Disease is prevalent. This gives pause because it means that the risk of pramipexole caused events that arise uniquely or at increased incidence among older patients (either because of their age, per se, or the presence of age related co-existing disease or the treatments used to control the latter), have not been reliably assessed.

These limitations of pramipexole's clinical testing are not, under current interpretations of the Act's requirements, sufficient to bar its approval for marketing. Nevertheless, they are important because they do affect the nature of the extrapolations reasonably drawn from the relatively uneventful clinical experience reported during pramipexole's clinical

⁶ Dopamine agonists have been used in the management of PD since the early to mid 1970s. The common acute adverse events reported for the two approved products, bromocriptine and pergolide, are quite similar including hypotension, nausea, and vomiting. Typically, with dose incrementation, hallucinations and dyskinesias appear.

⁷ To illustrate, the use of bromocriptine is believed to be causally related to the occurrence of pleuropulmonary effusion and fibrosis. While I have no reliable basis to estimate the true incidence of this rare complication, which by now is widely attributed to dopamine agonist therapy in general, the incidence is likely to be well below that which would be reliably detected in a drug development cohort of the size used to assess pramipexole.

testing and development. Specifically, given the selected nature of the patients recruited in the Mirapex development cohort, it is prudent to be cautious in regard to inferences concerning the product's capacity to induce orthostatic hypotension (see below).

The limitations enumerated notwithstanding, it is fair to state that in regard to the events that have been reported, Mirapex appears to present no new serious risks of use not already known to be associated with the use of dopamine agonists in the treatment of Parkinson's disease. A review of the causes (hallucinations, dizziness, nausea, somnolence, headache and confusion) for premature discontinuations from studies of pramipexole supports this assertion.

As to more serious morbidities and fatalities associated with the use of pramipexole, clinical experience raises no substantive concerns. I note, however, that a case of rhabdomyolysis following exercise that was associated with CPK elevations has raised some concern among staff about the mean elevation of CPK results seen in the safety database. Given the numerous potential causes for CPK elevation, I see no reason to do more than describe the case (e.g., in the Precautions section) and the CPK findings in labeling.

As to fatalities, only 12 occurred among pramipexole recipients. As a consequence, any estimates of the incidence within subgroups of the sample studied are likely to be unstable. We did, nonetheless, elect to examine fatality rates separately among early and advanced cases of PD because the patients in these two groups were deemed likely to be different in terms of their inherent risk of mortality, an assumption, incidentally, that is not supported by the point estimates of the fatality risk among placebo recipients in these groups. In any case, the rate per 100 patient years is approximately the same among early patients regardless of treatment (0.72 vs 0.9 favoring pramipexole). Among patients with advanced disease, however, the data provide a relative risk estimate of almost 3. (2.52 vs 0.88 deaths per 100 patient years). While unfavorable to Pramipexole, the difference in the estimates is due to a difference of 2 deaths. Accordingly, I am not persuaded the finding represents a signal worthy of pursuit.

Labeling Considerations.

In general, in developing labeling, we sought to maintain some degree of consistency with that of dopamine agonist products already marketed with anti-PD indications (Parlodel[bromocriptine] and Permax [pergolide]). This proved somewhat difficult given the long interval that has elapsed since the initial approval of those products.

We have acted as if certain findings are generalizable to all dopamine agonist treatments. Perhaps the most controversial consequence of this strategy is the warning statement we propose about the risk of hypotension associated with dopamine agonist use. Actually, hypotensive events for Mirapex were not reported to occur at an incidence greater than that seen among placebo patients, a point acknowledged in the warnings statement. As noted earlier, however, we are not fully reassured by the absence of a differential risk because of the highly selected nature of the population. Moreover, we are also concerned that the sponsor's classification system may have obscured the risk (i.e., the sponsor combined dizziness and hypotension, an act that may have caused a differential risk of orthostatic events to be missed).

Dosing

The sponsors fixed dose study failed to establish the shape of pramipexole's dose response surface. Directions for the product's use, therefore, reflect experience gained in the clinical development program.

Conclusions and Recommendations

Mirapex has been shown, within the meaning of the Act, to be effective in use and safe for use under the directions for use provided in the draft labeling developed by the Division. Accordingly, the ~~NDA should~~ be deemed approvable.

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Paul Leber, M.D.
December 6, 1996

cc NDA 20-667

HFD 101

Temple

HFD-120

Katz

Feeney

Burkhart

Balian

Knudsen

Steele

Fitzgerald

HFD -710

Hoberman

Grilley

Wheelous

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Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: June 23, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-667, Mirapex, [pramipexole]

TO: File NDA 20-667
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my formal recommendation that the NDA for Mirapex be approved. This recommendation reflects the Division's review team's conclusion that the firm has satisfactorily met the requests and conditions upon which final approval of the application was conditioned (see the agency's action letter of 12/23/96).

In memoranda to the file, Dr. Katz (6/16/97) and Dr. Burkhart (5/13/97) summarize the findings and evidence that led them each to recommend that the application be approved. Although I fully concur with their recommendations, I have a number of comments for the administrative file.

Safety Update [SU]

With the submission of the SU, the clinical data base for the Mirapex NDA now includes a total of some 2150 subjects (there were 1400 in the original NDA) who provide approximately 1925 patient-years of exposure experience.

No previously unrecognized risks of use have been identified.

Although Dr. Balian (2/27/97) concludes that the experience reported upon provides no finding that would cause the agency to reverse its conclusion that Mirapex has been shown to be safe for use, it bears note that a

sizeable fraction of the new information presented does not derive from experience gained with pramipexole in patients with PD, but from reports of studies of the drug in patients with depression or schizophrenia.

The relationship between dose and common ADRs has not been characterized

The firm has been unable to develop the information necessary to determine whether or not there is a linkage between ADR incidence and pramipexole dose. The review team is persuaded that their inability to do so is a consequence of 1) the fact that pramipexole dose was advanced by titration (i.e., thus, dose and time are confounded), and, 2) the small numbers of untoward events falling within any of the categories that would be created by an arbitrary partition of the dose and time continuum.

Labeling

The sponsor has persuaded the agency review team that a draft of product labeling differing in a number of ways from the labeling put forth in the approvable action is acceptable. The areas of labeling affected by these changes are identified in Dr. Katz's 6/16/97 memorandum.

Recommendation

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The application should be approved.

/S/

Paul Leber, M.D.
June 23, 1997

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APPEARS THIS WAY

cc NDA 20-667
HFD 101
Temple
HFD-120
Katz
Feeney
Burkhart
Balian
Knudsen
Steele
Fitzgerald
HFD -710
Hoberman
Grilley
Wheelous

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MEMORANDUM

DATE: December 2, 1996

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-667

SUBJECT: Supervisory Review of NDA 20-667 for the use of Pramipexole in patients with Parkinson's Disease

BACKGROUND

NDA 20-667, for the use of pramipexole, a D₂ receptor agonist (with greatest affinity for the D₃ receptor sub-type), in patients with idiopathic Parkinson's Disease (PD), was submitted by Pharmacia and Upjohn on December 28, 1996. The NDA includes reports of 9 controlled trials; 4 of the trials enrolled patients with relatively early PD who were not receiving concomitant dopaminergic therapy. In the remaining 5 trials, patients with later stage PD were enrolled, and these patients were receiving concomitant dopaminergic therapy.

The effectiveness data were reviewed by Dr. John Feeney (and Dr. James Sherry) of the Division, in a review dated 9/13/96, and a detailed statistical review of 3 of the controlled trials was performed by Dr. David Hoberman of Biometrics in a review dated 10/24/96. The safety database was reviewed by Drs. John Balian and James Knudsen of the Division in a review dated 11/13/96. In this memo, I will briefly review the efficacy and safety data, and offer my recommendation for action on the NDA.

EFFECTIVENESS

EARLY PD

As noted above, the sponsor has submitted the results of 4 controlled trials in patients with early PD; Studies 1, 4, 17, and 21. Study 21 was small, and Study 17 was single-blind. They will be discussed very briefly

here, but I will focus on the results of Studies 1 and 4.

Study 1

This was a multi-center, randomized, placebo controlled, parallel group trial in which patients with PD Stage I-III Hoehn and Yahr who were not receiving concomitant l-dopa therapy were enrolled. The Hoehn and Yahr scale is a frequently used PD staging instrument, in which I=minimal unilateral disease and V=confined to bed or wheelchair. Stage III=Mild to moderate bilateral disease with some postural instability but physically independent.

Patients were permitted to have received l-dopa in the past, but not for greater than 6 months and not for at least 60 days prior to randomization. Treatment was to be initiated at 0.125 mg TID (total daily dose of 0.375 mg), and weekly dose increments were to be carried out, to the patient's maximally tolerated dose or a maximum dose of 1.5 mg TID (total daily dose of 4.5 mg). This titration phase could last up to 7 weeks.

After the titration phase, patients entered a 6 month maintenance phase, which was followed by a 1 week dose reduction phase.

The protocol stated primary outcomes were change from baseline in the score of the Unified Parkinson's Disease Rating Scale (UPDRS) for the Activities of Daily Living (ADL) and Motor Score sub-scales.

The UPDRS is a frequently used multi-item scale which is designed to assess various aspects of the severity of PD. It consists of 42 items, grouped into 4 parts: Mentation, ADL, Motor Exam, Complications of Therapy. Part II (ADL) consists of 13 items, and Part III (Motor Exam) consists of 14 items, each of which are rated from 0-Normal to 4-maximum impairment. Scores for Part II can range from 0-Normal to 42 Maximal Disability. Scores for Part III can range from 0-Normal to 46-Maximal Disability. The items constituting the ADL are assessed for the previous week (both during "on" periods-during which the patient is functioning well, and during "off" periods-periods when the patient is relatively immobile), and the items for the Motor Score are assessed by the examiner during a study visit. These latter items consist of, for

example, assessment of tremor, rigidity, facial expression, speech quality, bradykinesia, posture, gait, etc.

A total of 300 patients were planned to be enrolled at 24 U.S. and Canadian centers.

RESULTS

A total of 335 patients were randomized (pramipexole 164, placebo 171) at 26 centers in the U.S. A total of 28 pramipexole and 34 placebo patients did not complete the trial, and 163 pramipexole and 170 placebo patients were included in the intent-to-treat, last observation carried forward (LOCF) analyses.

The following results were obtained for the primary analysis of UPDRS Parts II and III:

Part II (ADL)

	Change From Baseline	P-value
Pramipexole (N=163)	-1.9	
Placebo (N=170)	+0.4	<0.0001

Similar P-values were obtained for between treatment differences at weeks 0, 4, 8, 12, and 16 (week 0 is the end of titration). The magnitude of the between treatment differences seen at these times was approximately the same as is displayed. Likewise, an analysis of an Area Under the Curve (AUC) analysis for the entire Maintenance Phase yielded values of -57 and -5 for pramipexole and placebo, respectively, with a corresponding p-value of <0.0001. Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 22.

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Part III (Motor Score)

	Change From Baseline	P-value
Pramipexole	- 5	
Placebo	+0.8	<0.0001

Again, similar p-values were obtained at each assessment week during the Maintenance Phase, including at the end of titration, although the magnitude of the between treatment differences were slightly less than for the LOCF analysis displayed above. Further, an AUC analysis yielded values of -127 and -11 for pramipexole and placebo, respectively, a difference that was highly significant ($P < 0.0001$). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review on page 25.

As Dr. Hoberman notes in his review (page 3), on average, the patients the LOCF change from baseline for patients discontinuing pramipexole was better than that of dropouts from placebo. Finally, a time to failure analysis yielded a p-value (logrank test) of 0.0015 in favor of pramipexole.

Study 4

This was a multi-center, randomized, double-blind, parallel group study in which patients with idiopathic PD (Hoehn and Yahr I-III) were randomized to one of 3 fixed doses of pramipexole or placebo. Patients were not permitted to have received l-dopa within 3 months prior to the study.

Patients were titrated to their fixed dose over a maximum of 6 weeks. The maximum doses to be achieved were either 0.5 mg TID (1.5 mg/day), 1.5 mg TID (total daily dose of 4.5 mg), 2.0 mg TID (6.0 mg/day), or placebo. Patients not tolerating a given dose could be dropped back to their previous dose, and were not to receive higher doses. After the dose titration, patients entered a 4 week Maintenance Phase, followed by a 1 week Dose Reduction Phase.

Patients were seen every 2 weeks after randomization, at which time the

UPDRS, Parts I-III were assessed. At the final visit, Hoehn and Yahr staging was performed and several quality of life questionnaires were administered.

The primary outcome in this study was change from baseline of the sum of UPDRS Parts I-III. Analyses examining the dose to which patients were randomized as well as the dose actually received were planned.

RESULTS

A total of 264 patients were randomized at 20 centers in the U.S. and Canada. The following table displays the disposition of patients:

	Pr 1.5	Pr 3.0	Pr 4.5	Pr 6.0	Pbo
Randomized	54	50	54	55	51
Completed	44	48	50	46	50

The following table displays the results of analyses of the primary outcome for the doses to which patients were randomized.

	Pr 1.5	Pr 3.0	Pr 4.5	Pr 6.0	Pbo
Baseline	28.5	28.3	27.3	32.9	28.7
Mean Change	-6.1	-5.8	-6.6	-7.1	-1.2

All individual dose-placebo pairwise contrasts yielded p-values of <0.006 , (significant in the face of Bonferroni correction) with an overall p-value of 0.0022. Similar changes were seen when the results were analyzed according to the dose actually achieved (in this latter analysis, it is not clear in which group patients not achieving the dose to which they were randomized were counted, although it is true that most of the steps in the titration algorithms would yield one of the 4 "goal" doses).

The sponsor acknowledges that there was no dose response seen, although with placebo included in a regression analysis, a linear dose response was seen (P-value 0.03) for the analysis in which patients were counted in the

group to which they were randomized.

Although between treatment differences of about 1.5 were seen for the individual dose-placebo contrasts for UPDRS Part II (Motor Scale), the overall p-value was 0.06, while the overall p-value for Part III (ADL) was 0.005.

In general, results of the Quality of Life questionnaires did not achieve statistical significance.

Study 17

This was a single blind, randomized, placebo controlled, parallel group trial in PD patients who had not received l-dopa within 3 months. A total of 48 patients were to be enrolled. The trial had a 7 week titration phase, with a maximum dose of 4.5 mg/day. Following titration, there was a 3 week Maintenance Phase, followed by a 1 week dose reduction phase. The primary outcome was mean change from baseline on Parts II and III of the UPDRS.

RESULTS

A total of 56 patients were randomized, with 55 included in the ITT population analyzed. Analysis of observed cases performed by the sponsor yielded a p-value of 0.002 for the pramipexole (N=28)-placebo (N=24) contrast for UPDRS Part II, and a p-value of 0.10 for the between treatment contrast for UPDRS III.

Study 21

This was a double-blind, placebo controlled, randomized, parallel group study of patients with PD who had received no more than 1 week of l-dopa in the past. Patients were to be titrated to a maximally tolerated dose, up to 4.5 mg/day; the titration phase was to last a maximum of 9 weeks, after which they were to enter a 2 week maintenance phase, followed by a 1 week dose reduction phase. A total of 72 patients were to be randomized, to yield 52 completers.

The primary outcome was to be change from baseline in UPDRS, Part III.

RESULTS

Only 24 patients were enrolled. The sponsor performed an analysis excluding 2 of these patients, which they assert yielded a p-value of 0.02.

LATE PD

Study 10

This was a multi-center, randomized, parallel group, placebo controlled trial in which patients with idiopathic PD (Hoehn and Yahr Stages II-IV) who are not adequately controlled on maximally tolerated l-dopa (as well as other anti-PD medications) were randomized to receive adjunctive pramipexole or placebo.

Patients initially entered a titration phase, beginning with a dose of 0.25 mg TID (total daily dose of 0.375 mg) to be followed by weekly dosing increments to a maximum dose of 1.5 mg TID (to be achieved in 7 weeks) or to a lower maximally tolerated dose.

After titration, patients entered a 6 month maintenance phase, and then a 1 week dose reduction phase. During this maintenance phase, the dose of l-dopa could be reduced for control of dopaminergic adverse events. The l-dopa dose could then be increased, but was not to exceed the baseline dose. Other anti-PD medications were to be held constant during the study.

At monthly intervals, patients were assessed with the following measures:

- 1) UPDRS; the Motor Score was to be assessed during an "on" period.
- 2) Modified Schwab-England Disability Scale; this is an ADL scale.
- 3) Timed Walking Test
- 4) Hoehn and Yahr
- 5) Parkinson's Dyskinesia Scale

Patients were instructed to record a daily diary for at least 2 full days prior to clinic visits. On this diary, patients were to record the total time awake, as well as the total time spent "off", and the severity of the "off" periods (1-4 scale). Part II of the UPDRS, as well as the Schwab-England and Hoehn and Yahr Scales were to be rated for both "on" and "off" periods.

The primary outcomes were to be change from baseline in Parts II and III. The protocol specified that both outcomes would have to reach significance independently in order for the trial to be considered "positive".

A total of 300 patients were to be enrolled at 24 U.S. and Canadian centers.

RESULTS

A total of 360 patients (pramipexole 181, placebo 179) were enrolled at 26 U.S. and Canadian centers. A total of 351 patients (pramipexole 179, placebo 172) were included in the ITT population.

A total of 30/181 (16.6%) of pramipexole patients and 39/179 (22%) of placebo patients discontinued treatment prior to completing the trial.

The following table presents the results for the protocol specified primary outcomes:

Change From Baseline in UPDRS Part II

	LOCF Change	LOCF AUC for Maintenance
Pramipexole (N=179)	-2.7	-57
Placebo (N=171)	-0.5	-18
P-value	<0.0001	<0.0001

Statistically significant differences were seen for the between treatment change from baseline in Part II at all visits during the Maintenance Phase starting at visit 5. (Scores for Part II are averages of scores for "on" and

“off” times). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney’s review, page 90.

Change From Baseline in UPDRS Part III

	LOCF Change	LOCF AUC for Maintenance
Pramipexole (N=179)	-5.6	-114
Placebo (N=171)	-2.8	-64
P-value	0.01	0.01

A total of 7/12 between treatment differences were significant during the Maintenance phase (see Dr. Hoberman’s review, Figure 2). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney’s review, page 95.

As Dr. Hoberman notes, the consistency of the results over time suggest that there was little effect of dropouts on the LOCF analysis.

Dr. Feeney suggests in his review that Percent of Awake Time Spent “off” is a useful measure of effectiveness (this was a protocol specified secondary outcome) because, among other reasons, UPDRS Part II was to be an average of scores during “on” and “off” times, but did not take into account time spent in either of these states (theoretically, scores could have improved, but a patient might have spent more time “off”, a clearly undesirable outcome). In addition, Part III was to be assessed during an “on” period, also thereby not taking into account a potential increase in “off” time. Finally, he notes that Parts II and III appear to be independent, whereas total “off” time is, in his view, a more global measure of effectiveness.

The following table displays the results for Average Percent of Awake time spent “Off”:

	Baseline	Final	Change	P-value
Pramipexole (N=173)	37.2	24	-13	
Placebo (N=172)	38.3	35	-3	0.0006

The difference between treatments emerged by visit 4, increased until visit 6, then remained essentially constant throughout the Maintenance phase (see Dr. Hoberman's review, Figure 5).

Little difference was seen on the Schwab-England ADL scale or the Hoehn and Yahr scale.

The pramipexole group was able to tolerate a decrease in l-dopa dose of about 25% compared to a 6% reduction in the placebo groups ($P < 0.0001$).

Study 19

This was a 7 center randomized, double blind, placebo controlled, parallel group trial in patients with poorly controlled PD (Hoehn and Yahr II-IV) being treated concomitantly with l-dopa at a maximally tolerated dose. Patients were titrated over a maximum of 7 weeks to a maximum daily dose of 5 mg (presumably 1.25 mg QID), after which they entered a 4 week maintenance phase and then a 1 week dose discontinuation phase.

The primary outcome was change from baseline in total UPDRS score.

RESULTS

A total of 78 (pramipexole 34, placebo 44) were treated. According to the sponsor, the following results for the primary measure were obtained:

	Baseline UPDRS	Final UPDRS	P-value
Pramipexole	53.7	33.6	
Placebo	50.2	44.4	0.0002

Study 22

This trial was essentially identical to Study 19. It was performed at 9 centers in Denmark.

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RESULTS

A total of 69 patients (pramipexole 36, placebo 33) were enrolled. According to the sponsor, the following results were obtained:

	Baseline UPDRS	Final UPDRS	P-value
Pramipexole	51.9	35.0	
Placebo	56.7	47.7	0.018

Study 18

This was a single blind, placebo controlled, parallel group, randomized trial in patients with motor fluctuations on maximally tolerated l-dopa. A total of 48 patients were to be enrolled.

Patients were entered into a 7 week titration phase designed to reach a maximum dose of 4.5 mg/day. Following the titration phase, patients entered a 3 week maintenance phase, followed by a 1 week dose reduction phase.

The primary outcome was Mean Change from Baseline on UPDRS, Part II, and percentage of "off" time; both were to be significant independently in order for the study to be considered to demonstrate effectiveness.

RESULTS

A total of 50 patients (pramipexole 26, placebo 24) were enrolled at 6 U.S. Centers.

According to the sponsor, there were no significant between treatment differences seen in the change from baseline on Part II when examined during "on" and "off" times individually, nor were there significant between treatment differences on the percent of "off" time.

Study 20

This was to be randomized, s=double blind, parallel group, placebo

controlled trial of advanced PD patients. However, only 19 patients were enrolled, and the trial was not analyzable.

SAFETY

A total of 879 unique patients have been exposed to pramipexole in completed Phase 2/3 controlled trials. Of this total, 702 have been patients with Parkinson's Disease (416 have been patients not receiving concomitant l-dopa [early PD] and 286 were receiving concomitant l-dopa [late PD]); the remaining 177 have been patients with schizophrenia. An additional 260 subjects have been enrolled in Phase 1 trials, resulting in a total of 1139 patients/subjects enrolled in completed trials. However, the NDA contains reports of experience in a total of 1408 patients in Phase 2/3 trials and 253 Phase 1 subjects exposed to pramipexole, including those enrolled in extension trials at the time of the NDA cut-off date (1/95). Of these 1408 patients, 1231 were patients with PD.

Of the 1231 PD patients, 178 have been exposed for greater than 1 year (59 for greater than 2 years), and 365 have been exposed for between 6 months and 1 year. A total of 552/1231 (45%) of PD patients have received the maximum proposed dose of 4.5 mg/day for at least 12 weeks, and 981/1231 (80%) have received at least 1 day of this maximum dose. Of the 702 PD patients in controlled trials, 349 (50%) received an average dose of between mg/day. Of this group, 207 received this average dose for between weeks (this included extension trials).

DEATHS

A total of 17 deaths had occurred in the course of pramipexole's development as of 1/95; of these 17, 15 deaths (or the event leading to death) occurred within 30 days of the last dose of study drug. A total of 12 of the deaths occurred in pramipexole treated patients. In the controlled trials, the following comparisons are made:

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	Deaths	Rate/100 patient-years	Relative Risk
Early patients			
Pramipexole (N=416)	1	0.72	0.80
Placebo (N=262)	1	0.90	
Late Patients			
Pramipexole (N=286)	3	2.52	2.87
Placebo (N=289)	1	0.88	

For the entire pramipexole treated PD population, the early patients mortality dropped to 0.11 deaths/100 patient years, while the late patients mortality dropped to 1.83 deaths/100 patient years.

Of the pramipexole deaths, the reviewers considered 8 to be potentially cardiovascular in nature.

Of these 8, there were several documented or presumed MI or heart failures, mostly in patients with past history of severe cardiac disease. One patient had no history of cardiac disease, but had an MI during Study 10 (late PD), presumably sometime towards the middle to late portion of the Maintenance Phase. He died shortly thereafter.

Another patient with no real cardiac history died on day 61 of study 1 (early PD) from a presumed pulmonary embolus. A third patient with a past history of mild cardiac insufficiency and bronchitis suffered multiple episodes of dyspnea and syncope. He died after an episode of syncope, but no autopsy was performed.

DISCONTINUATIONS

Early PD

In controlled trials of early PD patients, the total dropout rate in

pramipexole patients was 14.4%, compared to 16.2% in placebo patients. The rate of dropouts secondary to adverse events was 12% for pramipexole patients, compared to 11% for placebo patients. The rates of discontinuations were variable in these studies, with the largest difference between drug and placebo occurring in Study 4; 12% and 2%, respectively. Most of these dropouts occurred secondary to adverse events at the highest dose (6 mg/day). The most common adverse events associated with discontinuation that were greater than 1% and also greater than the placebo rate were: hallucinations (3%), dizziness, nausea (2%), somnolence (1.55%), headache (1.3%), and confusion (1%).

Of the discontinuations due to adverse events, 8/388 (2.1%) of the pramipexole and 3/235 (1.3%) of the placebo patients had events considered serious. Of the 8 pramipexole patients, 1 died secondary to a cardiovascular event, and the remaining 7 included 1 case each of drowsiness, decreased platelets, abdominal pain, somnolence, paranoid psychosis, sensory hallucinations, and confusion/hallucination.

Late PD

In controlled trials in late PD patients, the overall discontinuation rate was 15.4% in pramipexole patients and 20.4% in placebo patients. In these studies, the dropout rate due to adverse events was 11.5% for pramipexole patients and 15.8% for placebo patients. The most common adverse events associated with discontinuation that were greater than 1% and also greater than the placebo rate were: hallucinations (2.7%), postural hypotension (2.3%), dyskinesia (1.9%), confusion, dizziness (1.2%).

Of the discontinuations due to adverse events, 8/259 (3.1%) of the pramipexole and 6/266 (2.3%) of the placebo patients had adverse events considered serious. Of these 8 pramipexole patients, 2 had cardiovascular events and died.

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Other Serious Adverse Events in Controlled Trials

Early PD

Of the 388 pramipexole treated patients in controlled trials, 20 (5%) had adverse events deemed serious, while 5.5% of placebo patients had such events. Of the 20 serious adverse events in the pramipexole patients, 7 were cardiovascular. One of these was discussed in the section on Deaths, and the other 6 were 2 MIs, 2 angina, and 1 case each of pulmonary embolism, and LV dysfunction.

Of the remaining 13, 7 have been discussed in the section on serious adverse events leading to discontinuation; the other 6 consisted of 2 cases of prostate cancer, and 1 case each of fractured hip, thyroid nodule, basal cell carcinoma, and rectal cancer.

Late PD

Of the 259 pramipexole treated patients in controlled trials, 18 (7%) had serious adverse events, compared to 7.5% of the placebo patients. Of the 18 serious adverse events in pramipexole patients, 3 were cardiovascular; 2 resulted in death, and one had angina. The other 15 consisted of the following: pneumonia, dyskinesia, fractures, somnolence, bladder cancer, paranoia, nausea, neck pain, CPK elevation, increase of periods, back pain, abdominal pain, confusion, and multiple myeloma.

Other serious events

It is difficult to tell from the documents available what the incidence of serious adverse events is in the entire PD database. However, Drs. Balian and Knudsen have highlighted several of the events as being worthy of note.

Cardiovascular

A 72 year old man experienced severe orthostatic hypotension after a single 0.125 mg dose of pramipexole. He was on multiple medications

(including treatment for prostatic CA). One hour after the dose, his supine BP was _____, but on standing his BP was essentially 0. He could not stand for about 3.5 hours after dosing. Apparently, his EKG was normal (time after dosing unknown to me).

Hematologic

A 72 year old man receiving pramipexole 4.5 mg/day (as well as nifedipine for about 260 days) was documented to have a platelet count of _____ mm³ after 40 days of treatment (baseline count was _____). Three days later the platelet count was _____. On day 47, pramipexole was discontinued; at the time, the count was _____. A bone marrow aspiration was not consistent with marrow suppression, and no further information is available.

Respiratory

A 77 year old man with a history of cardiac disease and LV dysfunction experienced dyspnea on day 32 of treatment with pramipexole (at the time his dose was 3 mg/day). Four days later, at a dose of 4.5 mg/day, he was hospitalized for dyspnea and was determined to have LV dysfunction and pulmonary congestion. His treatment was discontinued and underwent cardiac bypass surgery shortly thereafter.

Laboratory abnormalities

A 49 year old man experienced a marked increase in CPK (about _____) after 1 month of treatment. Medication was discontinued, and CPK began to decrease. The patient was admitted to the hospital and treated for rhabdomyolysis.

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Other Adverse Events

Early PD

The following adverse events were seen in at least 5% of the 388 pramipexole treated patients in controlled trials and at least twice as frequently as in the placebo patients:

Somnolence-22%

Constipation-14%

Hallucination-9%

Other adverse events seen at a greater incidence than placebo included confusion, anorexia, amnesia, hypesthesia, vision abnormality, dysphagia, weight loss, akathisia, thinking abnormal, decreased libido, myoclonus, and fever.

Late PD

The following adverse events were seen in at least 5% of 260 pramipexole treated patients in controlled trials and at least twice as frequently as in the placebo patients:

Hallucination-16.5%

Dry Mouth-6.5%

Urinary Frequency-5.8%

Other adverse events seen at a greater incidence than placebo included dyskinesia (47% compared to a placebo rate of 32%), chest pain, vision abnormality, rhinitis, twitching, peripheral edema, pneumonia, paranoid reaction, bursitis, CPK increase, myasthenia, delusions, sleep disorder, and diplopia.

Dose Response

Only Study 4 (early PD) was designed as a fixed dose study. In this study, nausea, and somnolence and insomnia were seen to be dose related. In both early and late controlled trials, the greatest risk for several adverse events was observed in the titration phases.

Abnormal Lab Values

In general, pramipexole produced no systematic abnormalities in routine laboratory tests.

However, in the combined controlled trial database (Studies 1, 4, and 10), 19 (3.5%) of the pramipexole treated patients and 9 (2.3%) of the placebo patients had CPK levels exceeding normal limits; this difference was not statistically significant. The number of patients with significant elevations is unclear, although it appears to be a relatively small proportion of the 19.

In other controlled trials, 2/76 (2.6%) of pramipexole treated patients experienced elevated CPK levels, compared to 0/83 (0%) of placebo patients. One of the patients had a CPK at day 48 of IU/L, resulting in discontinuation of treatment. CPK returned to normal after drug discontinuation.

There was one case diagnosed as rhabdomyolysis; this case has been discussed.

LFTs

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In the 3 controlled trials (Studies 1, 4, and 10), a total of 15/553 (2.7%) of pramipexole patients experienced elevations of LFTs (ALT, AST, and/or GGT) greater than 2.5 X ULN. A total of 5/394 (1.3%) of placebo patients had similar elevations. Most of the elevations in the pramipexole patients occurred in Study 10, in which there were 10 such patients (5.7%), compared to 2 (1.2%) placebo patients.

Of the 15 pramipexole treated patients with elevations, 8 had elevations of GGT only; 7 of these 8 had elevations of GGT prior to treatment with pramipexole. Of these 7, 3 had baseline elevations at least 2.5 X ULN; of the remaining 4 with baseline elevations, most had elevations close to X ULN, and the elevations noted on treatment for most of the 7 with baseline elevations were similar in degree to the pre-treatment elevations.

Most of the other LFT elevations were relatively mild (in most of these patients, the maximum value of either AST or ALT obtained was in the range of 1 patient had one ALT of . It is difficult to tell, from the reviews, the ultimate disposition of these patients. However, it appears that, for many of these patients, the elevations either stabilized or returned towards normal with continued treatment (for several other cases, alternative explanations for the elevations were available).

One patient (a 67 year old man) in Study 10 experienced a GGT of U/L (U/L) on day 50 of treatment; this was associated with an ALT of . Treatment was discontinued and LFTs returned to normal within 30 days. Throughout, his bilirubin was normal.

Orthostatic Hypotension/Syncope

In animal studies, pramipexole lowers blood pressure and pulse, presumably related to its D2 and alpha₂ agonism.

In Phase 1 studies, pramipexole was seen to cause dose related orthostatic hypotension, first seen after single doses of 0.2 mg. In some subjects, syncope occurred upon standing. In controlled trials in early PD patients, there were 5 episodes of syncope in pramipexole patients (1.3%), and 2 such episodes in placebo patients (1.0%).

In controlled trials of late PD patients, there were 4 episodes of syncope in pramipexole patients (2.2%), and 7 in placebo patients (3.4%).

In neither population was there a significant difference between drug and placebo patients in the rate of discontinuations for serious or non-serious adverse events.

Regarding orthostatic hypotension, this was reported at a frequency of 7.7% in early PD patients compared to 8.9% in early placebo patients. In late PD patients, 53% of pramipexole and 48% of placebo patients were reported to have experienced at least 1 episode of orthostatic hypotension. Few of these episodes were symptomatic, and a total of 7 pramipexole and 3 placebo patients discontinued from controlled trials

(combined early and late patients) because of orthostatic hypotension.

SUMMARY

The 3 randomized controlled trials (Studies 1, 4, and 10) described in this memo clearly demonstrate the effectiveness of pramipexole as a symptomatic treatment for patients with Parkinson's Disease. This conclusion applies to patients with relatively mild disease not receiving concomitant dopaminergic therapy, as well as to patients with more advanced disease who are receiving concomitant l-dopa.

The safety experience contained in the NDA provides no signal that pramipexole will be unacceptably dangerous when used according to appropriate labelling, although the safety database is not as large as we might hope. For example, we know that 552 patients have received this dose for at least 12 weeks, but we do not know how many have received this dose for longer durations. It would be useful for the sponsor to explicitly display the number of patients who received 4.5 mg/day for specific durations.

The panoply of adverse events seen are typical for D2 agonists, and there is some reassurance that the incidence of syncope/orthostatic hypotension appears not to have been greater than that seen in placebo patients in the controlled trials (again, given the limitations imposed by the relatively small number of patients in controlled trials). It is of some note that the mortality (deaths/100 patient years) in the late PD patients was 2.52 in pramipexole patients compared to 0.88 in placebo patients (relative risk of 2.9). However, this represents, in reality, 3 deaths in the drug treated group compared to 1 death in a placebo patient, with 95% CIs of (0.3, 27). Examination of the causes of death did not reveal any obvious, specific pramipexole relationship.

**APPEARS THIS WAY
ON ORIGINAL**

RECOMMENDATIONS

For the reasons stated above, I recommend that the attached Approvable letter be sent to the sponsor.

/S/

**APPEARS THIS WAY
ON ORIGINAL**

Russell Katz, M.D.

Cc:
NDA 20-667
HFD-120
HFD-120/Leber/Katz/Feeney/Sherry
HFD-120/Burkhart/Balian/Knudsen/Griffey
HFD-710/Hoberman

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

CHEMISTRY REVIEW(S)

AUG - 5 1996

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,667

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENTS:	15-MAY-96	20-MAY-96	22-MAY-96	15-JUL-96
	26-JUN-96	28-JUN-96	12-JUL-96	15-JUL-96

CHEMIST REVIEW: # 1 SPONSOR: PHARMACIA & UPJOHN

REVIEW CHEMIST: M.Zarifa, Ph.D ADDRESS: 7000 Portage Road
Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

Proprietary: To be established
USAN: NA
INN: PRAMIPEXOLE
Code Name/Number: SND 919 CL 2 Y; U-98528E

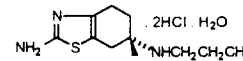
DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg, 1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:



Mol. Wt. 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: The n.d.s. is freely soluble in water.

The bulk drug is stable but the tablets are susceptible to photo degradation and have to be protected from light. In general, the CMC information is adequate except for specific information that appears to be missing/unclear and needs to be provided or clarified.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVABLE CONTINGENT UPON RECEIPT AND REVIEW OF REQUESTED INFORMATION. INSPECTION OF THE FACILITIES WAS DONE AND AN ACCEPTABLE RECOMMENDATION FROM COMPLIANCE WAS RECEIVED (SEE ATTACHED EER). AN EXPIRY DATE OF 18-MONTHS APPEARS REASONABLE AT THE PRESENT TIME.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/JPurvis
HFD-120/SBlum/MZarifa
HFD-810/CHoiberg (cover page, def.list only)
INIT:

APPEARS THIS ...
ON ORIGINAL

/S/

Mona Zarifa, Ph.D., Chemist

filename: N020667.000

/S/ 8/2/96

/ name = MIRAPEX

APPEARS THIS ...
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,667

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENT:	06-SEP-96	09-SEP-96	11-SEP-96	16-SEP-96

CHEMIST REVIEW: # 2

SPONSOR: PHARMACIA & UPJOHN

OCT 15 1996

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 7000 Portage Road
Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

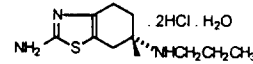
Proprietary: MIRAPEX
USAN: NA
INN: PRAMIPEXOLE
Code Name/Number: SND 919 CL 2 Y; U-98528E

DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg, 1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:

$H_{21}Cl_2N_3OS$ Mol. Wt. 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: In this amendment the sponsor responds to the CMC deficiencies telefaxed to them on August 12, 1996. All missing/unclear information is now provided/ clarified or will follow as requested (see Telecon. Report 9/13/96). Updated 18-month stability data are provided.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVED CONTINGENT UPON RECEIPT OF THE AGREED UPON REQUESTED INFORMATION. INSPECTION OF THE FACILITIES WAS DONE AND AN ACCEPTABLE RECOMMENDATION FROM COMPLIANCE WAS RECEIVED (SEE CMC REVIEW 1). THE REQUESTED EXPIRY DATE OF 24 MONTHS IS NOW ACCEPTABLE.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/JPurvis
HFD-120/SBlum/MZarifa
HFD-810/CHoiberg (cover page, def.table only)
INIT:

APPEARS THIS WAY
ON ORIGINAL

/S/

Mona Zarifa, Ph.D., Chemist

filename: N020667.001

/S/ 10/11/96

APPEARS THIS WAY
ON ORIGINAL

OCT 11 6 1996

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
 REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,667

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENT:	07-OCT-96	08-OCT-96	11-OCT-96	11-OCT-96

CHEMIST REVIEW: # 3 SPONSOR: PHARMACIA & UPJOHN

REVIEW CHEMIST: M.Zarifa, Ph.D ADDRESS: 7000 Portage Road
 Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

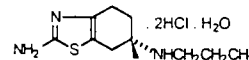
Proprietary: MIRAPEX
 USAN: NA
 INN: PRAMIPEXOLE
 Code Name/Number: SND 919 CL 2 Y; U-98528E

DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg, 1-mg, 1.25-mg, and 1.5-mg
 compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{10}H_{21}Cl_2N_3OS$ Mol. Wt. 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: In this amendment the firm provides the information agreed upon in the Telecon dated 9/13/96.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-667 FOR PRAMIPEXOLE
 TABLETS IS APPROVED as was recommended in CMC Review #2.

cc: ORIG: NDA
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 HFD-120/JPurvis
 HFD-120/SBlum/MZarifa
 HFD-810/CHOibera (cover page, def.table only)
 INIT:

APPEARS THIS WAY
 ON ORIGINAL

/S/

Mona Zarifa, Ph.D., Chemist

filename: N020667.002

/S/
10/11/96

APPEARS THIS WAY
 ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TRADE NAME NOT GIVEN

(Pramipexole) USAN, INN

COMPRESSED TABLET 0.125, 0.25, 1.0, 1.25,
1.5 mg

NDA 20-667

THE UPJOHN COMPANY

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL DRUG
PRODUCTS

(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-667

TRADE NAME NOT GIVEN

(Pramipexole) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Pramipexole, The UpJohn Company prepared an environmental assessment (attached) in accordance with 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Pramipexole is a chemically synthesized drug which is administered as a tablet in the treatment of Parkinson's disease. The drug substance will be manufactured by Boehringer Ingelheim KG, Ingelheim am Rhein, Germany. The drug product will be manufactured by The UpJohn Company, Arecibo, Puerto Rico. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

Pramipexole may enter the environment from manufacturing sites, disposal of pharmaceutical waste, and from excretion from patients. Due to the relatively small projected use in this country, adverse environmental effects from distribution are not anticipated.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages

will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

RETURN

MAY 8 1996

/S/

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

5/6/96
Date

APPEARS THIS WAY
ON ORIGINAL

/S/

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

5/6/96
Date

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet for drug substance
included

APPEARS THIS WAY
ON ORIGINAL

Copies:

HFD-120

Jack Purvis
Original NDA 20-667
Division File for NDA 20-667#

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger 5/6/96

APPEARS THIS WAY
ON ORIGINAL

NON-CONFIDENTIAL

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

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Pramipexole Tablets NDA
Item 3. Chemistry, Manufacturing and Controls
Part V. Environmental Assessment Report - Revised

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APPEARS THIS WAY
ON ORIGINAL

Pramipexole Tablets NDA
Item 3. Chemistry, Manufacturing and Controls
Part V. Environmental Assessment Report - Revised

ENVIRONMENTAL ASSESSMENT REPORT (EA)

1. DATE

December 8, 1995
February 22, 1996 (revision)

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address and telephone number of The Upjohn Company are:

7000 Portage Road
Kalamazoo, Michigan 49001
Corporate telephone number: (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Requested Approval

This environmental assessment is submitted in compliance with 21CFR Part 25.31a to accompany the New Drug Application (NDA) #20-667 for pramipexole tablets.

4.b. Need for Action

This environmental assessment is required to accompany the NDA #20-667 for pramipexole tablets. Pramipexole tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The first-year patient population is estimated to be 9,600.

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

4.c. Production Locations

Drug Substance

The drug substance will be purchased by The Upjohn Company (Upjohn) from:

Boehringer Ingelheim KG
 D-55216 Ingelheim am Rhein
 Germany

Drug Product

The drug product will be formulated and packaged at The Upjohn Manufacturing Company (UMC) in Arecibo, Puerto Rico, located south of Puerto Rico Highway No. 2 Km 60.0 (see non-confidential Appendix 1). This facility is in the Barceloneta Industrial Complex which was promoted by the Puerto Rico Industrial Development Corporation (PRIDCO) to attract pharmaceutical and other industrial plants. At this time, there are at least ten industries located in this industrial area. Some of those nearby companies include _____ The nearest school is approximately three kilometers east of the project site, on PR Highway No. 2. Most of the land surrounding the site continues to be used for agricultural purposes with pineapples as the chief crop. The plant site occupies a portion of 94.3 hectares lying south of State Road PR-2 and 3 kilometers west of State Road PR-140 at Cruce Dávilla. About 13.8 hectares of the Upjohn land consist of karst formation [an area of irregular limestone in which erosion has produced fissures, sinkholes, underground streams, and caverns]. The remaining 80.5 hectares of the land that were formerly used for cultivation of sugar cane and for pasture are relatively flat in a tropical climate. The Upjohn Manufacturing Company consists of nine main buildings and some outside facilities and storage tanks.

4.d. Locations of Use

The ultimate use and disposal of the finished product will be mainly at residences, hospitals, and clinics, and nursing homes. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale.

4.e. Disposal Sites

Disposal of drug substance or drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end user disposal of individual units of empty or partly empty finished product containers.

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

The present infrastructure at the proposed manufacturing sites provides for the following recovery and/or ultimate disposal mechanisms:

- Off-Specification Lots

Off-specification lots or rejected goods will be disposed of by incineration at Chambers Medical Technologies (CMT) in Hampton, South Carolina. [CMT has the following permits granted by the South Carolina Department of Health: air permit #1280-0021.CG; NPDES permit No. SC0042242.]

- Returned Goods

Returned goods of the drug product received at Upjohn will be incinerated in an on-site incinerator (interim status treatment storage and disposal facility).

- *Incinerator.* The incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions, until final administrative disposition of the owner's and operator's permit application is made.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

A hazardous waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality, MDEQ) in Lansing, Michigan. The Upjohn facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1996. The State air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 451, Part 111 licensing requirements.

Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management, Trade Waste Incinerator Division, 7 Mobile Avenue, Sauget, IL, operating under EPA ID No. ILD 098 642 424 and Illinois Environmental Protection Agency No. IEPA 1631210009;
- Systech Environmental Corporation in Alpena, MI, operating under EPA ID No. MID981200835 and State Air Permit No. 587-93; or in Paulding, OH, operating under EPA ID No. OHD005048947 and State Air Permit Nos. 0363000002P016 and 0363000002P017;
- Continental Cement in Hannibal, MO, operating under EPA ID No. MOD054018288 and Air Permit No. 1086-004A;
- Upjohn may use other facilities for such disposal which are suitable for that purpose and properly permitted.

We have identified hazardous waste as well as air permits as given to us by these facilities, but there may be other permits and licenses applicable which are currently held by the facilities. While Upjohn has contracts with each of these facilities that require compliance with all applicable laws and regulations, Upjohn does not own, operate, or control these facilities. The waste stream profiles established with the hazardous waste landfill sites contain an affirmation by the facility of its compliance status. All facilities are audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site.

• Discarded Product in Hospital or Clinic Setting

Any discarded product or product containers generated in a hospital or clinic setting would typically be disposed in accordance with applicable Federal, State and local regulations.

APPEARS THIS WAY
 ON ORIGINAL

Pramipexole Tablets NDA
Item 3. Chemistry, Manufacturing and Controls
Part V. Environmental Assessment Report - Revised

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

• • Pharmaceutical Formulation

The material safety data sheet (MSDS) for the drug substance, pramipexole, is included as non-confidential Appendix 2.

The list of ingredients used in formulating the drug product, pramipexole tablets, is included as non-confidential Appendix 3.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and drug product are not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. Pramipexole is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

6.a. Substances Expected to be Emitted

Portions of the ingredients, as listed in non-confidential Appendix 3, may be released to the environment as a result of the proposed action.

Please refer to format item 6.b. for further specific disposal operations covering air, water, and solid waste streams.

Permits and other actions covering specific environmental regulations in force at UMC's chemical processing complex, including permit numbers and expiration dates where applicable, are summarized in the Permits Chart included as non-confidential Appendix 5 to include:

- Permit Description
- Regulatory Agency
- Permit No.
- Issue Date
- Expiration Date

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

See also The Upjohn Company's Permits Chart included as non-confidential Appendix 6 for an itemization of regulations and permits specific to the on-site approved incinerator.

6.b. Controls Exercised

• **Chemical Process**

See the letter dated 26 October 1995 from the Ministry for the Environment and Forestry (non-confidential Appendix 4) certifying Boehringer Ingelheim's (BI) manufacture in accordance with all German environmental laws and regulations.

• **Pharmaceutical Formulation**

• Air Emissions

Particulate emissions from the drug product are controlled through the use of the following equipment, with efficiencies at 99% by weight.

- dust collectors
- pre-filter system followed by HEPA filters for each dryer plus dust collector at the dryer room

This equipment is covered by the Puerto Rico Environmental Quality Board (EQB) under Temporary Air Operation Permit No. PFE-09-1194-1317-I-O [see Appendix 4 for a listing of permits/renewal status]

• Aqueous Waste Streams

Aqueous waste streams are generated from washes of process equipment at the pharmaceutical area. The equipment is washed with water and detergents [LC-30 or _____, alcohol 3A, or isopropyl alcohol _____]. These streams are discharged to the Puerto Rico Aqueduct & Sewer Authority (PRASA). [see Appendix 4 for a listing of permits/renewal status]

• Waste Solvents

The pramipexole tablets process does not generate waste solvents.

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

• **Solid Waste**

Residues from dust collectors and rags and towels used on cleaning of packaging lines and drying of small equipment parts are stored onsite at the container storage area (CSA) (permitted area for storage of hazardous, special, and nonhazardous wastes) prior to shipment to Chambers Medical Technologies (CMT) in Hampton, South Carolina. [CMT has the following permits granted by the South Carolina Department of Health: air permit #1280-0021-CG; NPDES permit No. SC0042242.]

6.c. Citation of and Statement of Compliance with Applicable Emission Requirements

The following regulations or standards are cited as applicable to the proposed action:

1. P.R. Public Law 9, The Environmental Public Policy Act of 1970, as amended (local regulation applicable to the Commonwealth of Puerto Rico):
 - Air Pollution Control Regulations
 - Water Quality Standards
 - Regulations for the Control of Hazardous and Non-Hazardous Wastes
 - Underground Injection Control Regulations
2. Puerto Rico Public Law #163 of May 3, 1949, as amended, The Puerto Rico Aqueduct and Sewer Authority, as amended.
3. P.R. Occupational Safety and Health Act of 1907, as amended (local regulation applicable to the Commonwealth of Puerto Rico).

• ***Emission Requirements.*** UMC states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the manufacture of the drug product, pramipexole tablets, at its facilities in Arecibo, Puerto Rico, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of the drug product, pramipexole tablets, at its facilities in Arecibo, Puerto Rico.

• ***OSHA Requirements.*** Upjohn certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.d. Discussion of the Effect of the Approval on Current Emissions

Approval of the proposed action will not result in the modification of the UMC Puerto Rico site existing facilities.

Pramipexole Tablets NDA
 Item 3. Chemistry, Manufacturing and Controls
 Part V. Environmental Assessment Report - Revised

Projecting to the fifth year of production, all discharges from the production of pramipexole tablets are permitted and will not affect compliance with current emission requirements. Waste water emission for this drug product will be of the permit limit.

6.e. Maximum Expected Environmental Concentration (MEEC)

Estimations of the theoretical maximum environmental concentration (MEEC) can be made using the following equation:

$$\begin{aligned} \text{MEEC (ppm)} &= \text{lbs/yr production} \times 8.9 \text{ E}^9 \\ &= (\text{A})(\text{B})(\text{C})(\text{D})(\text{E})(\text{F}) \end{aligned}$$

where:

A	=	pounds per year production
B	=	year/365 days
C	=	day person/150 gallons
D	=	1/264 million person US population
E	=	gallons/8.34
F	=	1 million

Utilizing the fifth-year production forecast of kg, the maximum environmental concentration that could be achieved is ppm. This concentration assumes complete and instantaneous release of the entire year's production, with no degradation.

These MEECs reflect the worst-case assumptions of instantaneous release and dispersion of the entire year's production with no allowance for biodegradation, hydrolysis, or other removal mechanisms.

CDER has routinely found that drugs at concentrations ppb have no significant effect on relevant standard test organisms and therefore are unlikely to have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, 11, and 15 will normally not be needed whose expected introduction concentration is less than 1 ppb.

Since the calculated MEEC for pramipexole is ppb, the format items mentioned above have not been included.

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In summary, based on worst-case analysis, pramipexole may reasonably be anticipated to be nontoxic according to the definition found at 21 CFR 25.15(b)(6).

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

9. USE OF RESOURCES AND ENERGY

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

10. MITIGATION MEASURES

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

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12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

Jeffrey S. Mehring Environmental Quality and Safety Division
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John S. Purvis Supervisory Project Manager
 Food and Drug Administration
 CDER
 Rockville, Maryland

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13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document (pages 1-12) and Appendices 1-7 (pages A 13 - A 25) contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6. Appendix 8 (page A 26) contains confidential information that is not to be made available to the public.

Randal S. Senger

Randal S. Senger, Manager
 Corporate Environmental Affairs
 (telephone 616/323-5341)

Feb 23, 1996

Date

Jeffrey S. Mehring

Jeffrey S. Mehring, Manager
 Environmental Health Sciences
 (telephone 616/323-4746)

22 FEB 96

Date

14. REFERENCES

- A. Aerobic Biodegradation of Pramipexole in Water. Final Report #41293.
- B. Aerobic Biodegradation of Pramipexole in Water. Draft Raw Data Package
- C. Aerobic Biodegradation of Pramipexole in Water. Final Raw Data Package #41293R.
- D. Aerobic Biodegradation of Pramipexole in Water. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, April 17, 1995.

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- E. Determination of Air-Water Henry's Law Constant with Pramipexole. Final Report #42872. December 7, 1995.
- F. Determination of Air-Water Henry's Law Constant with Pramipexole. Final Raw Data Package #42872R. December 7, 1995.
- G. Determination of Air-Water Henry's Law Constant with Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, December 11, 1995.
- H. Determination of the Aqueous Photodegradation of Pramipexole. Final Report #41592. September 15, 1995.
- I. Determination of the Aqueous Photodegradation of Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, September 28, 1995.
- J. Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, CMC 6, November 1995.
- K. Microbial Inhibition with Pramipexole. Final Report #41294. March 23, 1995.
- L. Microbial Growth Inhibition with Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, April 4, 1995.

15. APPENDICES

Non-Confidential

- 1 Map of UMC's Puerto Rico Pharmaceutical Manufacturing site complex
- 2 MSDS for the active ingredient, pramipexole
- 3 Pramipexole Tablets: List of Ingredients Used in Formulation
- 4 Certification letter covering BI manufacture: Ministry of the Environment and Forestry, Mainz, Germany
- 5 The Upjohn Manufacturing Company Permits Chart
- 6 The Upjohn Company Permits Chart
- 7 Chemical Summary

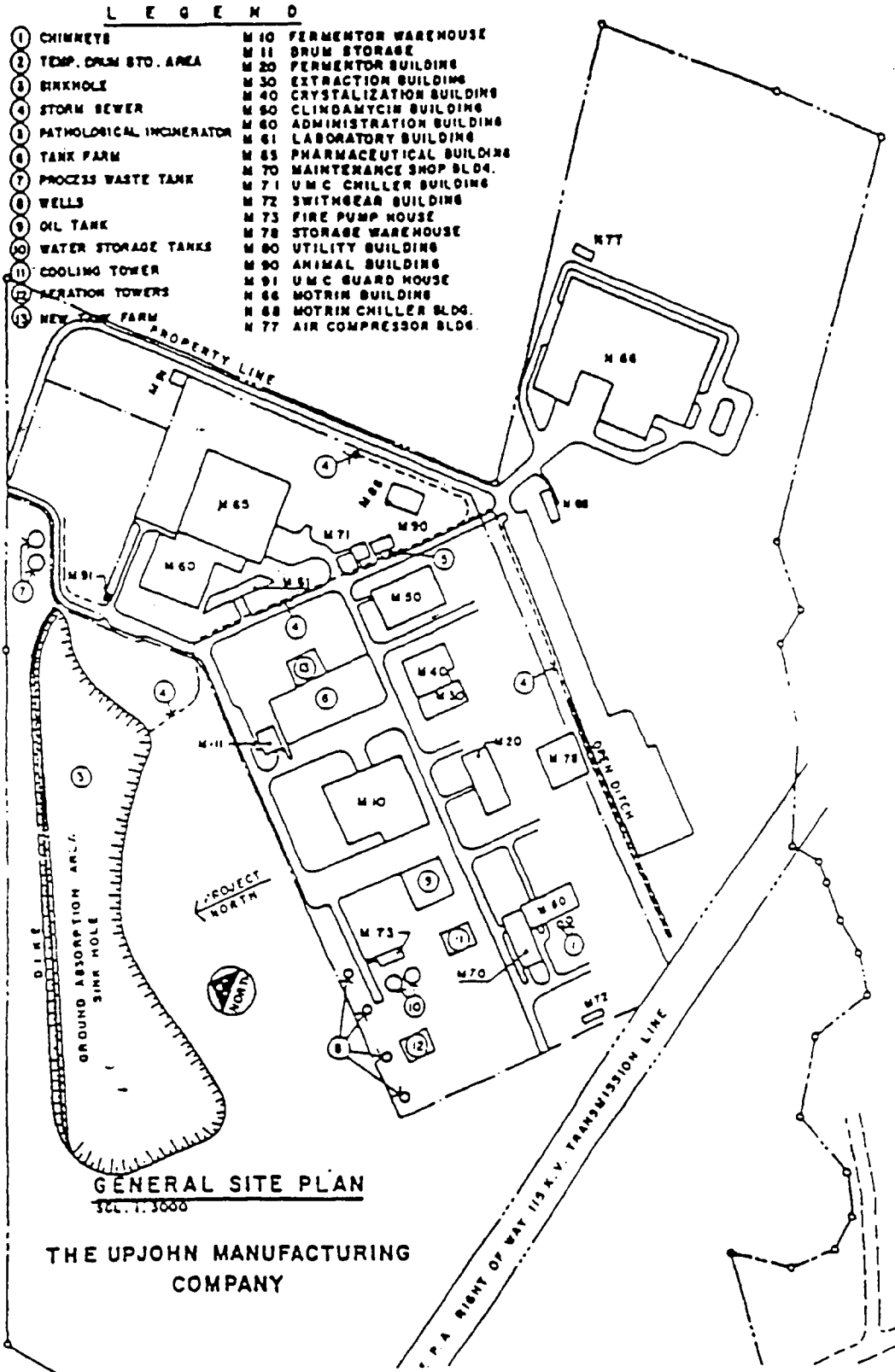
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- 8 Five-Year Marketing Figures

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APPENDIX 1

Map of UMC's Puerto Rico Pharmaceutical Manufacturing Site Complex



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APPENDIX 2

Material Safety Data Sheet
Pramipexole

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APPENDIX 2**

MATERIAL SAFETY DATA SHEET

Revision Date: November 21, 1995
Agent ID#: 54

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: PRAMIPEXOLE
SYNONYMS: 104632-26-0 - CAS NUMBER
(S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolodiamine
dihydrochloride monohydrate
U-98,528E - UPJOHN U#
MOLECULAR FORMULA: C10-H17-N3-S.2HCl.H2O
USE: Investigational drug for the treatment of Parkinson's disease.
MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN INC
7171 PORTAGE RD
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS: (616) 323-5122 - (24 HOURS)
(616) 323-7555 - (8:00 a.m. - 4:30 p.m.)
(616) 385-7358 - (SAMPLE REQUEST/TECHNICAL ASSISTANCE)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1

COMMON NAME: Pramipexole
CHEMICAL NAME: (S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolodiamine
dihydrochloride monohydrate
% BY WEIGHT: 100 %
CAS NUMBER: 104632-26-0
EXPOSURE LIMIT(S):
UPJOHN EXPOSURE LIMIT-TWA: 7 UG/M3

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation. As a hydrochloride, the substance is soluble in water, methanol and ethanol. The absorption from the gastrointestinal tract is

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very good. Absorption after inhalation of dusts and aerosols, after contact with the eyes and, under certain circumstances, absorption of solutions through the intact skin are to be expected. It is expected that as the free base, the compound will penetrate intact skin very easily; this can lead rapidly to high blood levels, especially after skin contact with solutions in hydrophobic solvents.

EFFECTS OF OVEREXPOSURE: Overexposure to this material may lower blood pressure (especially when standing upright; nausea, vomiting, weakness, headache, dizziness and reduced heart rates. Hallucinations and confusion is possible with exposure to high concentrations.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Hypotension.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.

SKIN: Wash with soap and water. Remove contaminated clothing.

INHALATION: Remove from exposure.

INGESTION: Call a physician.

ANTIDOTE: The antidote for pramipexole is metoclopramide {Reglan(R)}. It is diluted and administered as a continuous intravenous infusion.

NOTES TO PHYSICIAN: The compound exerts highly potent agonistic effects in special pharmacological models of pre- and postsynaptic dopamine D2 receptors. Depending on the animal species investigated and the dose administered, sedation or agitation, decrease in blood pressure, drop in heart rate, stereotypic behavior, vomiting and reduction in sleeping time were observed as general pharmacodynamic effects. In case of intoxication, the patient should not be placed in an upright position. If there is a severe drop in blood pressure, the shock recovery position (elevation of the legs) can be recommended. If the patient vomits, it must be ensured that the airways are kept free and vomit is not aspirated.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable (solid).

EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.

FIRE-FIGHTING PROCEDURES: Wear self-contained breathing apparatus and full body protective equipment.

UNUSUAL FIRE OR EXPLOSION HAZARDS: As with all finely divided organic powders, it is advisable to eliminate explosion hazards by methods such

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as grounding mechanical equipment in contact with the material to prevent the buildup of static electricity, inerting the atmosphere or controlling dust levels.

HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide. Carbon dioxide. Sulfur oxides. Nitrogen oxides. Acrid, flammable fumes may develop.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Remove ignition sources; control the generation of dust/vapors; provide ventilation and respiratory, skin and eye protection to prevent overexposure. Keep out of drains; prevent entry to surface water, groundwater and soil. Vacuum (with HEPA-filtered and explosion-proof equipment) or scoop spilled material and place in container.

7. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator or dust mask.

VENTILATION: Local exhaust at point of manufacture or use.

PROTECTIVE GLOVES: Rubber.

EYE PROTECTION: Safety glasses with side shields.

8. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: White, crystalline powder.

MELTING RANGE: 298 - 301 C (568 - 574 F) (with decomposition)

MOLECULAR WEIGHT: 302.27

SOLUBILITY IN WATER: > 10 % (at 20 C)

VAPOR PRESSURE: Negligible.

VOLATILITY: Negligible.

9. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:

SKIN IRRITATION (RABBIT): Non-irritating.

INTRAVENOUS TOXICITY: Single intravenous doses of 10 to 100 micrograms were well tolerated in normal, healthy individuals. Adverse effects were mild and included headache and fatigue. Hypotension and other adverse effects may occur at higher doses.

INTRAVENOUS LD50 (RAT): 210 MG/KG (approximate)

INTRAVENOUS LD50 (MOUSE): 155 MG/KG (males)

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IV LD50 for female mice is 188 mg/kg.

ORAL TOXICITY (HUMAN): In safety and tolerance studies in normal, healthy individuals, single oral doses up to 100 micrograms were well tolerated. Hypotension was observed at doses of 100 micrograms or above. The single oral maximum tolerated dose of 400 micrograms was established.

ORAL LD50 (RAT): 548 MG/KG (females)

Oral LD50 for male rats is > 800 mg/kg.

ORAL LD50 (MOUSE): 1,700 MG/KG (approximate)

OTHER STUDIES:

GENOTOXICITY: Negative in the Ames assay, Micronucleus test, Cell Transformation assay in SHE cells, and the Chromosome Aberration assay in CHO cells.

REPRODUCTION/FERTILITY: No treatment-related effects were observed in rats at oral dosages of 0.1 mg/kg. Decreased fertility and low birth weight were observed at higher oral dosages of 2.5 mg/kg.

TERATOGENICITY: Studies in rats and rabbits revealed no teratogenic effects.

10. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

11. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport Association (IATA). May be subject to state and/or local transportation requirements.

12. OTHER INFORMATION

REVIEWED BY: Environmental Health Sciences.

DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn, Inc. disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

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13. LABELING

UPJOHN PRECAUTIONARY LABEL CODE(S): P

HAZARD: POTENT MATERIAL.

SIGNAL WORD: DANGER!

STATEMENT OF HAZARD/RISK PHRASE: May cause immediate and serious adverse effects.

PRECAUTIONARY MEASURES: Do not get in eyes, on skin, on clothing. Avoid breathing dust, vapor, mist or gas. Keep container closed. Use with adequate ventilation. Wash thoroughly after handling.

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**Pramipexole Tablets NDA
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APPENDIX 3**

Pramipexole Tablets: Ingredients Used in the Formulation

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 APPENDIX 3**

Pramipexole Tablets: Ingredients Used in the Formulation

Name	CAS No.	M.W.	Formula	Appearance
Colloidal silicon dioxide	7631-86-9	60.09	SiO ₂	Fine white powder
Corn starch	9005-84-9	162.06	C ₁₆ H ₁₀ O ₅	White powder
Magnesium stearate	557-04-0	591.2	C ₃₆ H ₇₀ MgO ₄	Fine white powder
Mannitol	69-65-8	182.17	C ₈ H ₁₄ O ₆	White powder
Povidone	9003-39-8	N/A	(C ₆ H ₉ NO) _x	Off-white powder
Pramipexole	104632-26-0	302.27	C ₁₀ H ₂₁ Cl ₂ N ₃ OS	White crystalline powder

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pages of trade

secret and/or

confidential

commercial

information

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APPENDIX 5**

The Upjohn Manufacturing Company Permits Chart

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 APPENDIX 5

THE UPJOHN MANUFACTURING COMPANY PERMITS CHART

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Operating Permit	Puerto Rico Environmental Quality Board (EQB)	PFE-07-0391-0331-I-II-O	02/24/92	02/24/94 ¹
Temporary Air Operating Permit	EQB	PFE-09-0694-0731-I-O	6/20/94	12/31/95
Extension to Temporary Air Operating Permit	EQB	PFE-09-1195-1427-I-O	submitted to EQB 11/2/95	²
Underground Injection Control (Class VI)	Puerto Rico EQB	UIC 84-0253	10/20/92	10/19/97
Wastewater Discharge Permit	Puerto Rico Aqueduct & Sewer Authority (PRASA)	GDA-93-202-051	11/18/95	11/18/97
Well Water Extraction Franchise	Puerto Rico Department of Natural & Environmental Resources	RF-95-92	06/18/92	07/18/95 ²
Biomedical Waste Generator	Puerto Rico EQB	DBM-07-91-9-0028-R-95	9/19/95	11/20/97
RCRA Part B	U.S. EPA	PRD-090398074	12/26/91	12/26/96

¹Permit renewal application submitted on time; EQB sent letter extending permit until Title V permit is issued in 1995-1996.

²Permit renewal applications submitted on time; they remain in effect until acted upon.

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APPENDIX 6**

The Upjohn Company Permits Chart

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 APPENDIX 6

THE UPJOHN COMPANY PERMITS CHART

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Consent Judgment	Michigan Department of Natural Resources, Air Quality Division		03/15/91	08/01/96
Air Use Permit	MDNR, Air Quality Division	923-92	03/29/94	
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Natural Resources Michigan Water Resources Commission	MI0002941	09/20/90 reissued 12/1/95, effective 3/1/96	10/1/2000
RCRA/Michigan Hazardous Waste Management Act 451/Part 111 (On-site Incinerator)	Michigan Department of Natural Resources Waste Management Division	Incinerator operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 000820381 pending action on Act 451/ Part 111 permit application.		
Michigan Air Pollution Act 348 (On-site Incinerator)	Michigan Department of Natural Resources Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified

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PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

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APPENDIX 7**

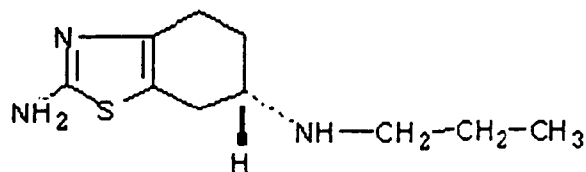
Chemical Summary

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APPENDIX 7

CHEMICAL SUMMARY

Structure



• 2 HCl

• H₂O

Chemical name	(S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazol dihydrochloride monohydrate
CAS Registry number	104632-26-0
Upjohn U-number	98528E
USAN approved generic name	Pramipexole
Empirical formula	C ₁₀ H ₂₁ Cl ₂ N ₃ OS
Molecular weight	302.27
Melting point	296-301 °C with decomposition
Appearance	white crystalline powder
Solubility, water (mg/mL)	> 20%

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

PHARMACOLOGY REVIEW(S)

Executive CAC
October 8, 1996

Committee members:

Joseph DeGeorge, Ph.D., Chair (HFD-024)
Joseph Contrera, Ph.D. (HFD-900)
Charles Resnick, Ph.D., Rotating member (HFD-110)
Glenna Fitzgerald, Ph.D., Team leader (HFD-120)
Sharon Olmstead, Exec Sec (HFD-006, non-voting member)

NDA 20-667 (Steele; HFD-120)
Pramipexole
Upjohn

Mouse Carcinogenicity Study:

The sponsor submitted carcinogenicity study results from a 2-year study in mice using 0.3, 2, and 10 mg/kg/day. The basis of the HD selection was made on the findings from the 13-week toxicity study in which 8 and 13 mg/kg/day produced significant reduction in body weight gain. In the 2-year study, a significant decrease in body weight gain was report in the MD and HD groups. No significant tumor findings were reported in the mouse. The sponsor provided full histology on all dose groups.

Committee Recommendations:

The committee concurred with the dose selection and study design of the carcinogenicity study in the mouse. The tumor findings were adequately addressed. In response to discussion on the effects of treatment on body weight, the committee recommended that if relative systemic exposure is provided in the labeling then all dose groups should be included in the description.

Rat Carcinogenicity Study:

The sponsor submitted carcinogenicity study results from a 2-year study in rats using 0.3, 2, and 8 mg/kg/day. The HD selection was based on the body weight gain decreases observed in the 13-week toxicity study using doses between 3 and 20 mg/kg/day. The severe body weight effects observed with the mouse were not seen in the rat. Significant findings using the trend test were reported in the males for Leydig cell adenomas by the company, but were reported as non-statistically significant but by the FDA statistician using $p < 0.005$ as the cut off for a common tumor.

Committee Recommendations:

The committee concurred with the dose selection and study design of the carcinogenicity study in the rat. The committee recommended that the tumor findings in the male rat be reanalyzed by FDA statistician using pairwise comparison. Specifically, a request should be made to OEB to conduct a pairwise comparison of Leydig cell tumors for each control separately. (The analysis indicated significance compared to one control but not the other.)

/S/

2/9/96

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ON ORIGINAL

Joseph DeGeorge, Ph.D.
Chair, CAC
Draft for comment Nov. 13

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT

FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

NDA: 20667 IND: DRUG CODE#: 10/8/96
CAS#: 104632-26-0 DATE: 10/8/96
DIVISION(s): HFD-120
DRUG NAME(s): Pramipexole; SND 919 CL2Y;
IUPAC: (S)-2-Amino-4,5,6,7-tetrahydro-6-propylaminobenzothiazole dihydrochloride monohydrate
CAS: (S)-N6-Propyl-4,5,6,7-tetrahydro-2,6-benzothiazolodiamine dihydrochloride, monohydrate
SPONSOR: Upjohn
LABORATORY: Boehringer-Ingelheim
P/T REVIEWER(s): Thomas Steele
P/T REVIEW DATE:
CARCINOGENICITY STUDY REPORT DATE: 5/5/94
THERAPEUTIC CATEGORY: Anti-Parkinson's Drug
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Dopamine antagonist

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): No

MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay):

Negative in Ames test, SHE cell transformation assay, V79 gene mutation assay, *in vivo* micronucleus test, and chromosomal aberrations in CHO cells. A potential impurity was weakly positive in the Ames test, but this compound has not appeared in any clinical batches to date.

RAT CARCINOGENICITY STUDY (multiple studies? Std1;Std2 etc.):

RAT STUDY DURATION (weeks): 104
STUDY STARTING DATE: 5/23/89
STUDY ENDING DATE: 6/20/91
RAT STRAIN: Wistar (Chbb:THOM)
ROUTE: oral, in diet
DOSING COMMENTS:

No. Rats in Control1 (C1):	50/sex	Control2 (C2):	50/sex
Low Dose (LD):	main: 50/sex;	TK:	5/sex
Middle Dose (MD):	main: 50/sex;	TK:	5/sex
High Dose (HD):	main: 50/sex;	TK:	5/sex

ADDITIONAL CONSIDERATIONS:

Effect on Mortality:

No significant relationship of drug treatment with mortality was identified by the sponsor or the Agency's statistical reviewer (Roswitha Kelly). Survival rates were 80-83% in the male rat groups, and 60-77% in the female rat groups (see attached tables).

**Table 1
INTERCURRENT MORTALITY RATES**

Weeks	MALE RATS mg/kg/day			
	0	0.3	2.0	8.0
0- 52	2/99 (2%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
53- 78	1/97 (3%)	0/50 (0%)	2/49 (6%)	1/49 (4%)
79- 92	6/96 (9%)	2/50 (4%)	1/47 (8%)	2/48 (8%)
93-107	8/90 (17%)	5/48 (14%)	2/46 (12%)	6/46 (20%)
Term. Sac.	82/99 (83%)	43/50 (86%)	44/50 (88%)	40/50 (80%)

Weeks	FEMALE RATS mg/kg/day			
	0	0.3	2.0	8.0
0- 52	3/100 (3%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
53- 78	7/97 (10%)	2/49 (6%)	0/50 (0%)	3/49 (8%)
79- 92	5/90 (15%)	5/47 (16%)	7/50 (14%)	1/46 (10%)
93-107	8/85 (23%)	12/42 (40%)	7/43 (28%)	6/45 (22%)
Term. Sac.	77/100 (77%)	30/50 (60%)	36/50 (72%)	39/50 (78%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

The slight impairment of body weight development in males should not have negatively impacted tumor formation. However, the marked impairment in females at both the intermediate and high doses interferes with the interpretation the data. In the 13-week study used for dose-range selection, a dose of 4 mg/kg pramipexole impaired body weight development in both males and females by approximately 30%. Thus, a marked effect of 8 mg/kg should not have been unexpected.

Exposure Data:

Plasma concentrations were determined in satellite groups during weeks 2, 50, and 100 at 2 and 8 hrs after the onset of the light phase. Estimates of t_{max} for orally administered pramipexole in rats was $\approx$ 1rs.

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Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study*

Sex	Dose (mg/kg)	Two Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	2.39	1.96	1.86	1.66	4.52	3.64
	2.0	14.86	16.08	19.30	19.54	22.66	18.80
	8.0	77.53	103.11	80.25	75.43	65.81	70.79
Male	0.3	1.71	1.60	2.12	2.13	3.18	2.85
	2.0	15.03	13.13	20.18	18.51	27.14	22.97
	8.0	77.20	78.44	93.21	70.11	140.66	133.95

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study*

Sex	Dose (mg/kg)	Eight Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	0.88	0.60	1.43	0.64	4.97	2.63
	2.0	3.73 (2.00-6.95)	7.09 (4.75-10.60)	6.73 (4.78-9.49)	5.93 (3.08-11.43)	26.10 (15.31-44.51)	19.50 (9.53-40.66)
	8.0	14.34	32.67	21.72	25.00	83.12	24.58
Male	0.3	0.34	0.75	0.96	1.03	1.51	1.38
	2.0	5.42	3.20	9.59	7.02	16.28	8.47
	8.0	24.59	25.23	57.09	47.30	65.52	47.17

MOUSE CARCINOGENICITY STUDY (multiple studies? Std1;Std2 etc.):

MOUSE STUDY DURATION (weeks): 105-106 weeks
STUDY STARTING DATE: 2/23/89
STUDY ENDING DATE: 1/3/91
MOUSE STRAIN: Chbb:NMRI
ROUTE: oral, in diet
DOSING COMMENTS:

No. Mice in Control1 (C1): 50 **Control2 (C2):** 50
Low Dose (LD): main: 50/sex; TK: 20/sex
Middle Dose (MD): main: 50/sex; TK: 16/sex
High Dose (HD): main: 50/sex; TK: 12/sex

MOUSE DOSE LEVELS (mg/kg/day):

Mouse LD: 0.3 mg/kg/day
Mouse MD: 2.0 "
Mouse HD: 10.0 "

Basis for Doses Selected (MTD; AUC ratio; saturation; maximum feasible):

The low dose was selected to correspond to times the expected human dose at the time the study was initiated. It was approximately 3 times the ED₅₀ for anti-parkinsonian activity in monkeys.

The high dose was selected on the basis of a 13-week study in which doses of 8 and 13 mg/kg markedly reduced body weight gain (by %).

Prior FDA Concurrence (Did/CAC)? (y/n;Date): none

MOUSE CARCINOGENICITY (negative; positive; MF; M; F):

Negative in both males and females.

MOUSE TUMOR FINDINGS:

None of the tumor findings exhibited a positive trend with dose according to analyses by the sponsor and by the Agency's statistical reviewer. Negative trends in tumor incidence were identified:

Neoplasm	Group/Incidence rate (%)				
	C1	C2	LD	MD	HD
malignant lymphoma (F)	46	42	32	22*	16*
adrenal cortical adenomas (M)	32	16	16	12	6*

Table 4

Results of Intercurrent Mortality Analyses

Male Mice

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C, L, M, H	pos	.067	.040*
C, L	pos	.012*	.011*
C, M	pos	.006**	.002**
C, H	pos	.011*	.005**
L, M	pos	.857	.507
L, H	neg	.882	.625
M, H	nrg	.982	.873

APPEARS THIS WAY
ON ORIGINAL

Female Mice

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C, L, M, H	pos	.253	.205
C, L	pos	.153	.077
C, M	pos	.768	.607
C, H	pos	.163	.084
L, M	neg	.445	.314
L, H	pos	.984	.999
M, H	pos	.470	.339

Effect on Body Weight Development:

APPEARS THIS WAY
ON ORIGINAL

MALES

Dose	wk -1	wk 74	diff.	% CON	wk 102	diff.	% CON
CON	29.4	48.1	18.8	-	45.5	16.1	-
0.3	29.4	48.3	18.9	100.6	46.3	16.9	104.6
2.0	29.4	41.7	12.3	65.7	39.0	9.6	59.7
10.0	29.1	38.7	9.6	51.1	38.8	9.8	60.6

FEMALES

Dose	wk -1	wk 74	diff.	% CON	wk 106	diff.	% CON
CON	24.1	38.9	14.8	-	37.6	13.5	-
0.3	26.0	40.6	14.6	98.6	39.3	13.3	98.5
2.0	24.4	33.0	8.6	58.1	32.9	8.5	63.0
8.0	24.6	31.5	6.9	46.6	32.0	7.4	54.8

MOUSE STUDY COMMENTS:

No evidence for a tumorigenic effect of pramipexole was found in either male or female mice.

A sufficient number of animals survived the study to adequately assess the long-term effects of the doses administered. The reduction in body weight gain, clinical signs (hyperactivity) and non-neoplastic lesions (fibro-osseous proliferation in femurs) evident at the intermediate and high test doses suggest that sufficiently high doses were used. However, the limited plasma exposure data suggests only a 13-fold difference between the highest exposures in mice and anticipated human exposure levels was achieved.

The marked impairment of body weight development precludes the use of higher doses, and interferes with the interpretation of the negative findings in this study from both the mid and high dose levels. The dose-response curve for reduction in weight gain in mice by pramipexole is very sharp; a dose as low as 0.5 mg/kg in the 13-week pilot study reduced weight gain by 17%. Thus, it seems unlikely that further evaluations of pramipexole tumorigenicity in mice using doses between the low and intermediate doses of this study would be useful.

RECOMMENDATIONS:

This study cannot be accepted as a valid assessment of the carcinogenic potential of pramipexole in mice because of the severe impairments of body weight gain at the intermediate and high dosage levels. Since similar problems with interpretation are likely to be encountered at doses between the low and intermediate doses of the present study, further evaluations of pramipexole tumorigenicity in this dosage range should not be required.

/S/

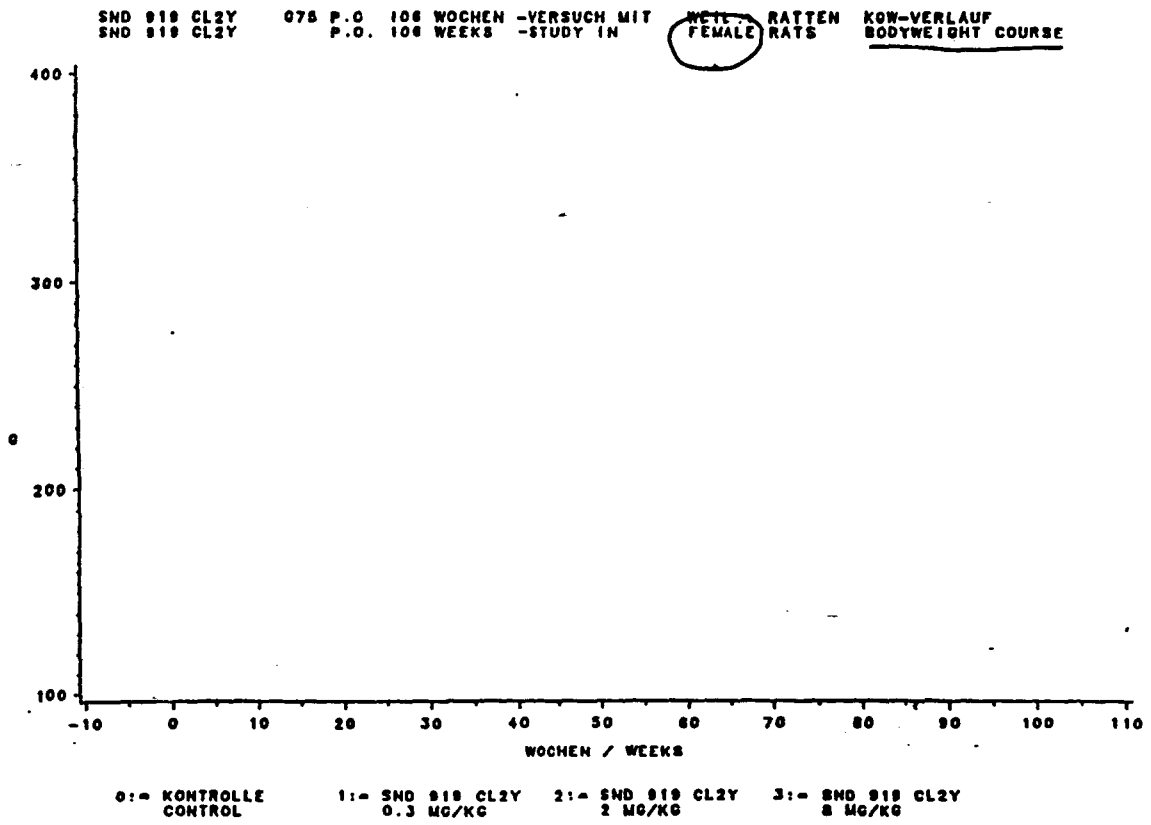
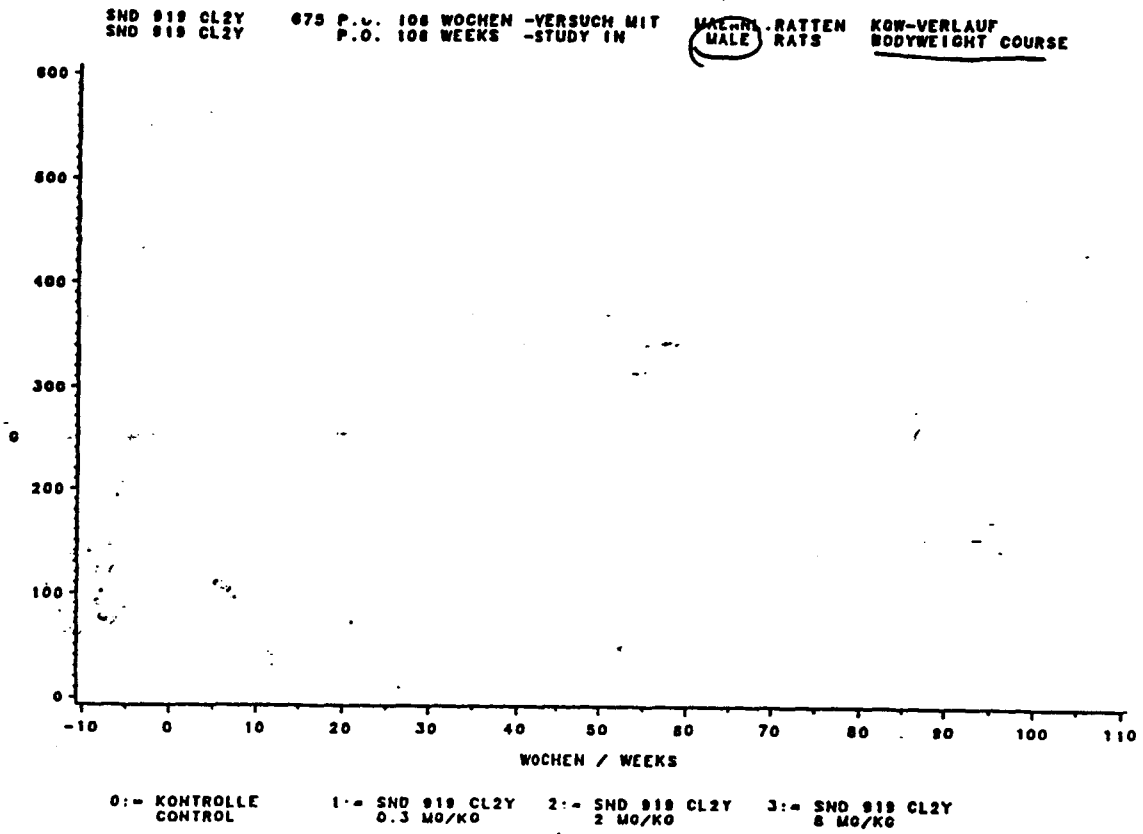
Thomas D. Steele, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

CC: NDA 20667
/Div. File, HFD-120
/GFitzgerald
/CAC
/TSteele

APPEARS THIS WAY
ON ORIGINAL

Fig. C.5.b.1.



Distribution of Neoplasms in Rats

Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT	ref. to III.E.210
Name of finished product		
Name of active ingredient Pramipexole (SND 919 CL 2 Y)		
		4/9 Page Number

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: 675 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)		Frequency according to dose and sex (n)									
		(0)		(4)		(1)		(2)		(3)	
		Contr. A		Contr. B		m		f		m	
Biometrical evaluation yes < x > no < >		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
KIDNEYS	TUBULAR ADENOMA	-	1	-	-	-	-	-	-	1	-
	NEPHROBLASTOMA	1	-	-	-	-	-	-	-	-	-
	LIPOSARCOMA	-	1	1	-	-	-	-	-	-	-
URINARY BLADDER											
	TRANSIT. PAPILOMA	-	2	-	1	-	-	-	1	1	1
	SQUAMOUS PAPILOMA	-	-	-	-	-	-	-	-	-	1
	TRANSIT. CARCINOMA	-	-	-	-	-	-	1	-	1	-
	SQUAMOUS CARCINOMA	1	-	-	-	-	-	-	-	-	-
TESTES	LEYDIG CELL ADENOMA**	13	-	9	-	17	3 [†]	22	-	22	-
OVARIES	GRANULOSA CELL TUMOR (B)	-	5	-	1	-	1	-	1	-	1
	THECA CELL TUMOUR	-	-	-	1	-	2	-	1	-	-
	LUTEOMA	-	-	-	4	-	-	-	1	-	-
	CARCINOMA, NOS	-	-	-	-	-	-	-	1	-	-
UTERUS	ADENOMA	-	-	-	1	-	-	-	-	-	-
	LEIOMYOMA	-	-	-	-	-	-	-	-	-	1
	HEMANGIOMA	-	-	-	-	-	-	-	2	-	1
	GRANULAR CELL TUMOUR	-	-	-	1	-	1	-	-	-	-
	ADENOCARCINOMA	-	2	-	2	-	2	-	2	-	1
	HEMANGIOSARCOMA	-	-	-	1	-	-	-	3	-	1

* P < 0.05 ** P < 0.01 (positive trend)

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Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT
Name of finished product	
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	
	ref. to ILL.E.210
	6/9
	Page Number

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: G75 Study period (years): 1989 = 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)		Frequency according to dose and sex (n)									
		(0)		(4)		-(1)		(2)		(3)	
		Contr. A		Contr. B		m		f		m	
Biometrical evaluation yes < > no < >		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
ADRENAL											
MEDULLA	MEDULLARY TUMOUR (B) f: ***	10	19	13	32	7	16	9	4	6	3
	MEDULLARY TUMOUR (M)	2	-	2	1	1	-	-	-	1	-
THYMUS	THYMOMA	-	-	-	-	-	1	-	-	-	-
MESENT.											
Lymph Node	HEMANGIOMA	-	-	5	1	2	-	3	1	4	-
HEMOLYMPH.											
SYSTEM	HISTIOCYTIC SARCOMA	-	1	1	1	-	1	-	1	-	-
	MALIGNANT LYMPHOMA	3	1	8	4	6	5	1	1	4	3
SPLEEN	HEMANGIOSARCOMA	1	1	-	1	-	1	1	-	2	-
SUBLINGUAL											
GLAND	ACINAR CARCINOMA	-	-	-	-	-	1	-	-	-	-
MAMMARY											
GLAND AREA	FIBROADENOMA	-	5	-	2	-	2	-	-	-	-
	ADENOMA	-	1	-	-	-	-	-	-	-	-
	PAPILL. CYSTADENOMA	-	-	-	-	-	1	-	-	-	-
	CARCINOMA	-	1	-	2	-	3	-	-	-	-
BONE	GRANULAR CELL TUMOUR	-	1	-	-	-	-	-	-	-	-
	SCHWANNOMA (M)	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

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Name of company BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT	
Name of finished product		
Name of active ingredient Prampexole (SND 919 CL 2 Y)		
	ref. to III.E.210	
	8/9	
	Page Number	

CNCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
 Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)	Frequency according to dose and sex (n)									
	(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
	m	f	m	f	m	f	m	f	m	f
Bimetricial evaluation yes <x> no <>										
Number of animals evaluated	50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour									
ADIPOSE										
TISSUE	LIPOMA									
	1	-	2	1	-	-	1	-	-	-
EARS	HEMANGIOMA									
	-	-	-	-	1	-	-	-	-	-
TAIL	SCHWANNOMA									
	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01

Test for Heterogeneity (Tab. C.5.b.8):

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: MALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
LIVER	HEPATOC. ADENOMA	0.5938
LIVER..	HEPATOC. CARCINOMA	0.3381
PANCREAS	ISLET-CELL ADENOMA	0.4029
TESTES	LEYDIG CELL ADENOMA	0.0100
PITUITARY	ADENOMA	0.0071
THYROID GLAND	C CELL ADENOMA	0.5848
THYROID GLAND	C CELL CARCINOMA	0.7685
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	0.3218
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	0.4930
MESENT. LYMPH NODE	HEMANGIOMA	0.7732
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.2421

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TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: FEMALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
OVARIES	GRANULOSA CELL TUMOR	0.5104
OVARIES	LUTEOMA	0.3011
UTERUS	HEMANGIOSARCOMA	0.1430
CERVIX	SQUAMOUS PAPILLOMA	0.0548
CERVIX	STROMAL SARCOMA	0.4969
PITUITARY	ADENOMA	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0723
THYROID GLAND	C CELL CARCINOMA	0.2787
PARATHYROID GLANDS	ADENOMA	0.0755
ADRENAL CORTEX	ADENOMA	0.4655
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.7136
MAMMARY GLAND AREA	FIBROADENOMA	0.0632
MAMMARY GLAND AREA	CARCINOMA	0.0887

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Mouse

Tab. C.5.a.6

TR No.: 7219-94-070

BOEHRINGER INGELHEIM KG Name of finished product	TABULATED STUDY REPORT	U93-0589
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210 2/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Bimetric evaluation yes <x> no <>		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
BRAIN	OLIGODENDROGLIOMA	1	-	-	-	-	-	-	-	-	-
	NEOPLASM (NOS)	-	-	-	-	-	-	-	-	-	1
LUNGS	ADENOMA	22	9	11	8	12	13	8	6	13	6
	CARCINOMA	1	2	-	-	-	2	-	1	-	-
LIVER	ADENOMA/HEPATOC.	5	-	7	1	2	-	-	-	2	-
	HEMANGIOSARCOMA	3	1	4	-	2	1	1	-	1	-
	CARCINOMA/HEPATOC.	-	-	-	-	1	-	1	-	-	-
TONGUE	CARCINOMA/SQUAMOUS	1	-	-	-	-	-	-	-	-	-
DUODENUM	SARCOMA/OSSIFYING	-	-	-	-	-	-	1	-	-	-
TESTES	LEYDIG CELL TUMOR	4	-	3	-	2	-	-	-	5	-
PROSTATE	ADENOMA	1	-	-	-	-	-	-	-	-	-
SEMINAL											
VESICLES	LEIOMYOMA	1	-	-	-	-	-	-	-	-	-
OVARIES	LUTEOMA	-	-	-	-	-	-	-	-	-	1
	ADENOMA/TUBULAR	-	1	-	2	-	1	-	2	-	-
	TUMOR/GRANULOSA CELL	-	1	-	4	-	2	-	5	-	3
	LIPOMA	-	1	-	-	-	-	-	-	-	-

* P < 0.05 ** P < 0.01

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TR No.: 7219-94-070

Tab. C.5.a.6 (cont.)

BOEHRINGER INGELHEIM KG Name of finished product		TABULATED STUDY REPORT		U93-0589											
Name of active ingredient Pramipexole (SND 919 CL 2 Y)		ref. to III.E.210													
		4/6 Page Number													
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data															
Ref. to document.: Volume: Page: to Addendum No.:				Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991											
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)						Frequency according to dose and sex (n)									
						(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Biometrical evaluation yes <x> no <y>						m	f	m	f	m	f	m	f	m	f
Number of animals evaluated															
Organ	Identification of the tumour														
ADRENAL															
CORTEX	ADENOMA/A-CELL					-	-	-	-	1	-	-	-	-	1
	ADENOMA/B-CELL					6	-	3	-	3	-	6	-	3	1
	ADENOMA/B-CELL/EXTD.** (males)					8	-	5	-	3	-	2	-	-	-
	ADENOMA/Z. FASCICUL.					3	-	-	1	1	-	-	-	-	-
ADRENAL															
MEDULLA	MEDULL. TUMOR/BENIGN					1	-	-	-	-	-	-	-	-	-
	MEDULL. TUMOR/MALIGN.					-	-	-	1	-	-	-	-	-	-
MESENT.															
LYMPH NODE	HEMANGIOMA					-	-	-	1	-	-	-	-	-	-
SYSTEMIC															
NEOPLASMS	THYMIC LYMPHOMA* (females)					3	18	4	16	4	13	4	8	4	7
	NONSPECIF. LYMPHOMA					1	-	1	1	1	-	-	-	-	-
	NON-THYMIC LYMPHOMA					3	5	4	3	6	3	3	3	4	1
	MAST CELL TUMOR					1	-	-	-	-	-	2	-	-	1
	BONE MARROW LYMPHOMA					-	-	-	1	-	-	-	-	-	-
	HISTIOCYTIC SARCOMA					-	1	-	4	4	2	-	2	-	1
	MYELOID LEUKEMIA					-	1	-	-	-	-	-	-	-	-

* P < 0.05, ** P < 0.01 (=negative trend)-

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Tab. C.5.a.7.

PATHOLOGY REPORT PAGE : 781
 STATISTICAL EVALUATION BOE PROJECT: G 70

TEST ARTICLE : SMD 919 CL 2 Y PATHOL. NO.: 91009 HHW
 TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING DATE : 11-MAY-93
 SPONSOR : BOEHRINGER INGELHEIM KG PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
 COMBINED PREVALENCE AND DEATH RATE METHOD (PEYO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4 SEX: MALE
 STATUS AT NECROPSY: KO INCL. +
 TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BRAIN	OLIGODENDROGLIOMA	2.204-	0.2776
LUNGS	ADENOMA	5.941+	0.4052#
LUNGS	CARCINOMA	2.197-	0.2776
TONGUE	CARCINOMA/SQUAMOUS	2.128-	0.2810
LIVER	ADENOMA/HEPATOC.	13.911-	0.1611#
LIVER	HEMANGIOSARCOMA	11.670-	0.1660#
LIVER	CARCINOMA/HEPATOC.	2.172-	0.3409
TESTES	LEYDIG CELL TUMOR	18.343+	0.0901#
PROSTATE	ADENOMA	2.203-	0.2776
SEMINAL VESICLES	LEIOMYOMA	2.176-	0.2776
PITUITARY GLAND	ADENOMA/P.DISTALIS	2.553-	0.2611
THYROID (BOTH LOBES)	CARCINOMA/FOLLICULAR	0.190-	0.4797
ADRENAL CORTEX	ADENOMA/B-CELL	2.901-	0.4286#
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	8.888-	0.1151#
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	35.780-	0.0094#
ADRENAL CORTEX	ADENOMA/A-CELL	1.876-	0.3050
ADRENAL MEDULLA	MEDULL.TUMOR/BENIGN	2.190-	0.2776
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	6.288-	0.1635
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	1.540+	0.4626#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	7.369+	0.3228#
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	7.470-	0.1539
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	2.517-	0.3483
SPLEEN	HEMANGIOSARCOMA	0.176-	0.4813
HARDERIAN GLANDS	ADENOMA	12.472-	0.0808
SKIN	HEMANGIOSARCOMA	2.405-	0.2611
SKIN	LIPOMA	2.149-	0.2776
BODY CAVITIES	SARCOMA/OSSIFYING	5.671+	0.1379

- ?? highest
 con. #11)
 - highest in con.

Explanation of Symbols

- p = one-tailed p-value
- = negative trend
- + = positive trend
- # = number of animals with tumors > 5% in at least one sex/dose group

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TR No.: 7219-94-070

Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

PAGE : 107/ 781
BOE PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4

SEX: FEMALE

STATUS AT NECROPSY: KO INCL. +

TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
LUNGS	CARCINOMA	9.616-	0.1170
LIVER	ADENOMA/HEPATOC.	2.242-	0.2743
LIVER	HEMANGIOSARCOMA	4.326-	0.1977
URINARY BLADDER	CARCINOMA/TRANSIT.C.	7.731+	0.0192
OVARIES	ADENOMA/TUBULAR	8.839-	0.1587
OVARIES	TUMOR/GRANULOSA CELL	4.570+	0.3707#
OVARIES	LIPOMA	2.190-	0.2743
OVARIES	LUTEOMA	7.810+	0.0170
UTERUS	SARCOMA/STROMAL CELL	0.012+	0.4996
UTERUS	LEIOMYOMA	1.019-	0.4653#
UTERUS	ADENOCARCINOMA	1.942-	0.3015
UTERUS	LEIOMYOSARCOMA	5.775+	0.1357
UTERUS	FIBROMA	7.758+	0.0188
UTERUS	GRANULAR CELL TUMOR	7.758+	0.0188
UTERUS	POLYP/STROMAL	15.578+	0.0778#
VAGINA	FIBROMA	2.282-	0.2709
PITUITARY GLAND	ADENOMA/P.DISTALIS	7.384-	0.2090#
THYROID (BOTH LOBES)	ADENOMA/FOLLICULAR	4.642-	0.1977
PARATHYROID GLANDS	ADENOMA	4.745-	0.1894
ADRENAL CORTEX	ADENOMA/B-CELL	7.758+	0.0188
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	2.242-	0.2743
ADRENAL CORTEX	ADENOMA/A-CELL	7.627+	0.0222
ADRENAL MEDULLA	MEDULL.TUMOR/MALIGN.	2.242-	0.2743
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	2.306-	0.2676
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	17.653-	0.1075#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	52.989-	0.0250#
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	2.242-	0.2743

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M+F
C = 9/20
LD = 3/100
MD = 6/100
HD = 4/100

Tab. C.S.a.7. (cont.)

PATHOLOGY REPORT

PAGE : 110/ 781
BOE PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HHW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3:6

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

SEX: MALES

ORGAN/TISSUE	TYPE OF NEOPLASM	P-VALUE
LUNGS	ADENOMA	0.4296
LIVER	ADENOMA/HEPATOC.	0.0663
LIVER	HEMANGIOSARCOMA	0.6462
TESTES	LEYDIG CELL TUMOR	0.1536
ADRENAL CORTEX	ADENOMA/B-CELL	0.5593
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	0.0720
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	0.5123
ADRENAL CORTEX	ADENOMAS/TOTAL	0.1450
HARDERIAN GLANDS	ADENOMA	0.3355
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.8941
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	-
SYSTEMIC NEOPLASMS	NONTHYMIC LYMPHOMA	0.5578
SYSTEMIC NEOPLASMS	MALIGN.LYMPHOMA/TOTAL	0.5740
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.0018

SEX: FEMALES

LUNGS	ADENOMA	0.1048
OVARIES	TUMOR/GRANULOSA CELL	0.5743
UTERUS	POLYP/STROMAL.	0.3589
UTERUS	LEIOMYOMA	0.9954
PITUITARY GLAND	ADENOMA/P.DISTALIS	0.1239
HARDERIAN GLANDS	ADENOMA	0.1154
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.0715
SYSTEMIC NEOPLASMS	NONSPEC.LYMPHOMA	-
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	0.6700
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	-
SYSTEMIC NEOPLASMS	MALIGN.LYMPHOMA/TOTAL	0.0204
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.9139

NOTE: STATISTICAL CALCULATION WAS PERFORMED ONLY IF THE NUMBER OF NEOPLASMS EXCEEDED 5% PER DOSE GROUP AND SEX.

END OF REPORT SECTION

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Tab. C.5.a. 8. (cont.)

NUMBER OF ANIMALS WITH METASTASES:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO. EXAM:	50	50	50	50	50	50	50	50	50	50
NO. AFF.:	0	0	0	1	0	1	0	0	0	1
% :	0.0	0.0	0.0	2.0	0.0	2.0	0.0	0.0	0.0	2.0

DOSE GR:	TOTAL	
SEX :	M	F
NO. EXAM:	250	250
NO. AFF.:	0	3
% :	0.0	1.2

NUMBER OF PRIMARY NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
PRIM. T.:	76	55	46	52	46	56	32	39	35	35

DOSE GR:	TOTAL	
SEX :	M	F
PRIM. T.:	235	237

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NO. OF BENIGN, UNCLASSIFIED, MALIGN. NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
BENIGN :	61	23	33	23	28	28	18	21	25	19
UNCLASS:	0	0	0	0	0	0	0	0	0	0
MALIGN.:	15	32	13	29	18	28	14	18	10	16

DOSE GR:	TOTAL	
SEX :	M	F
BENIGN :	165	114
UNCLASS:	0	0
MALIGN.:	70	123

Sentences 2 and 3: The findings and significance of Leydig cell adenomas and hyperplasia in rats should be simplified since there is no experimental support for an effect of PPX on LH secretion or LH receptor number:

"These findings are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice treated with PPX for 2 years, and the probable involvement of endocrine mechanisms that are not relevant to humans."

General: A statement that the results in mid- and high-dose female rats, and mid- and high-dose mice of both sexes are questionable or invalid due to the impairment of body weight gain needs to be included.

APPEARS THIS WAY
ON ORIGINAL

DEFINITION
OCT 29 1996

Statistical Review and Evaluation

OCT 24 1996

DATE:

NDA#: 20-667

APPLICANT: The Upjohn Company

APPEARS THIS WAY
ON ORIGINAL

NAME OF DRUG: Pramipexole Tablets

DOCUMENTS REVIEWED: Volumes 1.45, 1.49 Containing the Study Reports of the Mouse and Rat Studies and Volume 2.1 Dated Feb 13, 1996 Containing the Data Diskettes and Data Listings for these Studies.

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I. Background

Dr. Thomas Steele (HFD-120) requested from the Division of Biometrics I a statistical review of the rat and mouse studies data as well as an evaluation of the sponsor's findings.

II. The Rat Study

II.a. Design

The product was studied for 107 weeks in male and female Chbb:THOM rats. There were two control groups and three treated groups of 50 animals/sex each. The compound was administered orally in the diet at 0.3, 2.0, and 8.0 mg/kg/day. The two control groups were combined in the analyses. Terminal sacrifice was performed during weeks 108 and 109.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis

The exact logrank test was used in concluding that time of death of the animals was not related to dose. Cumulative mortality was graphed for each sex.

Tumor Data Analysis

Tumor data with at least three tumor-bearing animals in any group were analyzed. The sponsor found an increased incidence in Leydig cell hyperplasia and adenomas in the male rats for the intermediate and high dose-groups. There were no statistically significant positive trends with dose in tumor incidence rates among the females. There were significant negative trends in pituitary adenomas (both sexes), neoplasms of the mammary gland in females, primary neoplasms in general, and benign adrenal medullary neoplasms in females. The sponsor concluded that the compound had no direct carcinogenic effect in rats. The observed significant changes (positive trend in Leydig cell hyperplasia/adenomas and negative trends in several tumor types) could be traced to functional effects of dopamine release.

II.c. Reviewer's Analyses

This reviewer independently performed analyses on the survival and the tumor data. For survival analysis the methods described in papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society B 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika 52, 203-223, 1965) were used. The corresponding computer program was written by Thomas, Breslow, and Gart (Trend and homogeneity analyses of proportions and life table data, Computers and Biomedical Research 10, 373-381, 1977, Version 2.1). The tumor data were analyzed using the methods described in the

paper of Peto et al. (Guidelines for simple sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International Agency for Research against Cancer Monographs, Annex to Supplement, WHO, Geneva, 311-426, 1980) and the method of the exact permutation trend test developed by the Division of Biometrics. The following criteria for the levels of significance ensure a false positive rate of about ten percent for the trend tests of the usual two-species two-sexes studies: Tumors with less than 1.00% occurrence in the control group are considered rare and a positive trend test is statistically significant when it reaches a p-value of $\leq .025$ (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive trend is statistically significant when its p-value is less than .005 (one-sided). An approximate permutation trend test is used when fatal and incidental tumors of the same kind are combined and have overlapping time intervals. All tests are survival adjusted and treatment groups are weighted by the actual dose levels.

Survival Analysis

Survival at Terminal Sacrifice ranged from _____ percent (control - high dose) among the male rats and from 77 to 60 percent (control - low dose) among the female rats as can be seen in the Table 1. The life table analysis of the male mortality data showed no significant linear Cox trend statistic or generalized Kruskal/Wallis analysis, nor were any pairwise comparisons between treated and untreated groups significant. The life table analysis of the female mortality data showed a similar pattern of no statistically significant relationship of dose with mortality (Table 2 Figures 1 and 2).

There are some minor numeric differences between the number of animals being terminally sacrificed. It appears that the sponsor treated animals dying naturally during the weeks of terminal sacrifice as natural death whereas this reviewer treated them as terminally sacrificed. No difference in conclusion results from these slightly different approaches. Should an animal which died naturally during weeks 108 and 109 exhibit a fatal tumor, it would be properly handled as such by this reviewer as well.

Tumor Data Analysis

This reviewer constructed tumor incidence tables for each recorded tissue for any tumor, treating fatal, incidental, and undetermined separately. Possible positive tumor trends with dose were then statistically analyzed adjusting for mortality despite the overall nonsignificant difference in survival. Leydig cell adenomas in the male rats were common in all animals but showed such an increase in incidence with dose. The observed trend in incidental tumors resulted in a p-value of .0233; the undetermined tumors had a p-value of .0664. There were no fatal Leydig cell adenomas. Combining all tumor occurrences gave an overall trend statistic with $p=.0065$. However, as these tumors occurred also frequently among the control animals, this level is not considered sufficient (higher than $p=.005$) to be called statistically significant. At the request of the pharmacologist, the pairwise comparisons with each of the control groups and their

combination are given in Appendix 1. As these are only pairwise comparisons, the appropriate criteria for statistical significance are $p=.05$ for rare tumors and $p=.01$ for common tumors. Using the $p=.01$ for common tumors, it can be seen that comparisons with the second control group or with the combined control groups reach statistical significance for Leydig Cell adenomas coded as incidental or for all Leydig Cell adenomas. Comparisons with the first control group do not reach statistical significance, nor do any based on Leydig Cell adenomas coded as undetermined and analyzed as if they were incidental tumors.

Among the female rats, none of the possible positive trends reached the statistical criteria of significance.

This reviewer did not analyze any negative trends observed in the tumor occurrences. However, as the sponsor mentioned, some of these were very striking.

II.d. Validity of the Rat Study

Before concluding that the rat study (both for males and females) showed no tumorigenic effect of pramipexole, the validity of the study needs to be determined. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

- (i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?
- (ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

- (i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a

dosed group relative to the controls.”

(ii) “The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.”

(iii) “In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls.”

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, “Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is a indication that the treatment has been tested on levels at or approaching the MTD.”

The lowest survival of the animals at two years was 60 percent. Therefore, it is obvious that there were a sufficient number of animals throughout the study to manifest any late developing tumors.

From the attached Figures 3 and 4, the sponsor’s group mean body weight plots, one can see that the dosed animals experienced lower body weight than the controls. As given in the Tables below, at week 74 and at the end of the study, the medium and high dosed male rats experienced lower weight gain of up to 9 percent relative to that of their controls. For the female rats these differences were much more pronounced showing a 28 percent difference in weight gain of the controls versus the high dosed animals at the end of the study. Therefore, for the male rats, the findings would support the high dose being close to the MTD, whereas for the female rats one has to be concerned whether their lack of tumor incidences may be due, at least in part, to the fact that leaner animals develop less tumors, and that the carcinogenic potential of this compound cannot be assessed in this sex and species.

AVERAGE WEIGHT: MALE RATS

Dose	Wk: -1	Wk: 74	Diff.	% of C	Wk: 106	Diff.	% of C
C	145.897	585.375	439.478		588.082	442.185	
L	144.291	557.190	412.899	94.0	581.718	437.427	98.9
M	144.536	544.794	400.258	91.1	553.860	409.324	92.6
H	143.463	548.605	405.142	92.2	562.662	419.199	94.8

AVERAGE WEIGHT: FEMALE RATS

Dose	Wk: -1	Wk: 74	Diff.	% of C	Wk: 106	Diff.	% of C
C	132.379	305.833	173.454		315.891	183.512	
L	131.878	293.743	161.865	93.3	302.585	170.707	93.0
M	131.096	271.263	140.167	80.8	275.823	144.727	78.9
H	130.354	264.281	133.927	77.2	261.888	131.534	71.7

A numerically increasing mortality trend with dose, though not significantly so, is also a measure of assessing whether the high dose was close to the MTD. For the present data, neither the male nor the female mortality data showed any ordering with dose.

In summary, the data show that both the male and the female rats lived long enough to show any late-developing tumors. However, assessing whether the high dose was close to the MTD proved more difficult. The sponsor documented the reasons for choosing 8 mg/kg as the high dose, namely because it fell into the lower third of the toxic dose range. The application of the criteria put forth by experts to assess the high dose as being close to the MTD give inconclusive results. There was weight reduction in the dosed animals, but far beyond 10 percent for the female rats. Mortality did not show any association with dose. Trends in non-neoplastic findings may help the pharmacologist in the determination of the validity of this study.

III. The Mouse Study

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III.a. Design

This study was conducted in Chbb:NMRI mice for two years. For each sex there were 50 animals per group. The two control groups were combined in the analyses. The dosed animals received 0.3, 2.0, and 10.0 mg/kg/day in the diet. Terminal sacrifice was performed during weeks 105 and 106 on all surviving animals.

III.b. Sponsor's Analyses of the Mouse Study

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Survival Analysis

The sponsor used the exact logrank test for group comparisons of the mortality data and provided graphs of cumulative mortality. They stated that the rate of premature decedents was higher in

the treated animals than in the controls, significantly so among the male mice. The male mice also exhibited a significant level of heterogeneity.

Tumor Data Analysis

Tumor incidence rates were analyzed according to their context of observation. No statistically significant positive trends in tumor incidence rates with dose were observed for any neoplastic lesions. The sponsor discussed the significant increased incidence and severity of fibro-osseous proliferative lesions in the femurs of treated females and several (some significant) negative trends in a variety of tumors. These were attributed to the pharmacological actions of the product.

III.c. Reviewer's Analyses

The same statistical methods and approaches discussed for the rat study were applied to the mouse data.

Survival Analysis

The generalised Kruskal/Wallis test showed a significant trend with dose and significant heterogeneity for the male mortality data ($p=.040$ for trend and $p=.017$ for heterogeneity). The adjusted Cox test for trend did not reach significance for trend ($p=.067$), but also exhibited significant heterogeneity ($p=.016$). These findings were supported by significant pairwise comparisons of the dosed groups with the controls. No differences were observed between the mortality experiences of the dosed animals. The lifetable analysis of the female mice data showed no statistically significant trend with dose, nor any significant departure from linearity (Tables 3 and 4, Figures 5 and 6).

The intercurrent mortality tables of the sponsor and this reviewer differ slightly because this reviewer counted animals dying naturally during the time of terminal sacrifice as part of the sacrificed animals, whereas the sponsor treated them as natural deaths. No difference in conclusions results from this discrepancy.

Tumor Data Analysis

None of the tumor findings exhibited a possible positive trend with dose.

There was, however, one minor point of confusion: the sponsor called all tumor findings 'incidental' which in this Division is interpreted to mean that they did not cause the death of an animal. There are, however, some tumors recorded as fatal. The precise meaning in the sponsor's submission is not clear to this reviewer, but was taken to be of no importance.

III.d. Validity of the Mouse Study

Before concluding that the mouse study showed no tumorigenic effect of pramipexol, the validity of the study needs to be determined. The same criteria used in the assessment of the validity of the rat study will be applied to the mouse data.

The survival of the mice after two years of treatment was at least 56 percent, demonstrating that there were a sufficient number of animals available in any dose group to exhibit late developing tumors if the compound causes them.

Figures 7 and 8 are reproductions of the sponsor's average weights over the course of the study. It is clear that the medium and high dose animals experienced an early and sustained reduction in weight gain. The differences between the average weights of the high dose and the controls reach about 19 percent for both the male and female mice. The differences in weight gain are even more striking, with 49 and 53 percent at week 74, and 39 and 45 percent at week 102 for the male and female high dose mice respectively. These findings do not support a conclusion that the high dose was close to the MTD, but raise concerns whether these leaner animals exhibited fewer tumors because of their condition rather than because the compound was non-carcinogenic. The differences in weight gain between the medium dose animals and the controls were similar to those of the high dose animals and would not support the medium dose being close to the MTD on this measure.

AVERAGE WEIGHT: MALE MICE

Group	Wk: -1	Wk: 74	Diff.	% of C	Wk: 102	Diff.	% of C
C	29.386	48.127	18.841		45.503	16.117	
L	29.437	48.294	18.857	100.62	46.296	16.859	104.60
M	29.361	41.678	12.317	65.72	38.990	9.629	59.74
H	29.056	38.679	9.623	51.35	38.822	9.766	60.59

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AVERAGE WEIGHT: FEMALE MICE

Group	Wk: -1	Wk: 74	Diff.	% of C	Wk: 102	Diff.	% of C
C	24.144	38.932	14.788		37.628	13.484	
L	25.952	40.609	15.557	105.20	39.291	14.239	105.60
M	24.378	32.983	8.605	58.19	32.890	8.492	62.98
H	24.568	31.469	6.901	46.67	32.028	7.460	55.32

There was a trend in mortality with dose for the male mice but not for the female mice. For the females there was a somewhat higher mortality in the dosed animals than in their controls, but there was no direction in these with increasing dose. The pharmacologist may want to evaluate possible dose relationships in clinical signs and histopathological effects in his conclusion whether the study was conducted in such a way that tumors could have been detected if the compound causes them. From the statistical point of view, one cannot conclude that the compound is a non-carcinogen.

IV. Summary and Conclusion

The two year rat study seemed to be a well executed study in which the doses administered had no apparent effect on survival. The only possibly significant linear trend in tumor incidence rates with dose was Leydig cell adenomas in the male rats. The associated p-value was .0065, which, according to this Division's criteria to control for false positive findings, is not considered a statistically significant finding. Some of the pairwise comparisons of the high and mid doses with control group 2 or the combined controls did reach statistical significance when a level of significance appropriate for pairwise comparisons was used. Other pairwise comparisons did not meet this criterion. In the subsequent evaluation of the validity of this study, this reviewer found that there were sufficient numbers of animals surviving till final sacrifice to exhibit any late developing tumors. For the male animals one could conclude the high dose was close to the MTD by demonstrating that the differential in weight gain of the dosed animals with respect to their controls was not more than 10 percent. However, no ordering of survival with dose was found. For the female rats, the weight gain was suppressed by up to 28 percent, far exceeding the 10 percent criterion. Therefore, from a statistical point of view it cannot be concluded that the product is a non-carcinogen. The evaluation of clinical signs and of gross histopathological effects for dose relationships may help the pharmacologist in assessing the validity of this study.

The two year mouse study also appeared to be a well conducted experiment. The survival experience of the male mice was reduced with dose, significantly so by at least one statistical test. The associated significant heterogeneity points to the fact that the dosed animals experienced higher mortality but not in strict order with dose. The female mice showed no difference in mortality across groups. Neither the male nor the female mice exhibited any increase in tumor incidence rates with dose. In the evaluation of the study's validity it was found that there were sufficient numbers of animals living till the end of the study to exhibit any late developing tumors should the compound cause them. However, the mid and high dose animals gained substantially less weight than their controls. At the end of the study, the high dose females had gained only 55 percent of the weight their controls had gained and the males had gained only 61 percent of what their controls had gained. This clearly begs the question whether this large differential in weight gain could mask a tumorigenic potential of the compound if leaner animals develop fewer tumors.

A final point is, that the sponsor's statistical methods applied to the mortality data and to the tumor data were not clearly described and their results not presented. Therefore, a complete statistical review had to be performed.

/S/

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Roswitha E. Kelly
Mathematical Statistician

/S/

Concur:

Todd Sahlroot, Ph. D.
Acting Team Leader

/S/

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ON ORIGINAL

George Chi, Ph.D.
Director, DB I

APPEARS THIS WAY
ON ORIGINAL

cc:Archival NDA 20-667, Pramipexole Tablets, The Upjohn Company

HFD-120/Division File

HFD-120/Dr. Steele

HFD-120/Dr. Fitzgerald

HFD-710/Chron.

HFD-710/Dr. Chi

HFD-710/Dr. Sahlroot

HFD-710/Ms. Kelly

HFD-710/RKELLY/10/15/96/wp-pramipex.rev

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Table 1
INTERCURRENT MORTALITY RATES

Weeks	MALE RATS mg/kg/day			
	0	0.3	2.0	8.0
0- 52	2/99 (2%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
53- 78	1/97 (3%)	0/50 (0%)	2/49 (6%)	1/49 (4%)
79- 92	6/96 (9%)	2/50 (4%)	1/47 (8%)	2/48 (8%)
93-107	8/90 (17%)	5/48 (14%)	2/46 (12%)	6/46 (20%)
Term. Sac.	82/99 (83%)	43/50 (86%)	44/50 (88%)	40/50 (80%)

Weeks	FEMALE RATS mg/kg/day			
	0	0.3	2.0	8.0
0- 52	3/100 (3%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
53- 78	7/97 (10%)	2/49 (6%)	0/50 (0%)	3/49 (8%)
79- 92	5/90 (15%)	5/47 (16%)	7/50 (14%)	1/46 (10%)
93-107	8/85 (23%)	12/42 (40%)	7/43 (28%)	6/45 (22%)
Term. Sac.	77/100 (77%)	30/50 (60%)	36/50 (72%)	39/50 (78%)

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Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

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Table 2

Results of Intercurrent Mortality Analyses

Male Rats

Groups Compared	Direction	<u>Two-tailed P-Value of Test</u>	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.500	.484
C,L	neg	.748	.567
C,M	neg	.592	.489
C,H	pos	.821	.660
L,M	neg	.824	.881
L,H	pos	.541	.364
M,H	pos	.427	.317

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Female Rats

Groups Compared	Direction	<u>Two-tailed P-Value of Test</u>	
		Cox	Kruskal/Wallis
C,L,M,H	neg	.397	.385
C,L	pos	.083	.105
C,M	pos	.743	.715
C,H	neg	.972	.773
L,M	neg	.348	.349
L,H	neg	.097	.083
M,H	neg	.643	.518

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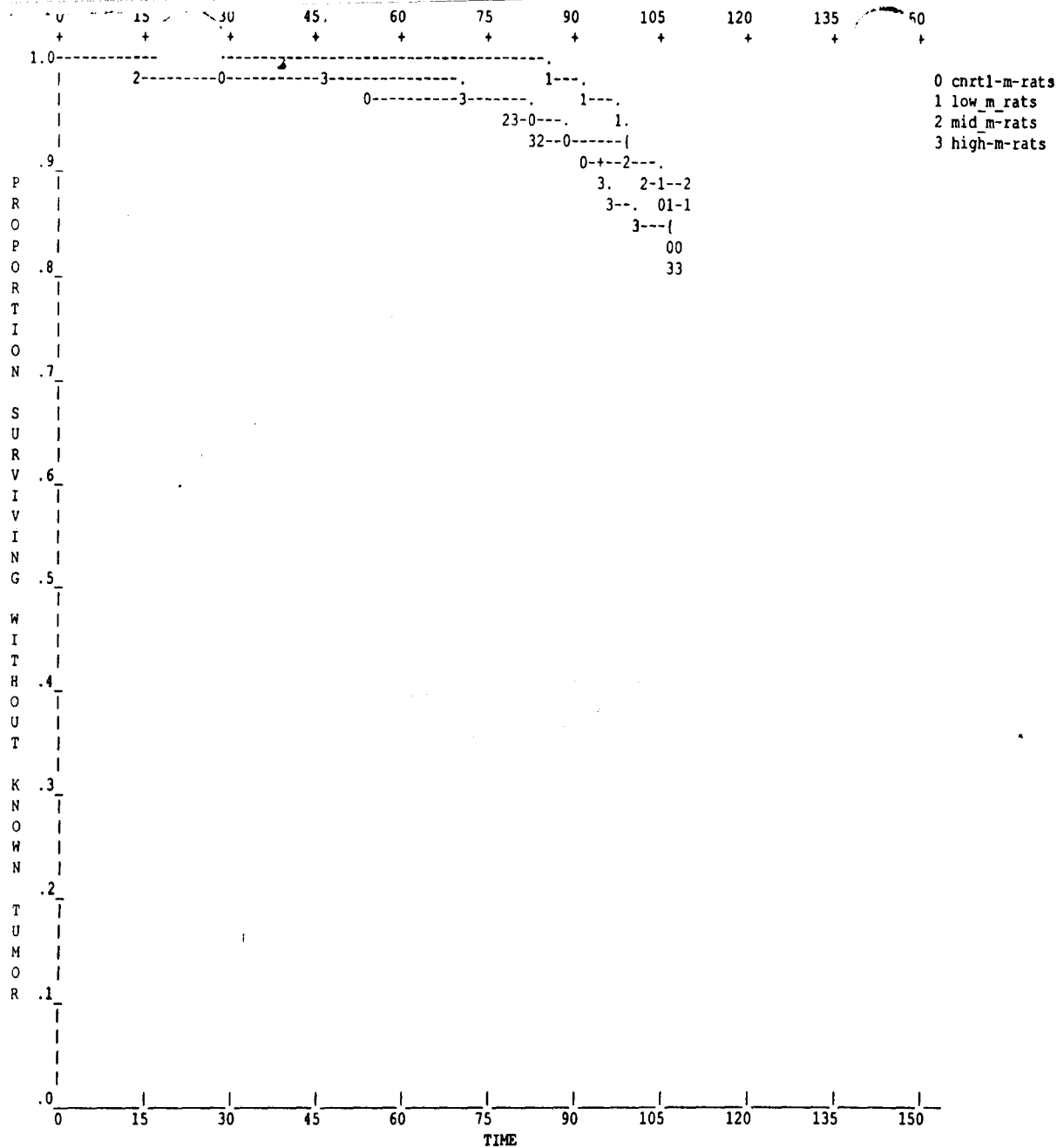
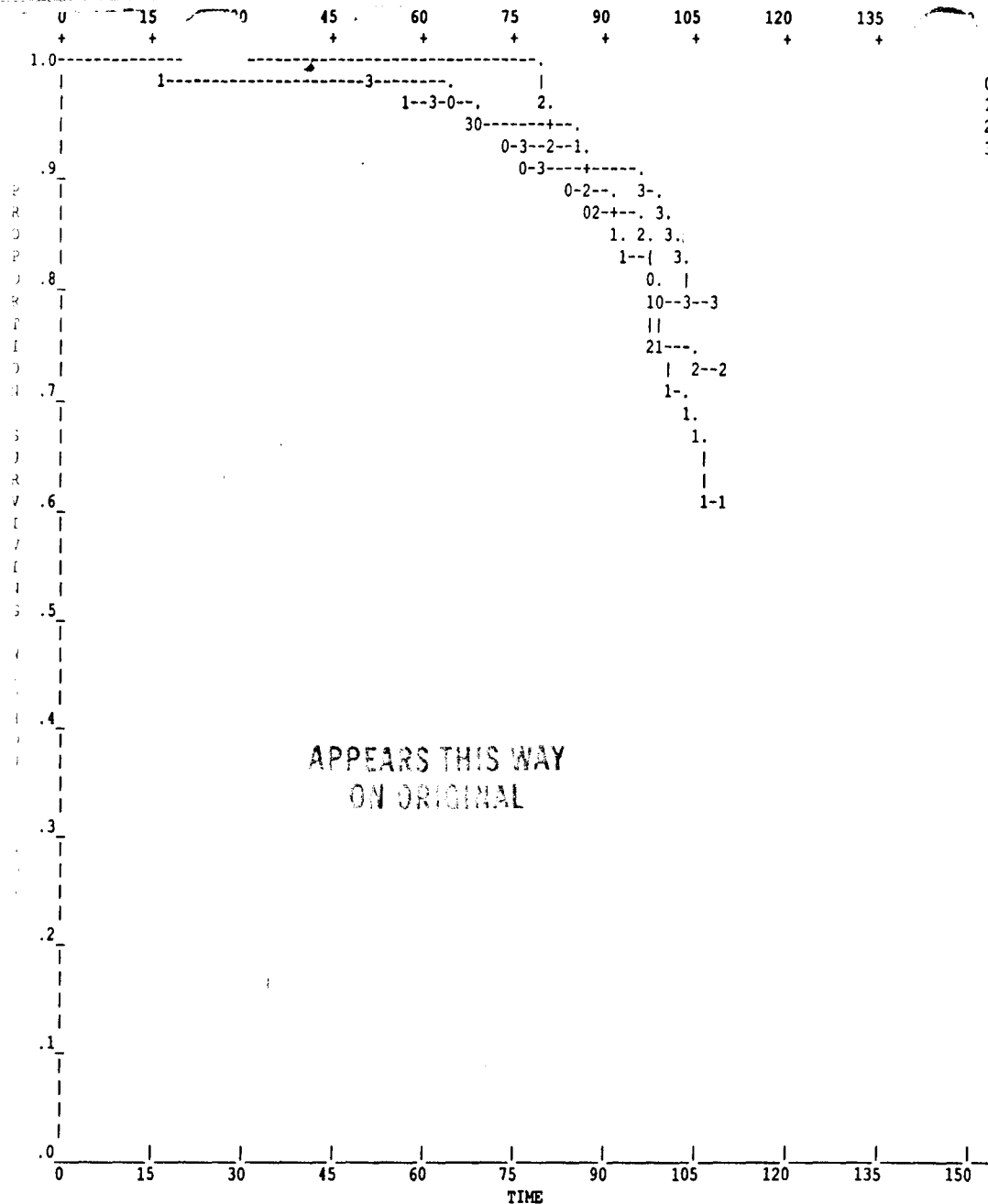


Figure 1

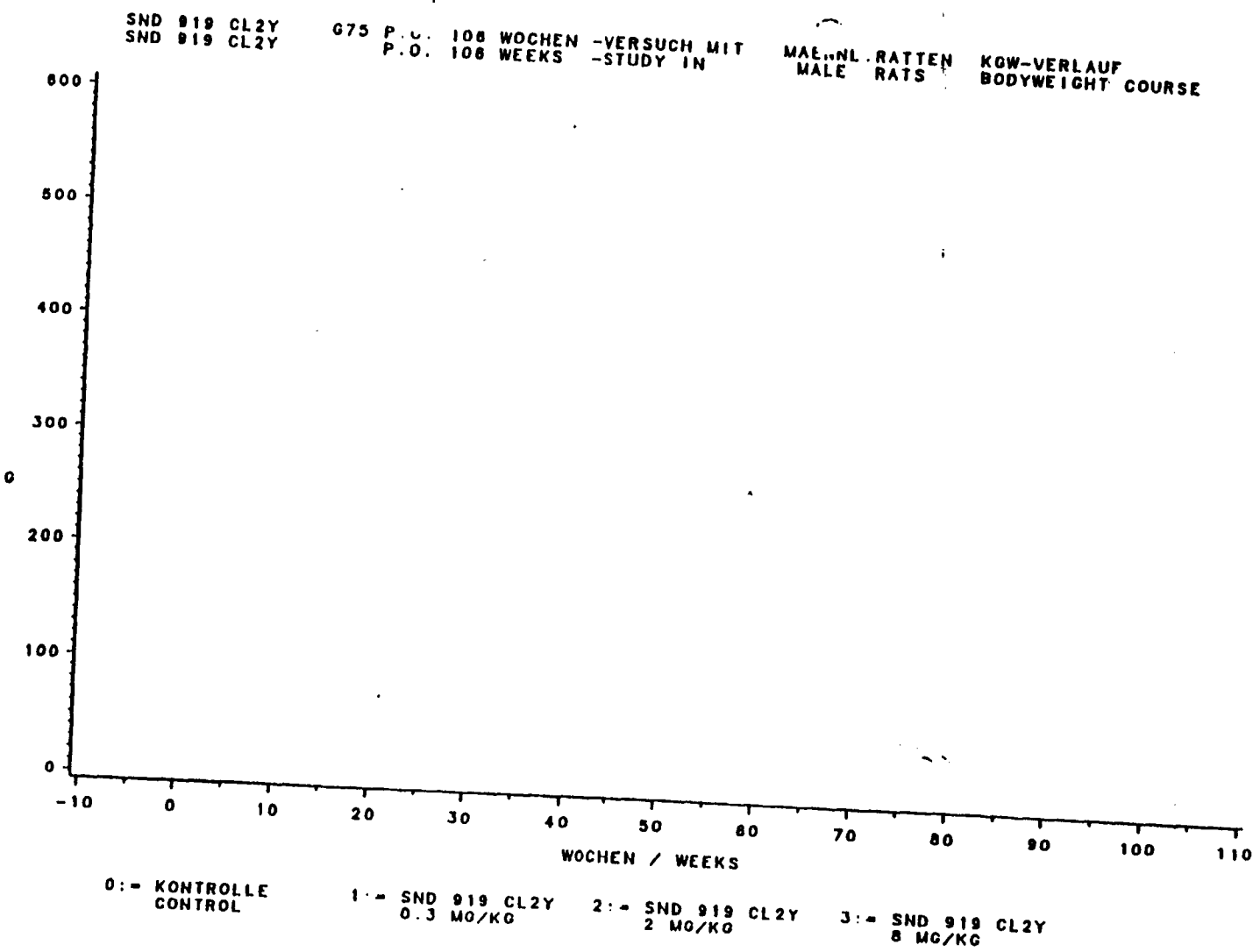


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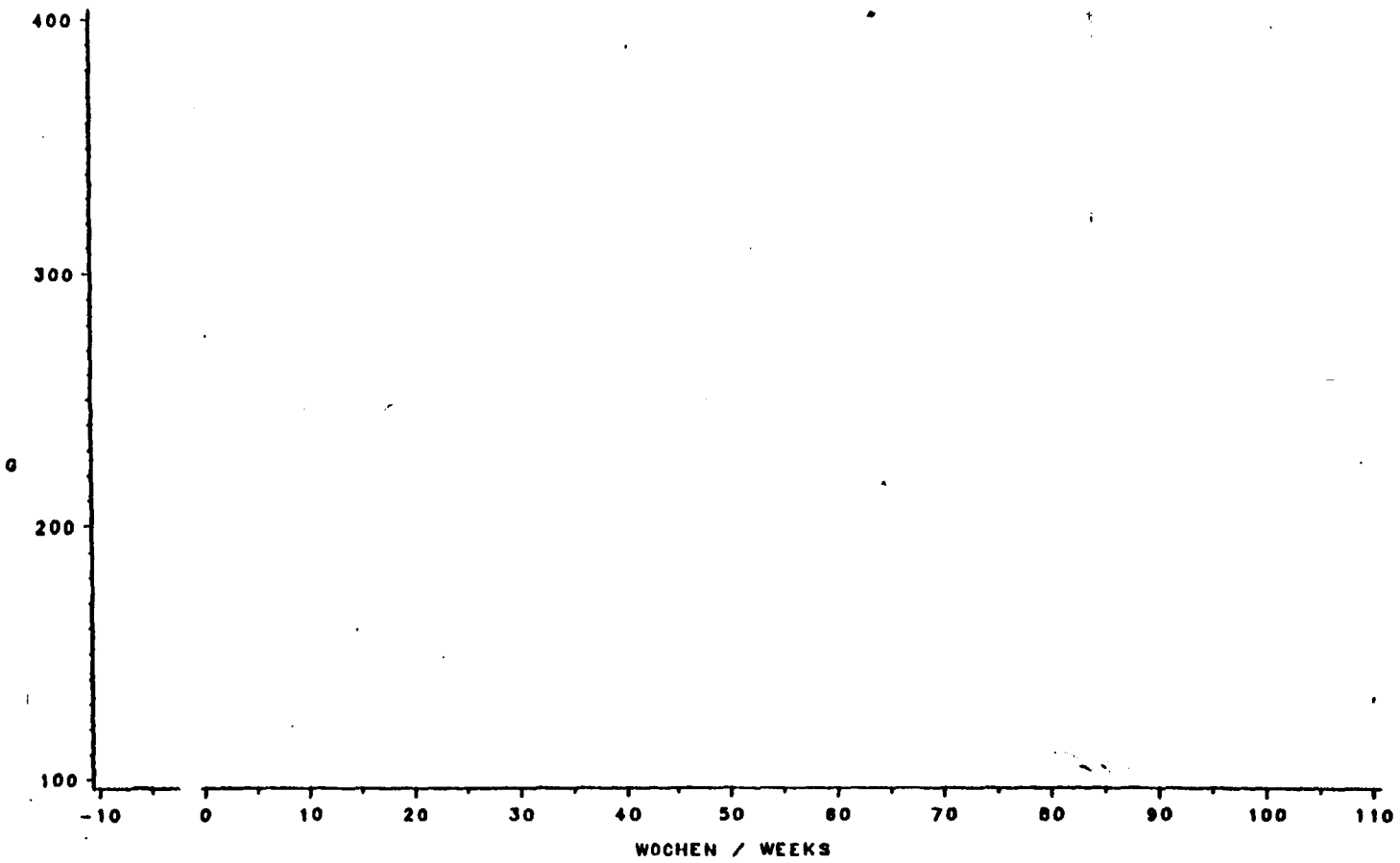
Figure 2



U-230

Figure 3

SND 919 CL2Y 075 P.C. 108 WOCHEN -VERSUCH MIT WEIL . . RATTEN KOW-VERLAUF
SND 919 CL2Y P.O. 108 WEEKS -STUDY IN FEMALE RATS BODYWEIGHT COURSE



0: = KONTROLLE CONTROL 1: = SND 919 CL2Y 0.3 MG/KG 2: = SND 919 CL2Y 2 MG/KG 3: = SND 919 CL2Y 8 MG/KG

Figure 4

U. 231

221

574231

Table 3
INTERCURRENT MORTALITY RATES

Weeks	MALE MICE			
	0	0.3	mg/kg/day 2.0	10.0
0- 52	1/100 (1%)	3/50 (6%)	6/50 (12%)	4/50 (8%)
53- 78	8/99 (9%)	2/47 (10%)	5/44 (22%)	9/46 (26%)
79- 92	7/91 (16%)	11/45 (32%)	7/39 (36%)	4/37 (34%)
93-104	5/84 (21%)	5/34 (42%)	3/32 (42%)	3/33 (40%)
Term. Sac.	79/100 (79%)	29/50 (58%)	29/50 (58%)	30/50 (60%)

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Weeks	FEMALE MICE			
	0	0.3	mg/kg/day 2.0	10.0
0- 52	0/100 (0%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
53- 78	5/100 (5%)	5/49 (12%)	2/48 (8%)	3/46 (14%)
79- 92	12/95 (17%)	8/44 (28%)	4/46 (16%)	8/43 (30%)
93-104	16/83 (33%)	8/36 (44%)	10/42 (36%)	7/35 (44%)
Term. Sac.	67/100 (67%)	28/50 (56%)	32/50 (64%)	28/50 (56%)

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Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

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Table 4

Results of Intercurrent Mortality Analyses

Male Mice

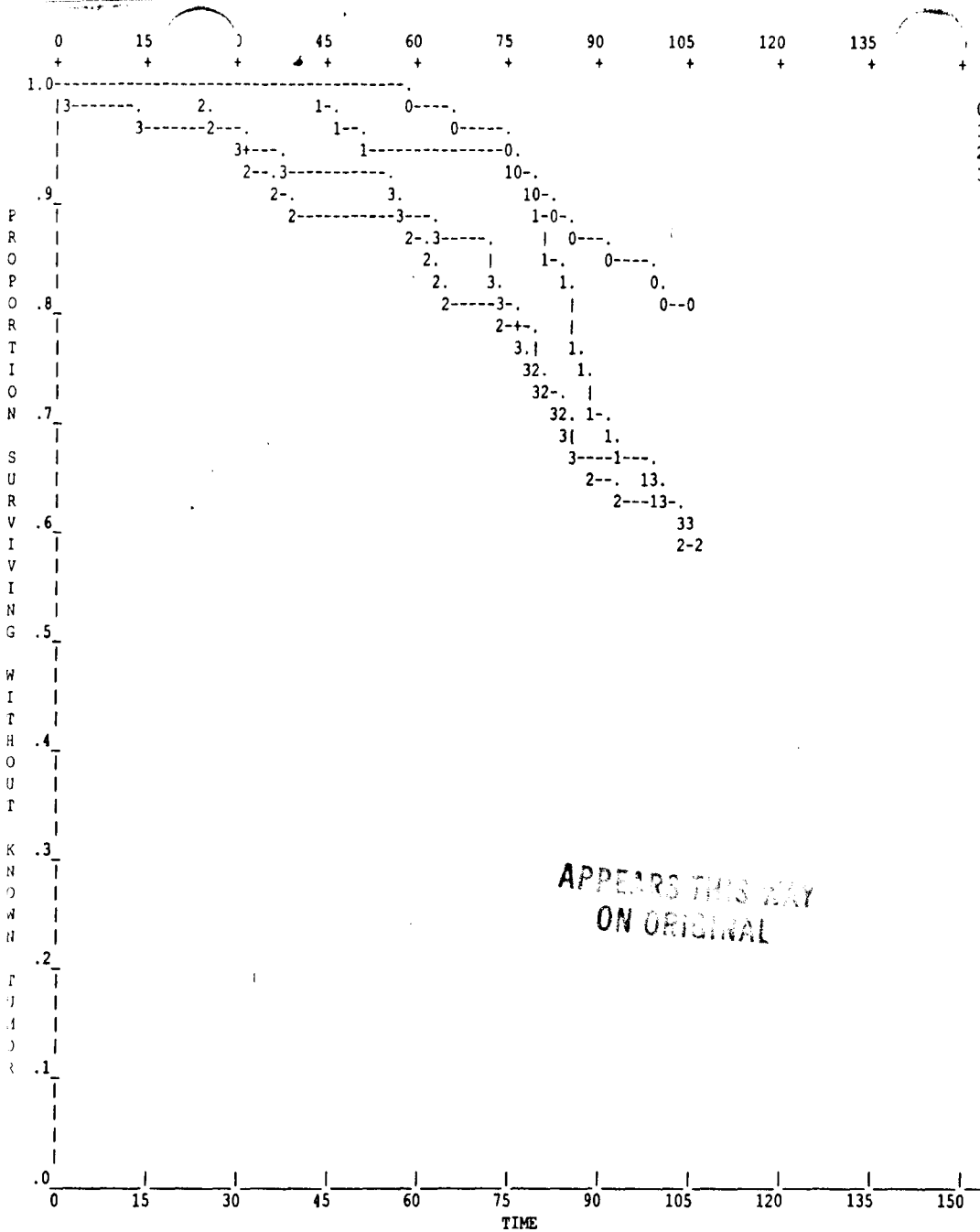
Groups Compared	Direction	<u>Two-tailed P-Value of Test</u>	
		Cox	Kruskal/Wallis
C, L, M, H	pos	.067	.040*
C, L	pos	.012*	.011*
C, M	pos	.006**	.002**
C, H	pos	.011*	.005**
L, M	pos	.857	.507
L, H	neg	.882	.625
M, H	nrg	.982	.873

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Female Mice

Groups Compared	Direction	<u>Two-tailed P-Value of Test</u>	
		Cox	Kruskal/Wallis
C, L, M, H	pos	.253	.205
C, L	pos	.153	.077
C, M	pos	.768	.607
C, H	pos	.163	.084
L, M	neg	.445	.314
L, H	pos	.984	.999
M, H	pos	.470	.339

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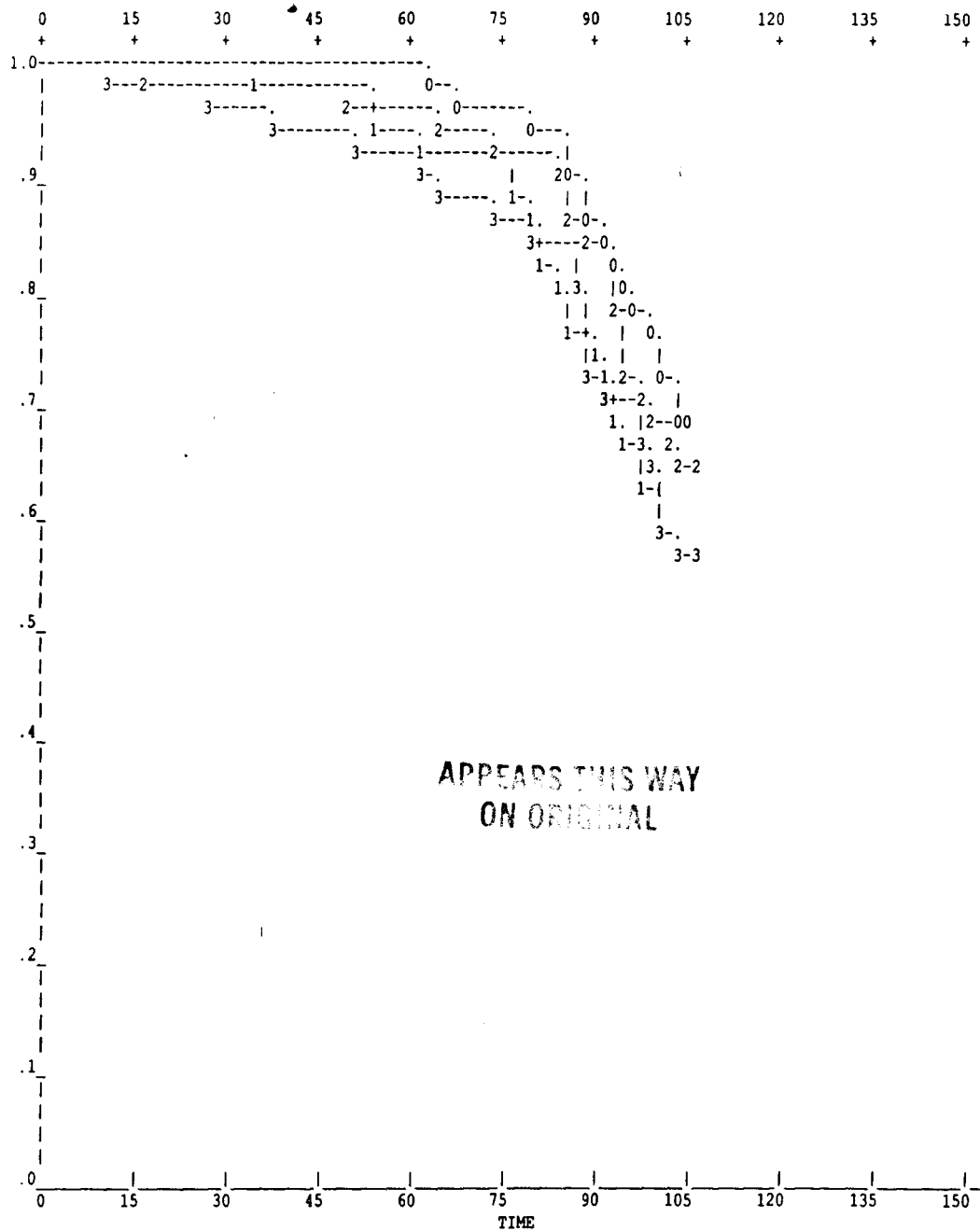


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Figure 5



0 cntrl-fem-mice
 1 low-fem-mice
 2 mid-fem-mice
 3 hi-fem-mice

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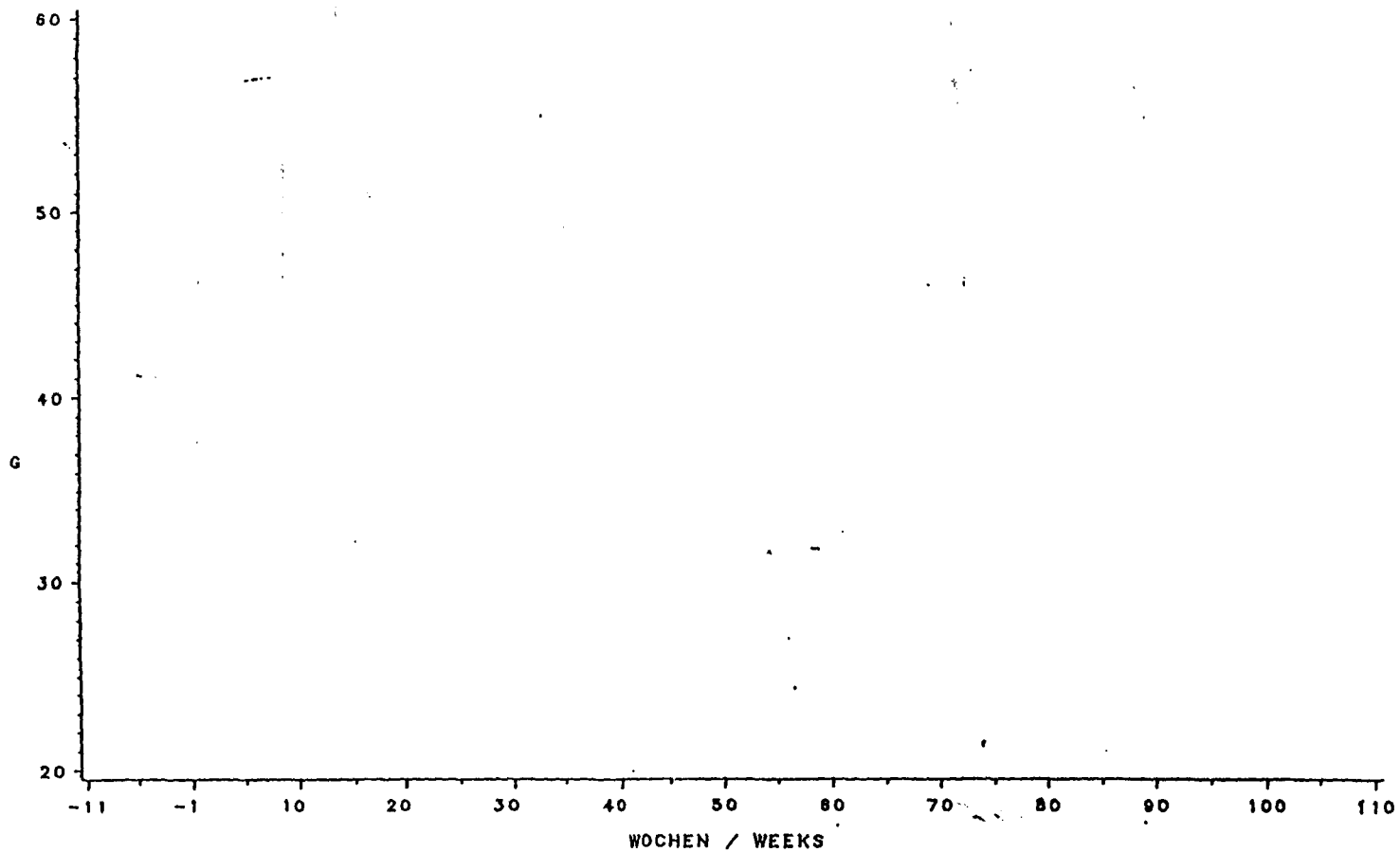
Figure 6

SND 919 CL2Y
SND 919 CL2Y

670 P.O. 104 WOCHEN -VERSUCH MIT
P.O. 104 WEEKS -STUDY IN

MAEN . . MAEUSEN
MALE MICE

KGW-VERLAUF
BODYWEIGHT COURSE



0: - KONTROLLE
CONTROL

1: - SND 919 CL2Y
0.3 MG/KG

2: - SND 919 CL2Y
2 MG/KG

3: - SND 919 CL2Y
10 MG/KG

Figure 7

U-185

TR No.: 7219-94-070

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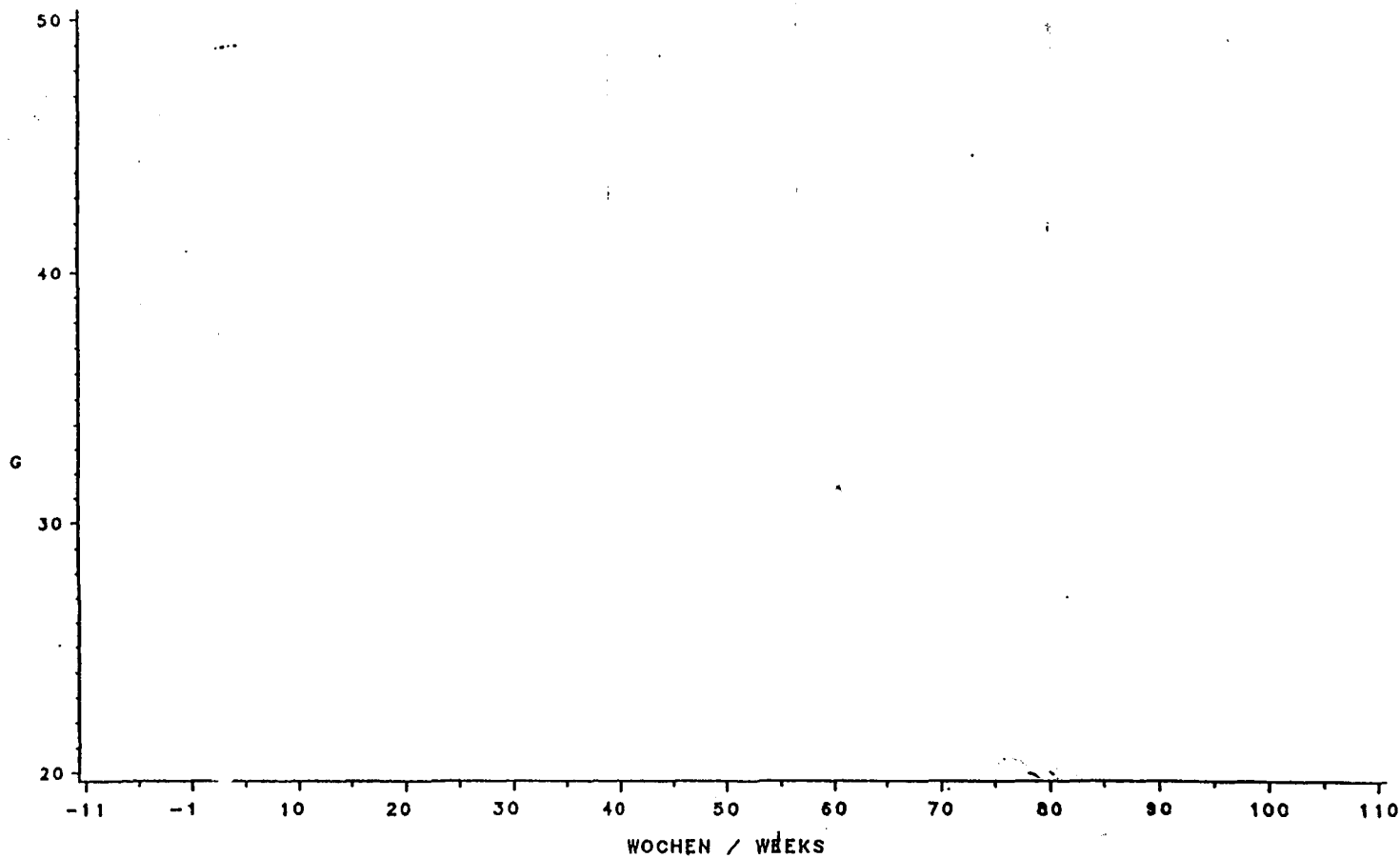
SND 919 CL2Y
SND 919 CL2Y

G70 P.O. 104 WOCHEN -VERSUCH MIT
P.O. 104 WEEKS -STUDY IN

WEIBL. MAEUSEN
FEMALE MICE

KGW-VERLAUF
BODYWEIGHT COURSE

TR No.: 7219-94-070



01- KONTROLLE
CONTROL

1:- SND 919 CL2Y
0.3 MG/KG

2:- SND 919 CL2Y
2 MG/KG

3:- SND 919 CL2Y
10 MG/KG

Figure 8

179

APPENDIX 1

P-VALUES ASSOCIATED WITH PAIRWISE COMPARISONS

Leydig Cell Adenomas Coded as Incidental:

<u>Comparison</u>	<u>Associated p</u>
Control 1 vs. High	.0604
Control 1 vs. Mid	.0322
Control 2 vs. High	.0075
Control 2 vs. Mid	.0031
Combined Crls vs. High	.0087
Combined Crls vs. Mid	.0029

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Leydig Cell Adenomas Coded as Undetermined:

<u>Comparison</u>	<u>Associated p</u>
Control 1 vs. High	.6000
Control 1 vs. Mid	.5333
Control 2 vs. High	.4371
Control 2 vs. Mid	.5833
Combined Crls vs. High	.3764
Combined Crls vs. Mid	.7143

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All Leydig Cell Adenomas:

<u>Comparison</u>	<u>Associated p</u>
Control 1 vs. High	.0620
Control 1 vs. Mid	.0610
Control 2 vs. High	.0067
Control 2 vs. Mid	.0028
Combined Crls vs. High	.0072
Combined Crls vs. Mid	.0040

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**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Original Summary**

NDA No.: 20667

Submission Date: 12/28/95

Drug: Pramipexole Oral Compressed Tablets

Sponsor: The Upjohn Co.
7000 Portage Rd.
Kalamazoo, MI 49001-0199

Reviewer: T.D. Steele

Indication: Parkinson's disease

Pharmacologic Class: Dopamine agonist

Chemical Information:

CAS Name: (S)-N6-Propyl-4,5,6,7-tetrahydro-2,6-benzothiazolodiamine, dihydrochloride, monohydrate

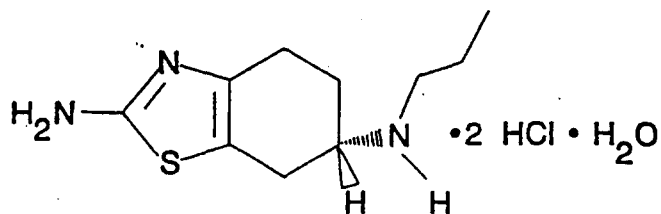
IUPAC Name: (S)-2-Amino-4,5,6,7-tetrahydro-6-propylaminobenzothiazole dihydrochloride monohydrate

Other Names: SND 919 CL 2 Y; U-98528E

Empirical Formula: $C_{10}H_{21}Cl_2N_3OS$

Molecular Weight: 302.27

Structure:



Note: Portions of this review were excerpted directly from the sponsor's submission:

Review Outline

	<u>Sponsor Volume</u>	<u>Review Page</u>
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A. PHARMACOLOGY

Volumes: 1.27-1.31 Boehringer-Ingelheim and Upjohn Technical Reports
1.62 Published articles

The following is a summary of preclinical pharmacology studies on the mechanism of action and efficacy of pramipexole. Most of these studies were reviewed under IND 34,850. The "Neuroprotection" studies (sec. A.3) that were submitted to support a labeling claim were not previously reviewed.

A.1. Mechanism of Action

A.1.a *In vitro* studies

In receptor binding assays, PPX displays high affinity for both D₃ and D₂ cloned receptors (4 to 8-fold higher at D₃; Tables A.1.a.1, 2). By comparison, the dopamine (DA) agonists bromocriptine and apomorphine are less potent and selective for D₃ and D₂ receptors, whereas pergolide has a higher affinity than PPX for both receptor subtypes (Table A.1.a.2). Consistent with the known receptor-effector coupling schemes for DA receptors, PPX binding to D₂ and D₄ receptors is inhibited by a non-hydrolyzable GTP analog indicating G-protein involvement in the mechanism; D₃ binding is not markedly affected. Autoradiographic studies indicate that the distribution of [³H]-PPX binding sites is consistent with receptor subtype mRNA distribution, high in mesolimbic areas (islets of Calleja, nucleus accumbens, olfactory tubercle) that are abundant in D₃ and D₂ receptors, and also in the D₂-rich caudate nucleus (Table A.1.a.3). Binding sites were less abundant in the ventral tegmental area (VTA) and the substantia nigra (SN). In a Novascreen receptor binding assay, the only other significant binding by PPX was at α_2 receptors (Table A.1.a.4).

In functional studies, PPX (0.1-100 μ M) decreased cAMP in primary cultures of cerebellar granule cells by a putative D₃ receptor mechanism. PPX inhibited electrically-stimulated DA release in rat striatal slices, presumably via activation of nerve terminal D₂ autoreceptors (i.e., block with haloperidol). PPX did not block synaptosomal uptake of radiolabelled monoamines at concentrations up to 10 μ M.

A.1.a.1
Table ~~2.2~~ Affinities of Pramipexole to Cloned Dopamine Receptors Expressed in Cultured Human Embryonic Kidney and Chinese Hamster Ovary Cells

Receptor	Radioligand	K _i * of pramipexole (nM)
Human D _{2L} receptor	[³ H]pramipexole	3.9†
Human D _{2S} receptor	[³ H]pramipexole	3.3†
Human D ₃ receptor	[³ H]pramipexole	0.5†
Human D ₄ receptor	[³ H]pramipexole	5.1‡

*K_i: Values are means of two to four experiments.

† Data from [22]

‡ Data from [23]

Tab. A.1.a.2

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TR No.: 7295-94-011

Table 1. Binding Affinities of Dopamine Agonists for Dopamine Receptor Subtypes.

Compound	Binding at Dopamine Receptors (K _i ± SEM in nM)			
	D1-Dopamine	D2-Dopamine	D3-Dopamine	D4-Dopamine
Bromocriptine U-43714E	3418 ± 129	27 ± 9	18 ± 2	373 ± 15
Apomorphine U-19542E	491 ± 29	26	17 ± 1	8.2 ± 1
Pergolide U-68326E	1300 ± 132	1 ± 0.2	0.4 ± 0.03	9.3 ± 1
Lisuride U-64047E	62 ± 4	0.3 ± 0.1	2.2 ± 0.2	3.2 ± 0.5
Pramipexole U-98528E	> 2,381	5.3 ± 0.3	1.3 ± 0.2	18 ± 4

Table 2. Binding Affinities of Dopamine Agonists for Serotonin Receptor Subtypes.

Compound	Binding at Serotonin Receptors (K _i ± SEM)			
	5-HT _{1A}	5-HT _{1Dα}	5-HT _{1Dβ}	5-HT ₂
Bromocriptine	24 ± 9	22 ± 5	708 ± 84	119 ± 37
Apomorphine	103 ± 11	1,399 ± 109	> 4,000	343 ± 51
Pergolide	1.8 ± 0.4	21 ± 6	111 ± 8	26 ± 7
Lisuride	0.2 ± 0.03	7.6 ± 0.8	20 ± 3	5.1 ± 1.1
Pramipexole	> 1,698	2,429 ± 301	> 4,000	> 1,131

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TABLE A.1.a.3

Densities of D₂ and D₃ Receptors Bound By [³H]-PPX in Areas of Rat Brain

The data were derived from quantification of autoradiograms produced from coronal sections.

Structure	Specific Bound (mean±SEM)*		B _{max} D ₂ Receptor*	B _{max} D ₃ Receptors*
	right	left		
N. accumbens	42±3		97±7	45±3
	42±9		97±21	45±10
Anterior cingulate cortex	13±4		30±9	
	12±5		28±13	
Sensory cortex	16±3		37±7	
	12±6		37±18	
Olfactory Tubercle	46±11		105±25	49±12
	47±15		108±34	50±16
Islets of Calleja Major	58±14		133±32	62±16
	60±14		138±32	64±16
Islets of Calleja Medial	52±8		120±18	62±9
	52±15		120±35	62±18
N. caudate	43±8		99±18	
	48±11		110±25	

* fmol/mg P based on K_d = 6.5 nM (D₂) or 0.37 nM (D₃).

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A.1.a.1

Table ~~5.1.1~~ Affinities of Pramipexole to Different Receptor Preparations From Brain Homogenates as Estimated by Receptor Binding Assays ([30] unless otherwise indicated).

Receptor	Radioligand	K _i of pramipexole (nM)
Dopamine D ₂ receptor	[³ H]spiroperidol	1350
Dopamine D ₂ receptor*	[³ H]spiroperidol (high affinity state)	105
Dopamine (D ₂) receptor†	[³ H]pramipexole	2.9
Dopamine D ₁ receptor‡	[³ H]SCH 23390§	>100,000
α ₁ -Adrenoceptor	[³ H]prazosin	28,700
α ₂ -Adrenoceptor	[³ H]clonidine	250
Muscarinic receptor	[³ H]QNB¶	30,700
Serotonin 5-HT ₁ receptor	[³ H]serotonin	4,200
Serotonin 5-HT ₂ receptor	[³ H]spiroperidol	>40,000
Histamine H ₁ receptor	[³ H]pyrilamine	>10,000
Histamine H ₂ receptor	[³ H]tiotidine	5,300
β ₁ -Adrenoceptor‡	[³ H]DH-Alprenolol	>10,000
β ₂ -Adrenoceptor‡	[³ H]DH-Alprenolol	>10,000
Serotonin-5-HT _{1A} ‡	[³ H]8-OH-DPAT	3,069
Adenosine-A ₂ ‡#	[³ H]CGS 21680	>100,000
Benzodiazepine‡	[³ H]Flumitrazepam	>10,000
NMDA/MK-801‡#	[³ H]MK-801	>10,000
NMDA/Glycine‡	[³ H]DCKA	>100,000
AMPA#	[³ H]Glutamate	>10,000

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A.1.b. *In vivo* studies

In behavioral studies, low doses of PPX decreased locomotor activity in mice ($ED_{50} = 0.084$ mg/kg, p.o.). This is presumably due to activation of D_2 autoreceptors which shut down release of endogenous DA. Higher doses of PPX (mg/kg, s.c.) stimulated locomotor activity in rats, but did not induce apomorphine-like stereotypic climbing in mice (0.003 - 10 mg/kg, p.o.). Other behavioral effects of PPX that are likely attributed to postsynaptic D_2 receptor activation are yawning in rats (mg/kg, s.c.), reversal of haloperidol-induced catalepsy in rats ($ED_{50} = 4.4$ mg/kg, s.c.), dose-dependent induction of gnawing in rats (mg/kg, s.c.), and stimulation of locomotor activity in reserpinized mice (9 mg/kg, i.p.).

The primary *in vivo* neurochemical effects of PPX appear to result from stimulation of presynaptic D_2 autoreceptors which reduces dopamine turnover. PPX decreased DA synthesis as measured by inhibition of DOPA accumulation in striatum and limbic system after γ -butyrolactone lesions of dopaminergic pathways:

	ED_{50}
striatum	0.13 mg/kg, s.c.
limbic forebrain	0.05 mg/kg, s.c.

The effect of PPX in the striatum was blocked by haloperidol indicating a D_2 receptor-mediated action. The more potent, but not statistically significant, effect in the limbic forebrain was suggested to be due to D_3 activation. No pharmacological evidence was provided in support of this contention. A PPX-induced decrease in dopamine release was also demonstrated in α -methyltyrosine-treated rats ($ED_{50} = 0.04$ mg/kg, s.c.) and by *in vivo* microdialysis.

Evidence for activation of DA autoreceptors by PPX was also obtained in electrophysiology studies where decreases in the firing rate of nigrostriatal (SNPC) and mesolimbic (VTA) neurons were observed:

	ED_{50}
SNPC	0.066 mg/kg, i.v.
VTA	0.082 mg/kg, i.v.

In anterior caudate neurons, PPX stimulated the firing of postsynaptic neurons at higher doses (10 mg/kg, i.v., increased firing by 60%). This was suggested to be a D_3 effect since other D_2 -preferring agonists did not affect firing.

A.2. Efficacy in Parkinson's Disease Models

PPX (mg/kg, s.c.) caused contralateral turning in rats with 6-hydroxydopamine (6-OHDA)-induced lesions of the medial forebrain bundle. The ED_{50} (0.026 mg/kg, s.c.) indicated that PPX was equipotent to apomorphine ($ED_{50} = 0.03$ mg/kg, s.c.). Maximal effects of PPX occurred between () min, whereas the duration of action for apomorphine was ≤ 80 min. The effect was completely blocked by haloperidol, and partially blocked by the D_1 antagonist SCH 23390.

In the MPTP-induced Parkinson's-disease model in primates, PPX (mg/kg, i.m.) dose-dependently reversed parkinson-like symptoms ($ED_{50} = 0.045$ mg/kg, i.m.). A dose of 0.06 mg/kg relieved virtually all of the symptoms. In a second experiment, an oral dose of 0.075 mg/kg reversed Parkinsonian symptoms for 5-24 hr. Several other Parkinson's agents did not consistently affect symptomology (≤ 2 mg/kg biperiden, p.o., <300 mg/kg amantadine, p.o., ≤ 2 mg/kg bromocriptine, p.o.). L-DOPA/carbidopa (15 mg/kg, p.o.) was effective for 2 hrs (Table A.2.a). When tested in combination with the monoamine oxidase inhibitor l-deprenyl (Eldepryl, 0.2 mg/kg, i.m.), the effectiveness of PPX (μ g/kg, i.m.) was not potentiated.

Boehringer Ingelheim KG

Tab. A.2.a.

Substance	Optimal efficacy from (mg/kg)	Duration of action	Side effects at high dosage
Combination L-dopa (+ ben- serazide and carbidopa)	15 p.o.	h	salivation motor restlessness
Biperidene (Akineton)	up to 2.0		
Amantadine (PK-Merz)	up to 300	unsatisfactory effect	
Bromocriptine (Prävidel)	up to 2.0		
B-HT 920	0.05 p.o.	h	sedation, ataxia
SND 919 Y	0.075 p.o. 0.05 i.m.	h	occasional sali- vation raised reactivity

Tab. 9: Effect of antiparkinsonian drugs and agents under development on MPTP-induced Parkinson's disease in monkeys.

A.3. Neuroprotection

The sponsor proposes a labeling claim suggesting neuroprotective effects of pramipexole based on data from three preclinical models:

1. Prevention of post-ischemic retrograde degeneration of nigrostriatal dopamine neurons following transient forebrain ischemia (Bilateral Carotid Artery Occlusion Model, BCAA) in gerbils
2. Attenuation of methamphetamine-induced nigrostriatal dopaminergic neurotoxicity in mice
3. Attenuation of L-DOPA neurotoxicity *in vitro*

In the gerbil transient forebrain ischemia study, pramipexole (1 mg/kg, p.o., b.i.d. for 28 days beginning on the day of surgery) attenuated by 40% the loss of tyrosine hydroxylase (TH)-positive neurons in the substantia nigra (Fig. A.3.a.1). A much smaller degree of protection was afforded in the CA1 region of the hippocampus (cresyl-violet staining), and statistically significant in only a preliminary experiment (Fig. A.3.a.2). Details regarding the timing of drug administration relative to the ischemic insult were not provided. In the *in vivo* methamphetamine neurotoxicity study, four daily doses pramipexole (1 mg/kg, p.o.) beginning 1 hr after the last methamphetamine injection (10 mg/kg, i.p., every two hrs for four doses) completely prevented the loss of TH-positive neurons in the substantia nigra of mice five days after methamphetamine dosing (Fig. A.3.a.3). The proposed protective mechanism is prevention by pramipexole of methamphetamine-induced elevations in dopamine turnover which, if not prevented, would lead to tissue damage *via* the generation of oxygen-derived free radicals. In the *in vitro* experiment, nanomolar concentrations of pramipexole prevented the loss of TH-positive cells due to micromolar concentrations of L-DOPA in primary cultures of rostral mesencephalic tegmentum cells (Fig. A.3.a.4). Preliminary evidence suggested the involvement of a heat-sensitive trophic factor in the protective effect of pramipexole.

The gerbil BCAA transient forebrain ischemia model is an acceptable preclinical efficacy screen for drugs proposed in the treatment of stroke. The clinical relevance of the *in vivo* methamphetamine and *in vitro* L-DOPA neurotoxicity models is not established. The results from the ischemia study would provide some preclinical support for a clinical trial proposal, although only one of the two regions examined appeared to be significantly protected. The potential clinical relevance of these findings is further compromised since no mechanistic basis of protection was evaluated. For instance, the observed protection may simply be a consequence of the hypothermic effects of pramipexole, and not related to inhibition of dopamine release. Thus, a labeling claim suggesting that pramipexole "reduces dopamine-induced neuronal degeneration", which has significant and far-reaching clinical implications, is not supported by these preclinical findings.

FIGURE 2. Dose-response for pramipexole's effect on the loss of tyrosine hydroxylase-positive neurons 28 days following a 10-min BCO in the gerbil. Data given as mean $\pm$ SEM.

A.3.a.1

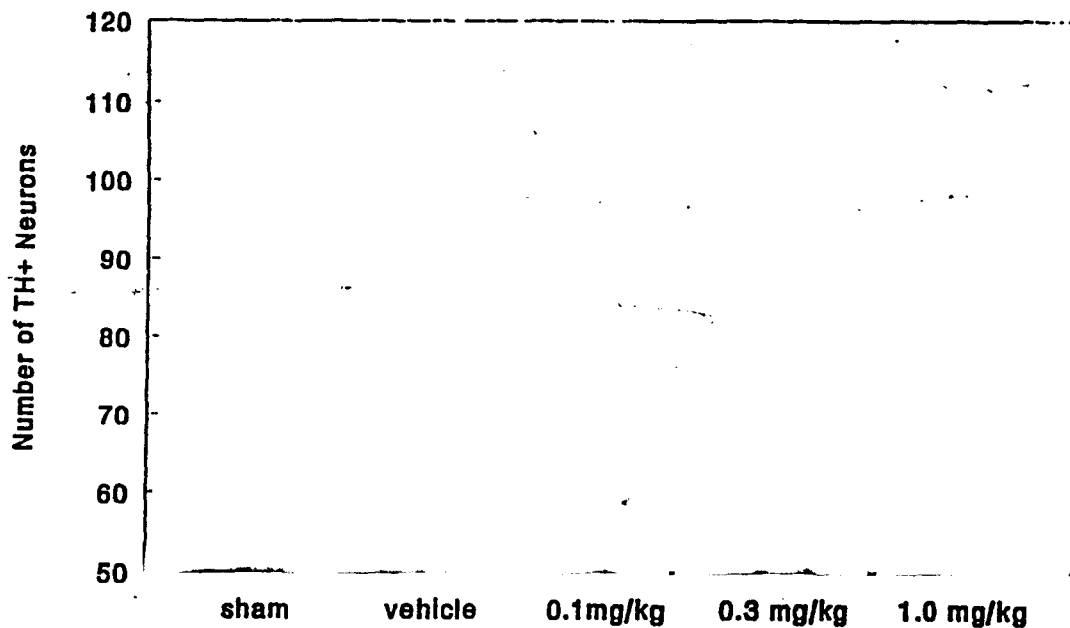


FIGURE 3. Dose-response of pramipexole's effect on neuronal damage in the CA₁ region of the hippocampus 28 days following a 10-min BCO in the gerbil. Data given as mean $\pm$ SEM.

A.3.a.2

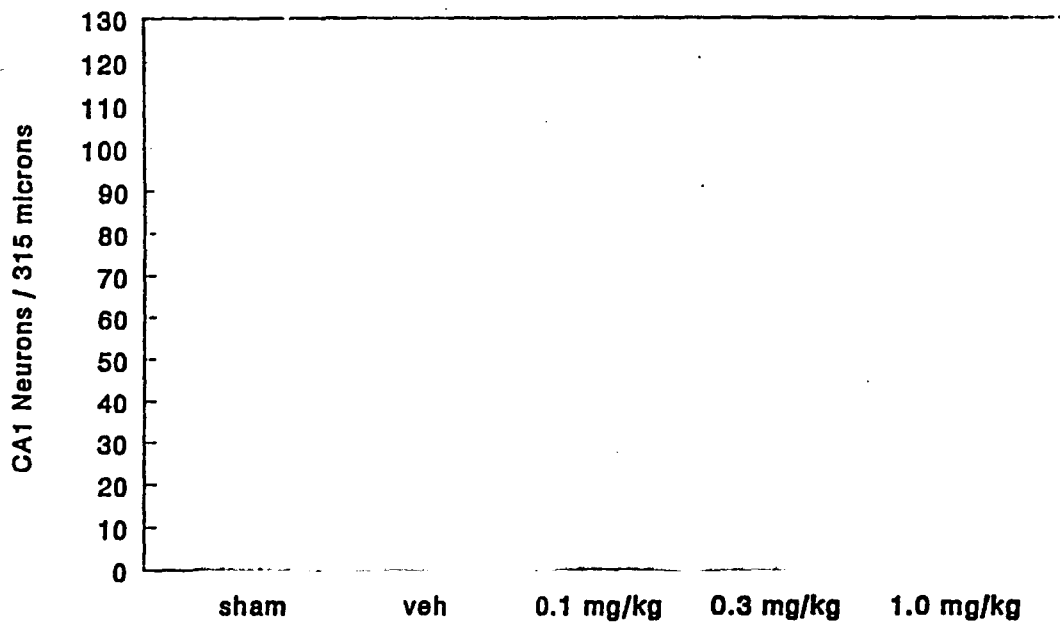
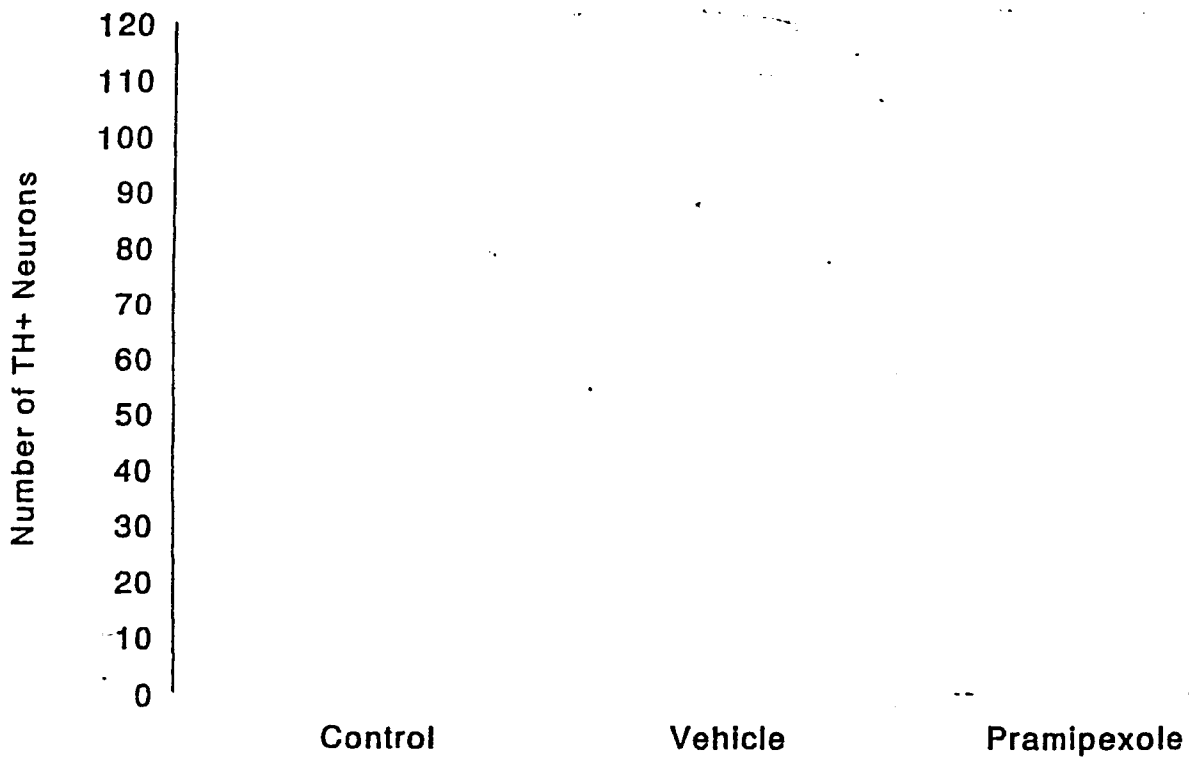


Fig. A.3.a.3

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**Effects of Pramipexole (1 mg/kg)
on the Loss of Tyrosine Hydroxylase Positive Neurons
5 Days Following Methamphetamine Treatment in Mice**



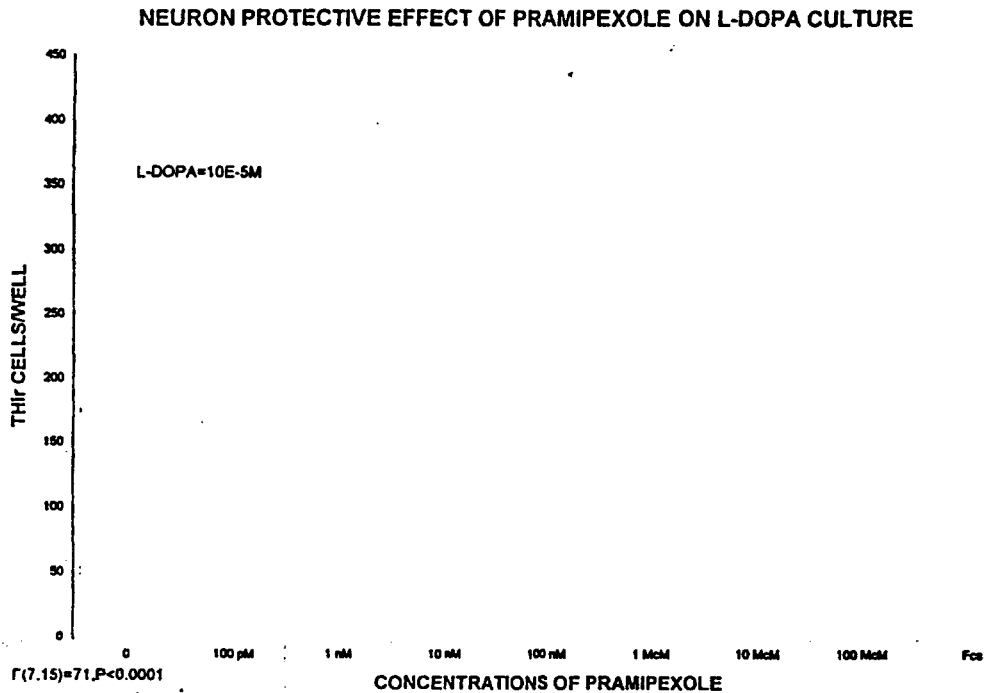
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FIGURE 3.a. 1.

Dose-dependent neuroprotective effects of pramipexole in an L-dopa toxicity model of THIR cells. Data are mean and S.E. for at least two experiments. Procedures for culture methodology, immunostaining and cell count assessment are described in the Methods. Immediately following plating, RMT cultures were exposed to various concentrations of pramipexole with or without L-dopa (10 μ M) for 72 hrs and THIR cells were counted.



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A.4. Other Indications

The sponsor has submitted several preclinical studies to demonstrate the efficacy of PPX in other indications including anxiety, depression and schizophrenia. These studies are not considered relevant to the present application and were not reviewed.

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B. SAFETY PHARMACOLOGY

B.1. Central Nervous System Effects

Aside from the aforementioned behavioral changes, relatively few significant CNS effects were induced by acute treatment with PPX. Ataxia did not occur in mice at PPX doses of mg/kg , p.o., or mg/kg , s.c. Doses of mg/kg , s.c., did not lower the threshold for pentylenetetrazol-induced seizures in mice. Monkeys were slightly sedated by doses of $\mu\text{g/kg}$, i.m. and $300 \mu\text{g/kg}$, p.o. REM and non-REM sleep in rats was suppressed by 0.3 mg/kg , p.o. A biphasic effect on sleep was observed in cats; low doses (0.1 mg/kg , p.o.) increased non-REM sleep initially, followed by reduction in REM and non-REM sleep. Higher doses (0.3 mg/kg) completely suppressed sleep. PPX decreased body temperature in mice by 2°C with an ED_{50} of 0.23 mg/kg , s.c.

B.2. Cardiovascular/Respiratory Effects

In anesthetized cats, PPX (mg/kg) caused a slight, transient (min), non-dose-dependent decrease in blood pressure and a slight bradycardia at 1 mg/kg , but did not alter respiration. In anesthetized rabbits, 0.03 mg/kg , i.v. decreased blood pressure, and 0.1 mg/kg decreased both pressure and heart rate. The cardiovascular effects of 0.3 mg/kg PPX were blocked with dopamine antagonists. In spontaneously hypertensive rats (SHRs), mg/kg , i.v., PPX lowered blood pressure by a D_2 -receptor mechanism. Higher doses (0.1 - 1 mg/kg , i.v.) increased blood pressure by a peripheral α_2 -receptor mechanism. After oral administration of 3 and 30 mg/kg PPX to SHRs, a slight bradycardia was the only effect observed. In a study with anesthetized SHRs, PPX (mg/kg , i.v.) decreased blood pressure and the effect could be blocked by either a D_1 or D_2 antagonist.

A special series of studies were conducted in rhesus monkeys to evaluate the cardiovascular effects of pramipexole in combination with other drugs used in Parkinson's disease (i.e., Sinemet and Eldepryl; mg/kg). In a pilot study, a dose of 0.05 mg/kg p.o., but not 0.1 mg/kg , lowered blood pressure for up to 6 hrs. Doses of mg/kg produced a non-dose-dependent bradycardia, although the duration of effect increased with dose (hr). In the combination study, slight (non-significant) decreases in heart rate, diastolic blood pressure, and mean arterial blood pressure following 0.05 mg/kg PPX, p.o., were not potentiated by either Sinemet (100 mg/kg L-DOPA/ 10 mg/kg carbidopa, p.o.) or Eldepryl (0.2 mg/kg , p.o.).

B.3. Gastrointestinal Effects

Like other dopamine agonists, PPX induced emesis in dogs (ED_{50} s = 0.0067 mg/kg , p.o., and 0.0052 mg/kg , s.c.). The effect was blocked with a dopamine antagonist. PPX inhibited gastrointestinal transit in mice (ED_{50} = 0.033 mg/kg , p.o.).

B.4. Renal Effects

Conflicting results were obtained in assessments of the renal effects of PPX in rats. In conscious rats, PPX (0.3 mg/kg, p.o.) produced a moderate decrease in urinary volume; electrolyte excretion was not significantly affected. In a study from an independent investigator with anesthetized normotensive (WKY) and spontaneously hypertensive (SHR) rats (Kaneko, et al., J. Auton. Pharmacol., 10(suppl. 1):s53, 1990), PPX (_____ mg/kg, i.v.) increased urine volume and Na excretion. The low dose effects of PPX were antagonized by a D₁ antagonist and the high dose effects by a D₂ antagonist. The contrasting effects of PPX in conscious and anesthetized animals may have been due to the anesthesia, PPX dose, strains of rats, or the use of water-loading in the former, but not the latter study. The effectiveness of the D₁ antagonist against PPX in this study suggest that the renal effects of PPX may be mediated by D₁ receptors, and additional biochemical data support this hypothesis.

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C. TOXICOLOGY

C.1. Acute Toxicology

Conducted by: Boehringer Ingelheim KG
Department of Experimental Pathology and Toxicology
D-6507 Ingelheim am Rhein
West Germany

Sponsor Volume: 1.31

These studies complied with GLP

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Summary

Acute toxicology studies were conducted in mice, rats and dogs. Animals were observed for up to 14 days following treatment. The lethality of PPX was approximately 10-fold higher in mice and 4-fold higher in rats by the intravenous versus oral route of administration. Common signs of toxicity were exophthalmus, piloerection, tremors/convulsions, ataxia and hypomotility, nervousness/agitation and hypermotility, and tachypnea or dyspnea. Most deaths following i.v. treatment occurred shortly after dosing, whereas delayed deaths were more common following oral administration. The primary sign at autopsy of animals that died following drug treatment was hemocongestion of large organs. Animals that were sacrificed at the end of the study did not show any consistent pathologies. The dog studies were limited by the pronounced emetic effect of PPX.

C.1.a. Acute Oral Toxicity in Mice

Doses: 1400, 2000 mg/kg n = 10 (5M, 5F)

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Results:

	# deaths	
	1400 mg/kg	2000 mg/kg
0-6 hr	2	3
6-24 hr		3
1-7 days	1	2

Signs: exophthalmos, piloerection, tremors/convulsions, hypomotility

LD₅₀: ca. 1700 mg/kg

C.1.b. Acute Intravenous Toxicity in Mice

Doses: 100, 125, 160, 200 mg/kg n = 10 (5M, 5F)

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Results:

	# deaths			
	100 mg/kg	125 mg/kg	160 mg/kg	200 mg/kg
0-6 hr	0	0	6	7

Signs: exophthalmos, convulsions, tachypnea

LD₅₀s: male: 155, female: 188, m+f: 169

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C.1.c. Acute Oral Toxicity in Rats

Doses: Study I: 100, 200 mg/kg n = 10 (5M, 5F)
 II: 200, 400, 560, 800 mg/kg n = 10 (5M, 5F)

(In study I, animals were housed in plastic cages, and deaths were attributed to choking on bedding. In study II, the animals were housed in suspended cages)

Results:

	# deaths					
	100 mg/kg	200 mg/kg	200 mg/kg	400 mg/kg	560 mg/kg	800 mg/kg
0-6 hr					1	3
6-24 hr						
1-2 days	1	1				
2-7 days	2	4	1		2	2
7-14 days						1

Signs: exophthalmos, chewing, ataxia, automutilation

LD₅₀s:

	<u>0-24 hr</u>	<u>> 24 hr</u>
male:	> 800	> 800
female:	> 852	> 548
m + f:	> 957	> 809

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C.1.d. Acute Intravenous Toxicity in Rats

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Doses: Study I: 100, 140 mg/kg n = 10 (5M, 5F)
II: 200, 400, 560, 800 mg/kg n = 10 (5M, 5F)

(In study I, animals were housed in plastic cages, and deaths were attributed to choking on bedding. In study II, the animals were housed in suspended cages)

Results:

	# deaths				
	100 mg/kg	140 mg/kg	140 mg/kg	180 mg/kg	225 mg/kg
0-6 hr					7
6-24 hr		1			
1-2 days	2	1			
2-5 days	2	3			

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Signs: exophthalmos, dyspnea, convulsions, ataxia, hypomotility
Autopsy: pulmonary hemocongestion
LD₅₀: ca. 210 mg/kg

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5. Acute Oral Toxicity in Beagles

Doses: 0.001, 0.01, 0.1, 1.0 mg/kg; n = 1/sex/dose

Results: 0.01-1 mg/kg caused emesis; 1 mg/kg caused mydriasis and decreased food intake

6. Acute Intravenous Toxicity in Beagles

Doses: 1, 3, 5, 10 µg/kg; n = 1/sex/dose

Results: 3 µg/kg caused salivation; doses ≥ 3 µg/kg in females and ≥ 5 µg/kg in males caused emesis

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C.2. Chronic Toxicology

C.2.a. 52-Week Toxicity Study in the Rat

Conducted by: Boehringer Ingelheim KG
Dept. Exp. Pathol. and Toxicol.
D-6507 Ingelheim am Rhein
Germany

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Document #'s: BI Document 90-0557
Upjohn TR 7219-94-067

Sponsor Volumes: 1.34-1.36

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This study complied with GLP

Significant notation:

The sponsor has attached an Amendment (no. 2) to the original report. The basis for the amendment was a discrepancy in the terminology used by histopathologists evaluating the data from the 52-week rat chronic toxicity study and the 2-year rat carcinogenicity study. Briefly, mammary gland changes were observed in female rats from the mid- (3.0 or 2.0 mg/kg) and high- (15.0 or 8.0 mg/kg) dose groups of both studies. In the 52-week study, the changes were described as an "increase in mammary gland acini (control: 13/20, low dose: 6/20, mid dose: 17/19, high dose: 20/20) with concurrent hypertrophy and/or hyperplasia of the glandular epithelium (controls 0/20, low dose: 0/10, mid dose: 8/19, high dose: 19/20)...". In the 2-year rat carcinogenicity study, these changes were designated as a "change in the normal glandular growth pattern", according to the work of Cardy ("Sexual dimorphism of the normal rat mammary gland", Vet Pathol, 28:139-145, 1991). Consequently, the histopathology slides from the 52-week rat study were re-evaluated using the terminology of Cardy. Diagnoses that were originally described as "increase in glandular acini" were changed to "proliferation of glandular epithelium". Original diagnoses of "hypertrophy" or "hyperplasia" were changed to "mixed tubuloalveolar/lobuloalveolar pattern" or "lobuloalveolar pattern." According to the redefinition, only one case of mammary gland hyperplasia (alveolar) was identified in the 52-week rat study (1 LDF).

Summary:

Pramipexole was administered in the diet to Wistar rats (Chbb:THOM) for 52 weeks at dose of 0, 0.5, 3.0 and 15.0 mg/kg. Toxicology dosage groups were composed of 20 rats/sex; a satellite group of 7 rats/sex/dose were used for toxicokinetic analysis. Administration of the lowest test dose resulted in slight behavioral activation in both sexes, and decreased body weight gain, cholesterol and triglycerides in females. Body weight gain was reduced in both sexes by the mid and high doses. The female clinical chemistry changes were more evident at the mid and high doses. In addition, sporadic, modest elevations in transaminases, alkaline phosphatase and urea, and decreases in serum potassium occurred at the mid and high doses,

generally more frequently in females than in males. Slight thrombocytopenia (MD, HD) and slight-to-moderate increase in the granulocyte/lymphocyte ratio were evident in females. Organ weight changes were reduced liver weights in HDM, and reduced thymus weights in MDF and HDF. Ovarian weights were increased at all dosage levels, and enlarged corpora lutea were observed at the mid and high dose. Histopathological changes in the uteri (dilatation, serous contents, pyometra) and mammary glands (the above-mentioned glandular pattern changes) were also evident in MDF and HDF. Leydig cell hyperplasia occurred only in PPX-treated males, but the incidence was highest at the low dose level. Eleven animals (4 control, 7 PPX-treated) were identified with tumors, none of which could be clearly attributed to PPX treatment. One control and one LDM had Leydig cell adenoma.

Toxicokinetic analyses suggested that PPX concentrations tended to increase dose-proportionally in females, but were greater than dose-proportional in males. This resulted in higher plasma levels in HDM compared to HDF at week 26 and 52.

The "No Toxic Effect" level was considered as 0.5 mg/kg. The plasma levels measured at 1 hr after the start of the light phase during week 26 and 52 at this dose (4.0 - 6.5 ng/ml) approximate the steady-state C_{max} in humans administered the projected maintenance dose of 1.5 mg PPX, t.i.d (5.5-7.2 ng/ml).

Methods:

Dosages: 0.5, 3.0, 15.0 mg/kg (Batch II)

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Route of Administration: Drug-in-diet

Species/Strain/Number: Rat/Wistar (Chbb:THOM)

80 males, 80 females for toxicology
21 males, 21 females for plasma toxicokinetics

Mean initial weights: males: 296.1g
females: 193.8g

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Dosages/Group Designation:

Group	Dosage (mg/kg/day)	Number of animals	
		males	females
0 (control)	0	20	20
1 (low dose=LD)	0.5	20	20
2 (middle dose=MD)	3.0	20	20
3 (high dose=HD)	15.0	20	20
4 (for determination of plasma con-	0.5	7	7
5 centrations only)	3.0	7	7
6	15.0	7	7

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Parameters monitored/Intervals:

Clinical - daily
Body weight - weekly
Food consumption - weekly
Water consumption - weekly (weeks 14, 26, 36, 48)
Spontaneous Activity - during weeks 1, 17, 34, 49 for a 22-hr period
Ophthalmology - weeks -1 & 51 (groups 0 and 3); weeks 12 & 25 (3 only)
Hematology - weeks -2, 6, 13, 27, 39, 52

Erythrocytes
Haemoglobin
Haematocrit
MCV, MCH, MCHC
Reticulocytes

Leucocytes
Differential blood count
Thrombocytes
Thromboplastin time (TPT)

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Clinical Chemistry - weeks -2, 6, 13, 27, 39, 52

GPT
GOT
Alkaline phosphatase
Bilirubin
Cholesterol
Triglycerides
Urea
Creatinine

Glucose
Sodium
Potassium
Calcium
Chloride
Inorganic phosphate
Protein
Protein electrophoresis

Urinalysis - weeks 12, 25, 38, 42, 50 (groups 0 and 3)
weeks 38, 42 (groups 1 and 2)

Specific gravity
pH
Protein
Glucose

Blood
Ketone bodies
Bilirubin
Urobilinogen
Nitrite
Examination of
sediment

Plasma Conc - weeks 1, 26, 52 at hrs 1 and 8

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Organ Weights - termination

Brain
Pituitary gland
Salivary glands (Glandula submaxillaris et
sublingualis major)
(Parotid gland if required)
Thyroid gland
Thymus
Heart

Lungs
Liver
Spleen
Kidneys
Adrenal glands
Gonads
Prostate

Histopathology

Tongue
 Cervical lymph nodes
 Both pinnae with ear tattoo
 Trachea and larynx (latter not sectioned)
 Oesophagus
 Aorta
 Sternum
 Pancreas
 Stomach
 Small intestine (duodenum, jejunum, ileum)
 Large intestine (caecum, colon, rectum)
 Mesenteric lymph nodes
 Urinary bladder
 Seminal vesicles
 Uterus (incl. cervix uteri and vagina)
 Mammary tissue
 Skin
 Skeletal muscle (M. semimembranosus)
 Femur with stifle joint
 Sciatic nerve
 Spinal cord
 Injection site (parenteral studies)

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Results:

Mortality:

Group	0		1		2		3	
	m	f	m	f	m	f	m	f
Died	0	2	2	0	0	0	2	1
Sacrificed	1	0	0	0	0	0	1	0
Total	1	2	2	0	0	0	3	1
†	5	10	10	0	0	0	15	5

No deaths could be directly attributed to the drug. Six animals (2 CON, 1 LD, 3 HD) died under anesthesia for blood sampling, and 1 LDM had abscess-forming pneumonia. One sarcoma-bearing control male, and one cachectic HDM were sacrificed.

Clinical: increased activity - MD, HD (both sexes); effect more evident in females (wk 1,17, 34, 49)

Body Weight Gain:

MDM - sig. reduction - weeks 10, 11
 HDM - sig. reduction - weeks 1-32, and 39
 All F groups - sig. reduction throughout study

Food Intake: During week 1, food intake was decreased in MDM, HDM, and all treated females. The animals recovered during week 2, and some significant increases were recorded over the course of the study in MDM and all female groups. The diet delivered the targeted drug dose generally within 2%.

Water Intake: No drug-related effects

Ophthalmology: No drug-related oculotoxic effects were apparent. Cataracts and corneal abnormalities (opacity, calcium deposits) appeared to be spontaneous lesions.

Hematology:

Significant mean changes were noted on various parameters over the course of the study, but few clearly dose- or time-related effects were evident.

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granulocyte/lymphocyte ratio-	-	gradual increase in F
decrease RBC	-	dose-dep. in F (wk 13) MDF (wk 6) HDF (wk 6, 39, 52)
decrease Hb	-	MDF (wk 6, 13) HDF (wk 13)
decrease Hct	-	dose dep in all F (wk 13) MDF (wk 6) HDF (wk 52)
decrease platelets	-	MDF (all times except wk 39) HDF (all times)
decrease lymphocytes	-	LDF (wk 6) MDF (wk 6, 27, 52) HDF (wk 6, 27, 39, 52)

To assess the relative magnitude and frequency of thrombocytopenia in individual female rats, the occurrence of platelet count decreases on the order of 20% and 40% were noted:

	Control	LD	MD	HD
week 6	-	1, 0	1, 0	2, 0
" 13	-	-	1, 0	-
" 27	1, 0	2, 0	5, 1	6, 0
" 39	0, 1	7, 0	5, 0	9, 1
" 52	2, 2	7, 0	8, 1	5, 4

first number = # of animals with 20% reduction; second number = # of animals with 40% reduction

As shown, the number of female rats with reduced platelet counts tended to increase with time and dose. However, there was not a clear worsening in all animals with time.

In males, no clear dose or time dependent effect on reduction of platelet counts was evident. Generally, 2-4 animals in each group including controls had marginal reductions in platelets. However, platelets in one MD male were reduced by 67% at week 52.

Clinical Chemistry:

The most dramatic, clearly dose-related effect was decreased cholesterol in females. The mean elevations in SGPT and SGOT in females were significant ($p < 0.05$), but marginal; only sporadic instances of significant individual elevations (2X control values) were recorded. By week 52, no elevations were evident in PPX-treated female rats. At week 52, SGPT and SGOT levels were elevated in 1 LD and 1 HD male rats, and SGPT was elevated 1 MD male. Serum bilirubin levels fluctuated in all dosage groups throughout the study.

increased SGPT	-	MDF (wks 6-27) HDF (wks 6-39) MDM (wk 6) LDM, MDM (wk 27)
increased SGOT	-	MDF, HDF (wks 6-52)
increased AP	-	MDF, HDF (wks 6-52)
decreased cholesterol	-	dose-dep decrease in females, marked at HD; (wk 6-52) no changes in males
decreased triglycerides	-	all females, not dose-dep (largest effect in MD); (wk 6-52) MDM, HDM - small effect
increased urea	-	MDF, HDF (wk 6-52) MDM (wk 13, 27, 39)
decreased K	-	dose-dep decrease in females (wk 6- 52); HDM (wk 6-52)

Protein Analysis:

The noted changes were generally within the normal range. Individual variations that were outside of the normal range at week 52 were elevated γ -globulin in 1 LDM and increased α_2 -globulin in 1 HDF.

decreased total protein	-	MDF, HDF (wk 39 & 52) MDM (wk 39)
decreased albumin	-	MDF, HDF (wk 6-52)

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	-	HDM (wk 52)
increased globulin	-	MDF, HDF (wk 6-52)
decreased globulin	-	MDM (wk 39)
increased γ -globulin	-	MDF, HDF (wk 6-52) HDM (wk 13, 27, 52) MDM (wk 27)
decreased γ -globulin	-	LDM (wk 39)
decreased α_1 -globulin	-	LDF (wk 52) MDF (wk 13, 39, 52) HDF (wk 39, 52)
decreased α_2 -globulin	-	MDM (wk 27) HDM (wk 27, 39)
increased α_2 -globulin	-	LDM (wk 39)
increased β -globulin	-	MDF, HDF (wk 39, 52)

Urinalysis:

blood/RBCs	-	MDF, HDF (also found in some controls, LDM, MDM)

Organ Weights:

↓ liver	-	HDM
↓ thymus	-	MDF, HDF
↑ ovary	-	LDF, MDF, HDF

Gross Pathology:

Premature decedents: - no drug-related findings

Survivors:

uterine dilatation	-	2/20 LDF 5/20 MDF 6/19 HDF
ovarian size increase	-	14/20 MDF 18/19 HDF
thymus, small	-	3/19 HDF

Histopathology:

Males:

Leydig cell, hyperplasia - 10 LDM
7 MDM
2 HDM

adenoma - 1 ConM
1 LDM

kidney, pyelonephritis - 2 MDM, 1 HDM

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Females:

corpora lutea, enlarged - 2 CON
0 LD
18 MD
19 HD

pyometra - 1 MD
5 HD

adrenals, decreased lipids/
birefringent substances 3 HD

kidney, pyelonephritis 1 HDF

uterus, dilatation - similar incidence rate (% in all groups)

squamous metaplasia - 4 HDF

glandular cystic metaplasia - 1 MDF
1 HDF

pyometra - 1 MDF
5 HDF

bladder, squam. metaplasia - 1 HDF

mammary gland - see discussion of amendment

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Neoplasia:

A total of eleven animals were diagnosed with tumors during the study. The tumors are known to occur spontaneously in Wistar rats. No clear pattern of frequency or distribution was identified; thus, the tumors were not clearly related to PPX administration (Tab. C.2.a.1).

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Incidence of tumor types, listed according to animal number and primary site per group and sex (G 59 - SNO 919 CL 2Y, feed, rat, 52 weeks)

Study group	0		1		2		3	
	m	f	m	f	m	f	m	f
Heart								
Neurilemmoma*								316
Testis								
Leydig cell adenoma	008 ^{++u}		116 ^{u++}					
Pituitary gland								
Adenoma nos.		058		159				
		064						
		065						
Cervical lymph node(s)								
Malignant lymphoma						204		
Thymus								
Malignant lymphoma						204		
Skin/subcutis								
Fibrosarcoma								369
Sarcoma nos.	015							
Brain								
Granular cell tumor								161

*m = male, f = female

+ = according to the classification of Alison et al.¹

++u = unilateral

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Plasma Concentrations:

In females, plasma concentrations of PPX were proportional to dose. In males, plasma concentrations were greater than dose-proportional. The plasma concentrations of PPX in males 1 hr after dosing appeared to be much higher during week 26 and 52 compared to week 1. Plasma concentrations in males 8 hrs after dosing were highest during week 26 compared to weeks 52 and 1. In females, time-related differences were not marked (Tab. C.2.a.2).

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Table 1. Rat Mean Plasma Pramipexole Concentrations (ng/mL)
C.2.a.2 in the 52-Week Toxicity Study*

1 Hour After Start of Light Phase					
Sex	Dose (mg/kg)	Week			Mean
		1	26	52	
Female	0.5	4.79	6.45	5.04	5.43
	3	22.45	36.24	25.25	27.98
	15	176.77	189.74	163.49	176.67
Male	0.5	1.87	4.10	4.02	3.33
	3	13.33	32.74	37.23	27.77
	15	174.46	385.39	332.98	297.61
8 Hours After Start of Light Phase					
Female	0.5	2.37	5.09	2.72	3.39
	3	11.74	21.65	10.18	14.62
	15	39.72	99.93	56.29	65.31
Male	0.5	1.41	2.65	2.53	2.20
	3	12.08	21.82	22.20	18.70
	15	87.15	219.94	136.04	147.71

* [18] arithmetic means

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C.2.b. 52-Week Chronic Toxicity Study in Rhesus Monkey

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Document #(s): BI Document U90-0513
Upjohn TR 7219-94-065

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Sponsor Volumes: 1.39-1.41

This study complied with GLP

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 2.0 mg/kg/day to rhesus monkeys (4/sex/dose) for 52 weeks. Few notable drug-related toxicities were apparent, but dosing was limited to 2.0 mg/kg because of drug-induced injurious behavior in the animals during the early phase of the study. The most significant drug-related effect was bradycardia with increased R-R and Q-T intervals recorded during weeks 29/30, 36/37, and 47/48 at 1.5 to 6 hrs post-dose; however, this effect was only observed in mid-dose males. One death, a low-dose female, occurred late in the study; death did not appear to be drug-related. Behavioral changes (agitation, jumping, swinging, gripping) occurred early in the study but diminished over the course of treatment. Body weight and food consumption were not affected by PPX. There were no treatment-related hematological or urinary changes, and only some modest changes in clinical chemistry were noted. Organ weights were not altered and no histopathological findings were attributed to PPX. Plasma concentrations of PPX were measured 2, 4, 6 and 24 hrs after drug treatment during weeks 1, 26, and 50. Monkey plasma concentrations 2 hrs after dosing were approximately 2- (low test dose) to 80-fold (high test dose) higher than the human C_{max}, following the projected human PPX maintenance dose of 1.5 mg, t.i.d. (5 ng/ml). Thus, oral administration of mg/kg/day PPX for 52 weeks does not produce significant pathologic effects in monkeys.

Methods:

Dosages: 0.1, 0.5, 2.0 mg/kg/day (Batch II)

Low dose is two times the expected human dose (at the time of study initiation). The high dose was selected as the highest tolerable dose based on a range-finding study.

Route of Administration: oral (gastric intubation after feeding)

Species/Number: Rhesus monkeys (16 males, 16 females)

Mean initial weights:

males: kg
females: kg

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Toxicokinetic Analyses:

Blood was sampled during weeks 1, 26 and 50 at 2, 4, 6 and 24 hrs after drug administration. (Note: The analysis was by an RIA method rather than the HPLC/EC method used in rodent studies.)

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly
Food consumption	-	weekly
Fecal Occult Blood	-	predose and wks 13, 26, 40 and 52
Hematology	-	predose and wks 6, 13, 26, 39 and 52

- hemoglobin concentration (Hb)
- mean cell volume (MCV)
- red blood cell count (RBC) and derived indices:
 - mean cell hemoglobin (MCH)
 - packed cell volume (PCV)
 - mean cell hemoglobin concentration (MCHC)
- thrombin time (TT)
- prothrombin time (PT)
- partial thromboplastin time (PTT)
- total and differential white blood cell count (WBC)
- reticulocytes
- platelets
- blood sedimentation rate

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With the exception of thrombin time (TT), prothrombin time (PT), and partial thromboplastin time (PTT), all the above parameter were examined on blood collected in EDTA anticoagulant.

Thrombin time (TT), prothrombin time (PT), and partial thromboplastin time (PTT) was determined on blood collected into trisodium citrate (0.11 mol/l, ratio 1:9).

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Clinical chemistry - predose and wks 6, 13, 26, 39 and 52

- glutamate oxalacetate transaminase (GOT) ✓
- glutamate lactate dehydrogenase (GLDH) ✓
- glutamate pyruvate transaminase (GPT) ✓
- alkaline phosphatase (AP) ✓
- leucine aminopeptidase (LAP) ✓
- creatin kinase (CK) ✓
- γ -glutamyl transferase (γ -GT) ✓
- sodium (Na^+) ✓
- calcium (Ca^{++}) ✓
- potassium (K^+) ✓
- chloride (Cl^-) ✓
- phosphorus (P^{---}) ✓
- total protein (TP) ✓
- total bilirubin ✓
- urea
- creatinine ✓
- albumin ✓
- albumin/globulin ratio (A/G ratio) ✓
- glucose ✓
- cholesterol ✓
- triglycerides ✓
- butyryl cholinesterase

In addition, protein electrophoresis (albumin, alpha 1, alpha 2, beta, and gamma) was performed.

Urinalysis - predose and wks 6, 13, 26, 39 and 52

The following measurements were performed:

- pH
- volume
- specific gravity

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The following semiquantitative estimations were made:

- protein
- blood
- glucose
- ketones
- bilirubin
- urobilinogen
- reducing substances
- microscopy of centrifuged deposits: epithelial cells, leucocytes, erythrocytes, organic components, casts, and inorganic components

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Plasma Conc - wks 1, 26, 50
 Ophthalmology - predose and wks 13, 26, 39 and 52
 ECG, BP - months 7, 9 and 12 (1.5, 3, 6 and 24 hrs after dosing)
 Myelogram - from sternum
 Histopathology - on the following tissues:

Samples of the following tissues (with exception of the eyes which were fixed in Davidson's fluid) were preserved in 10 per cent neutral buffered formalin:

- adrenals
- aorta (arch and anterior abdominal)
- bone marrow
- brain (cerebral, cortex, thalamus, midbrain, medulla, cerebellum)
- cecum
- colon
- duodenum
- epididymides
- esophagus
- eyes (and optic nerve)
- gall bladder
- Harder's gland
- heart
- ileum
- jejunum
- kidneys
- liver
- lungs (with mainstem bronchi)
- lymph nodes (mandibular and mesenteric)
- ovaries
- pancreas
- pituitary
- prostate
- rectum

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- rib and bone marrow (beyond the requirements of the study protocol)
- salivary gland (submaxillary)
- sciatic nerve
- seminal vesicle
- skeletal muscle
- skin and mammary gland
- spinal cord (cervical)
- spleen
- sternum and bone marrow
- stomach
- testes
- thymus
- thyroids (with parathyroids)
- tongue
- trachea
- urinary bladder
- uterus
- all unusual lesions

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The above tissues were transferred to the study sponsor for further processing and examination.

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Histopathology was conducted by the sponsor.

Statistics

Body weight, food consumption and organ weight comparisons were made by one-way ANOVA and Newman-Keuls test for multiple comparisons. Hematology, clinical chemistry, ECG, BP, and organ/body weight ratios were compared by one-way ANOVA based on ranks, and Newman-Keuls test for multiple comparisons. Plasma concentration data were evaluated by ANOVA to assess the dose-proportionality relationship.

Results:

Mortality: One LDF died on day 364 of study. Signs of a persistent bacterial infection (chronic purulent pericarditis and pleuritis), but no signs of systemic toxicity were present.

Clinical Signs:

Dose-related increases in agitation occurred during the first months of the study. The effect was most prominent the night of the first administration as indicated by the presence of wounds caused by thrashing in cages. In the following weeks, the behavioral changes (jumping, swinging, gripping) that started 3-4 hrs after treatment and persisted for several hours diminished, such that during the final months of treatment these behaviors did not occur.

Body Weight Gain:

No statistically significant changes were observed (Fig. C.2.b.1).

Food Intake:

Occasional statistically significant effects were observed, but no clear drug-related trends (Fig. C.2.b.2).

Ophthalmology:

According to the sponsor, no treatment-related ocular changes occurred, but a number of notations appeared in the Pathologists report (i.e., visible cribrosum plate, pale optic disc). These findings were discussed with Dr. Tony Carreras of HFD-540 who concurred with the sponsor's conclusion.

Fig. C.2.b.1

Figure 1

Project No. 059-018

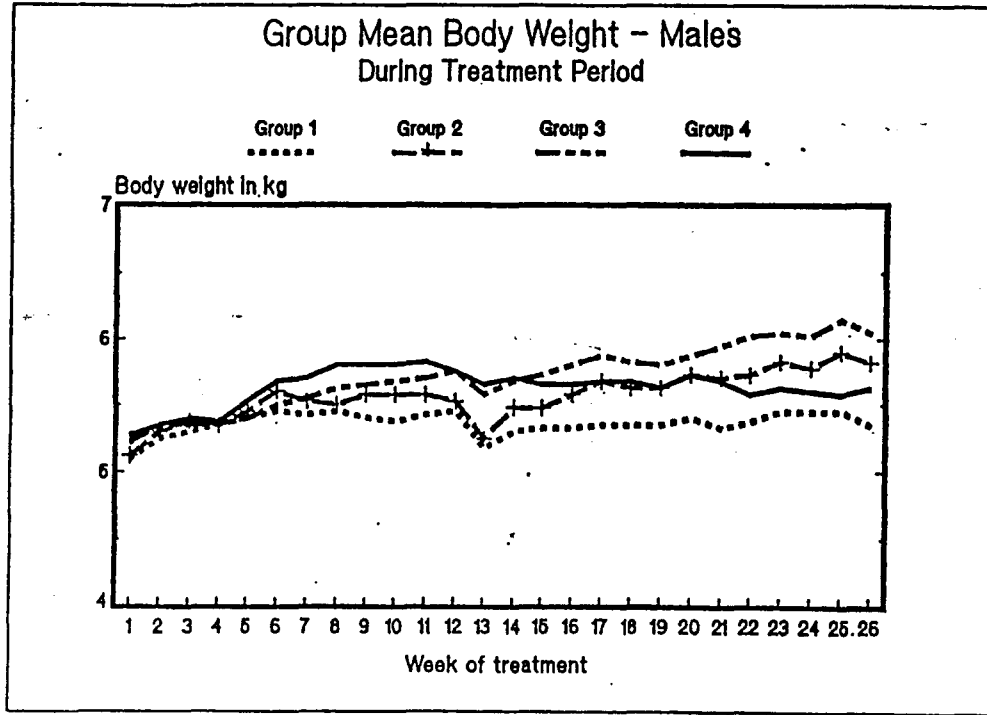
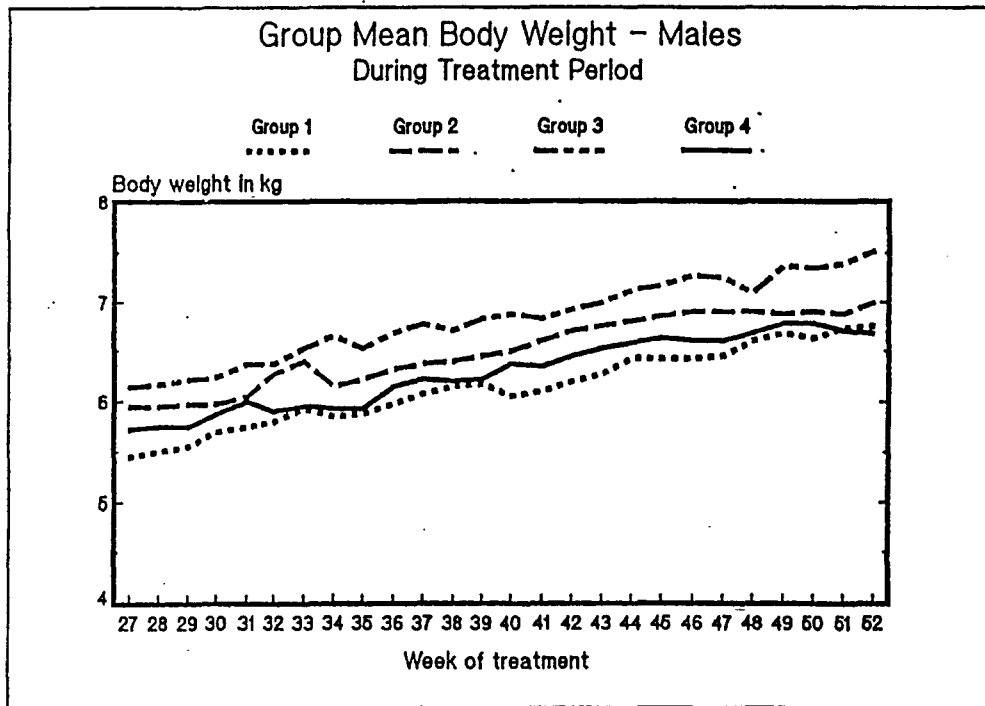


Figure 1 (cont.)

Project No. 059-018



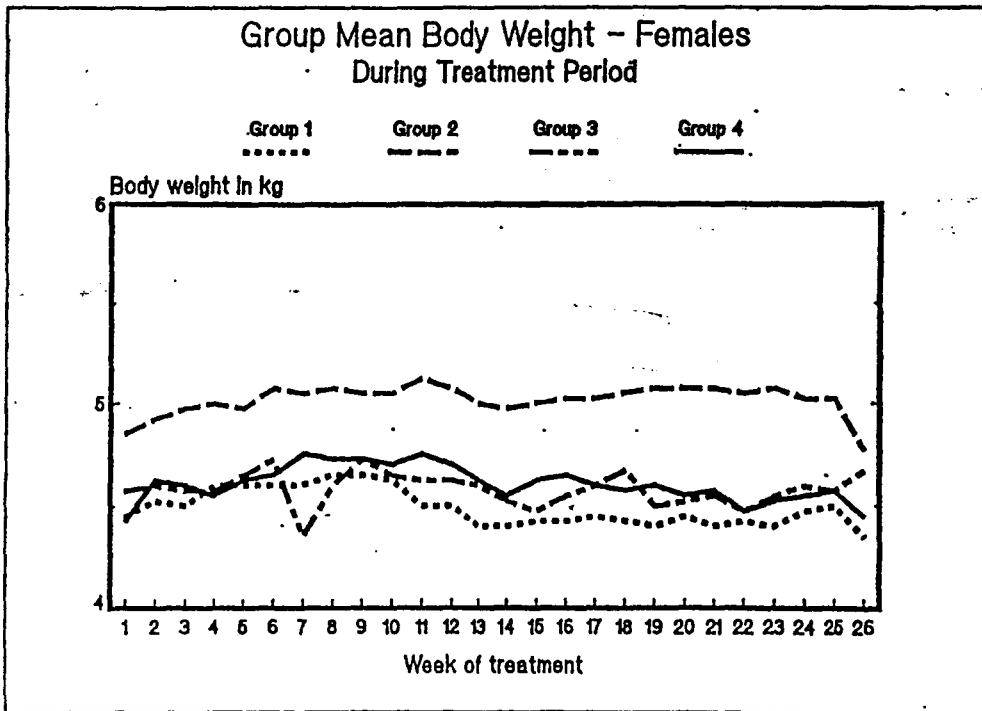
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Figure C.2.b.1 (cont.)

Figure 2

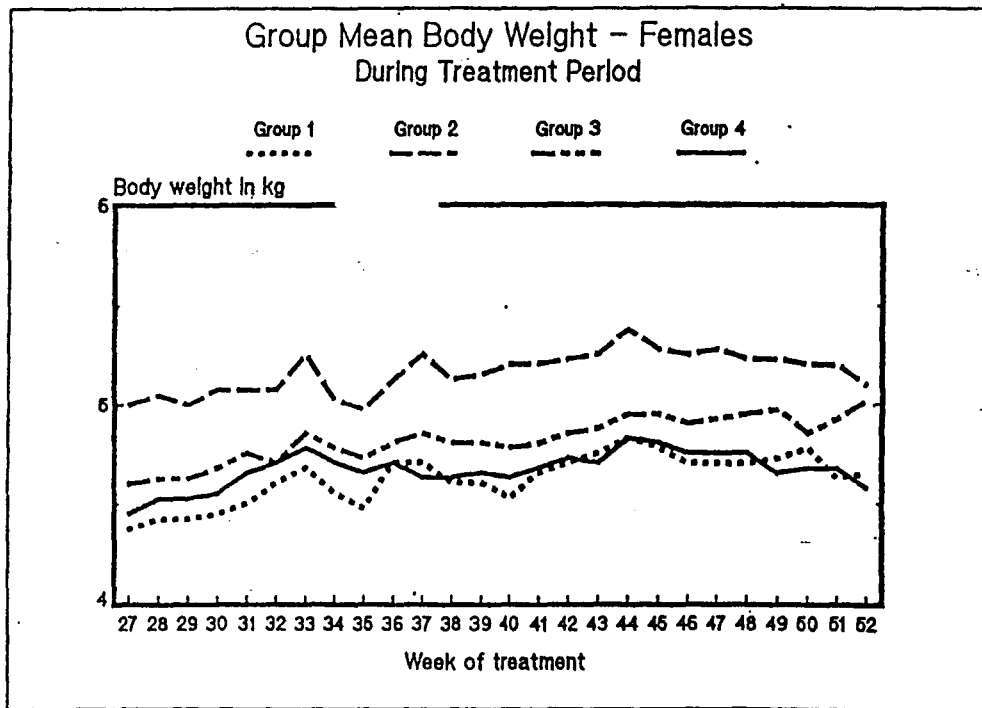
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Figure 2 (cont.)

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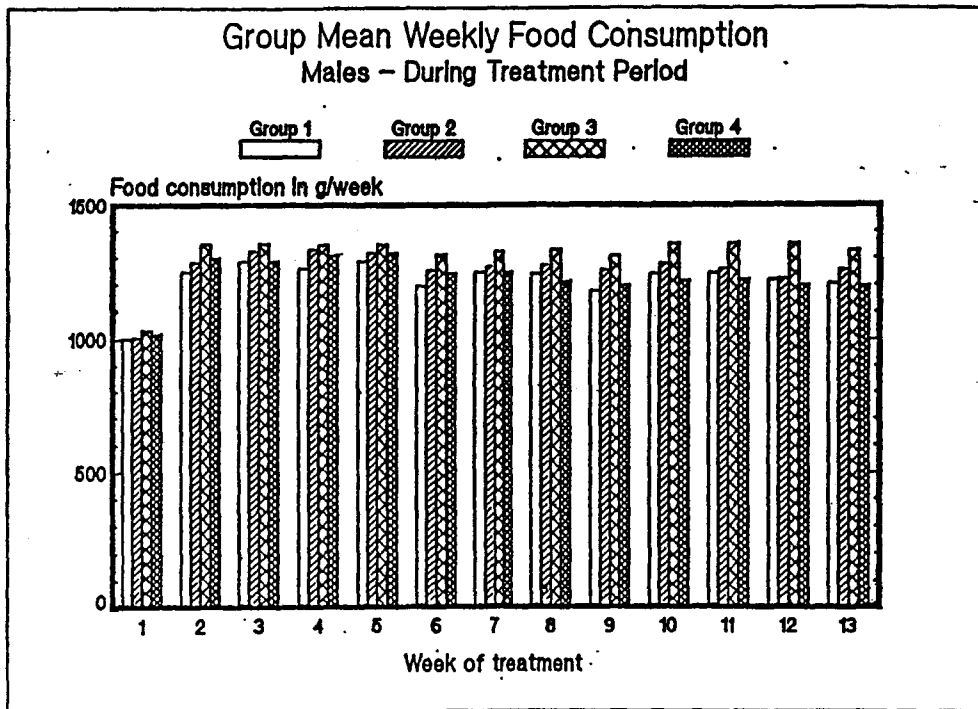


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Figure C.2.b.2.

Figure 3

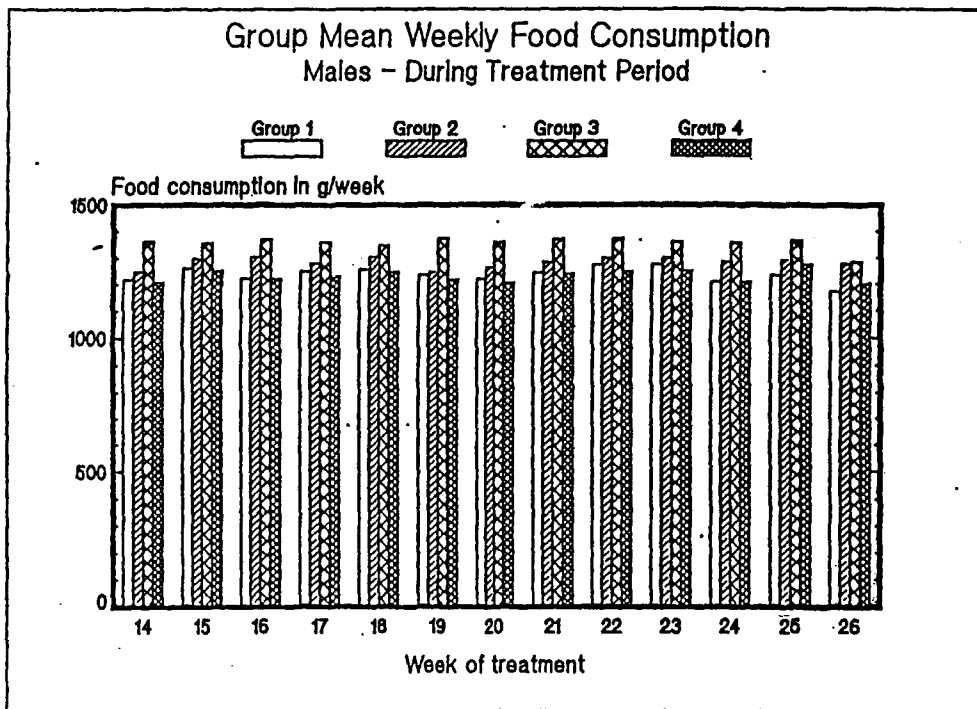
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Figure 3 (cont.)

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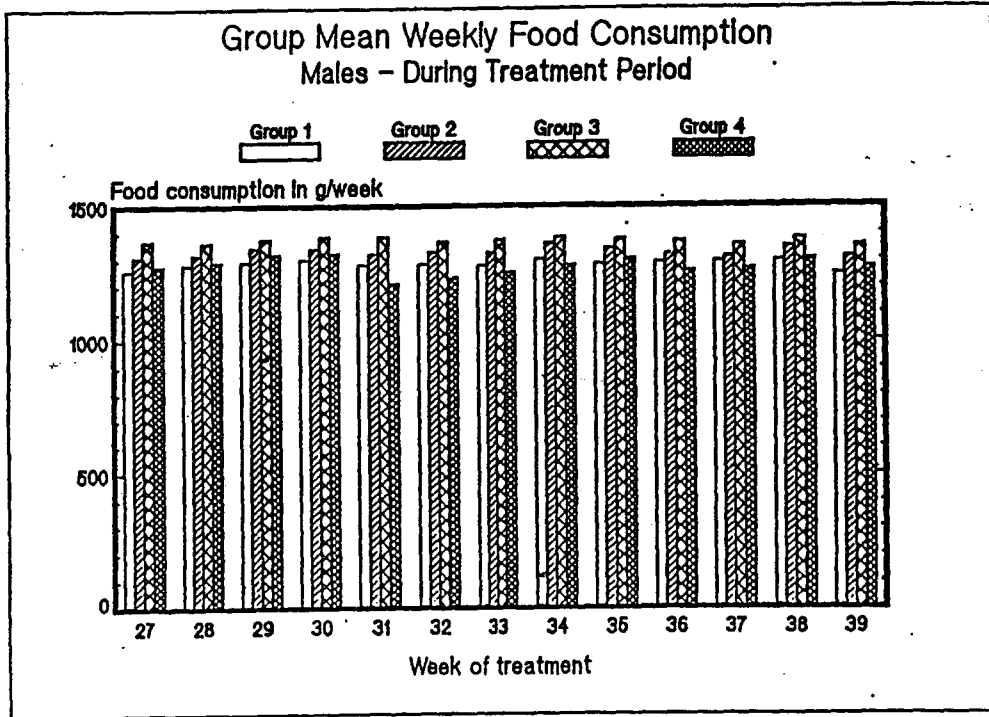


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Fig. C.2.b.2. (cont.)

Figure 3 (cont.)

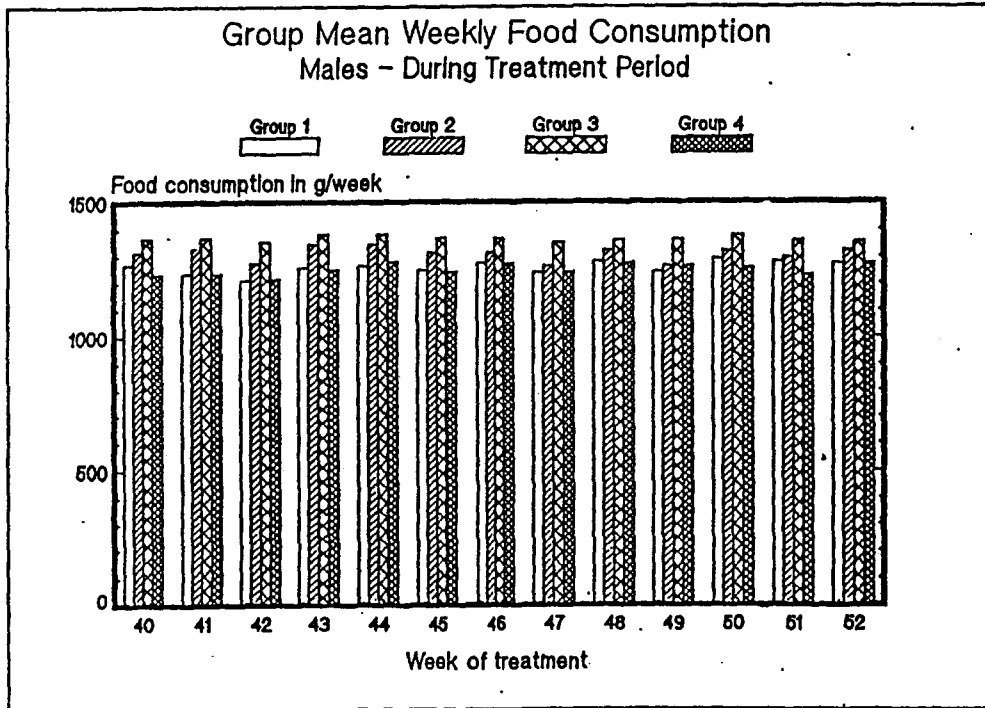
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Figure 3 (cont.)

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Figure C.2.b.2. (cont.)

Figure 4

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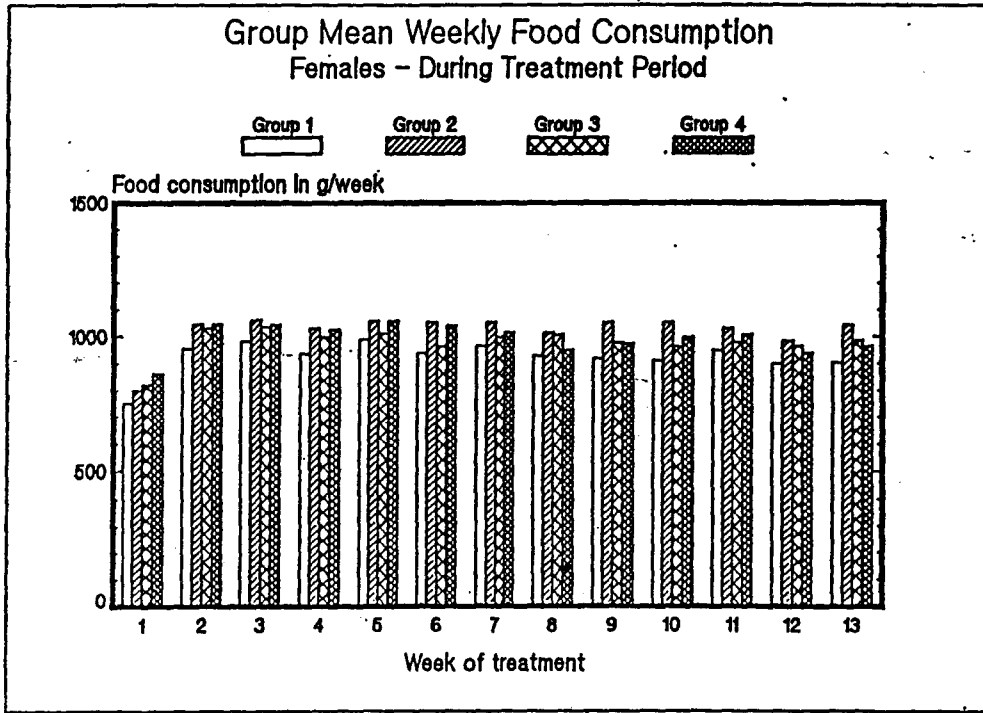
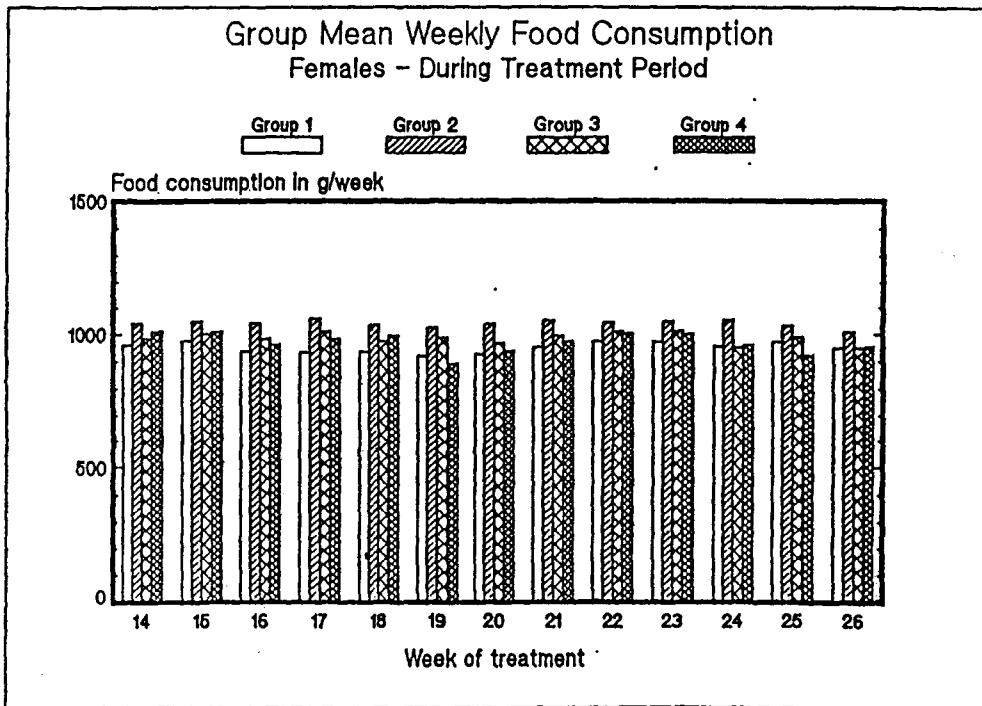


Figure 4 (cont.)

Project No. 059-018



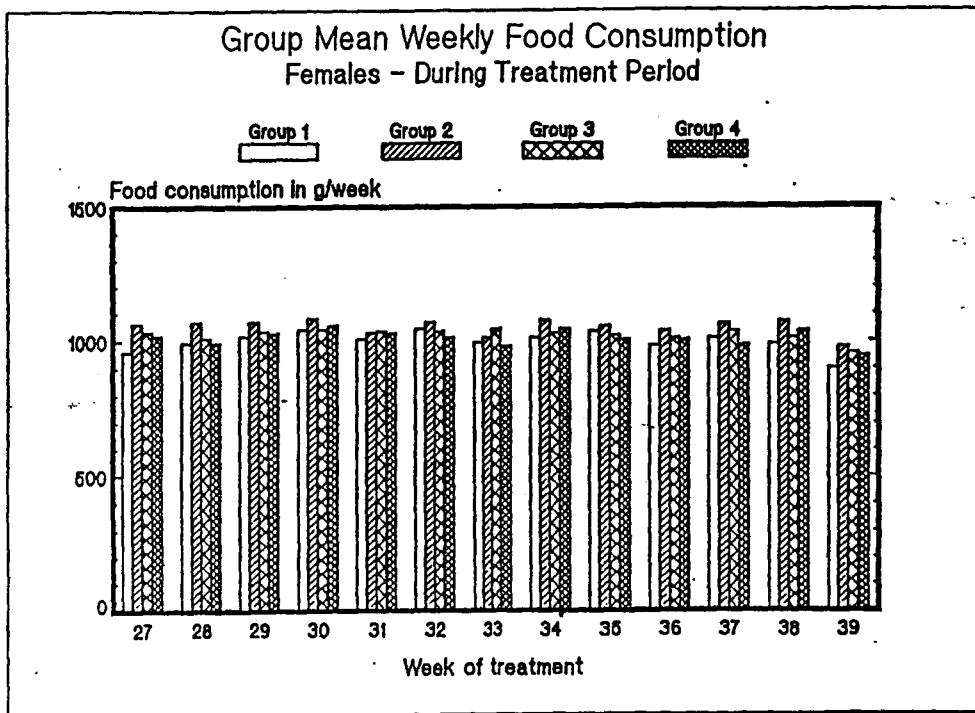
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Figure C.2.b.2. (Cont.)

Figure 4 (cont.)

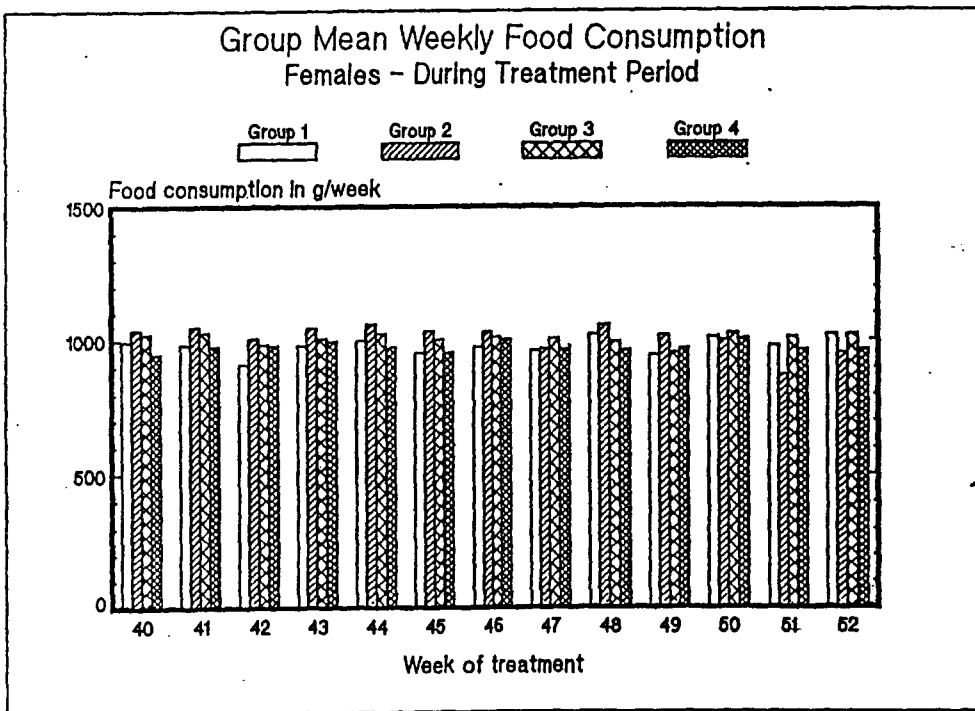
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Figure 4 (cont.)

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Hematology:

Group variations:

There were occasional statistically significant events, but no clear drug-related trends and variances were within a normal range.

- increase PT - MDF (wk 39)
- decrease PT - MDF (wk 52)

- increase PTT - LDM (wk 26)
MDM (wks 6, 13, 26, 39)
HDM (wks 26, 39)
MDF (wks 39, 52)

Individual variations:

- decrease RBC (RBC range) - 2 0F (wk 52)
1 LDM (wks 26, 52)
1 MDM (wk 26)
1 HDM, 1 HDF (wk 52)

- decrease WBC (range = /L) - 2 0F (wk 52)
1 LDM (wk 0, 26)
1 LDF (wk 0, 13, 26, 39, 52)
1 HDM (wk 0, 6, 39)

- increase WBC - 1 LDM (wk 6)

- increase Baso % (≥ 4) - 1 MDM (wk 6)
1 MDF (wk 6)
1 HDF (wk 6)

- increase Eos % (≥ 10 -m, 8-f) - 1 LDF (wk 6), 1 LDF (wk 26)

- decrease Lymphos % - (≤ 25) - 1 0F (wk 26)
1 LDF (wk 52)
1 MDM (wk 6)
1 MDF (wk 6, 26)
1 MDF (wk 26)
1 HDF (wk 13)

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Clinical Chemistry

Group variations:

There were occasional statistically significant events, but no clear drug-related trends.

Individual variations:

Listed are variations that occurred outside of a reference range (in parentheses) in drug-treated animals only.

increase LDH - 1 HDF (wk 13)
(3x con & predose)

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increase AP - 1 LDM (wks 13, 26)
(2x pre & >1000) - 1 LDF (wk 52)

increase BUN - 4 LDM (wk 52)
(2x con & predose) 3 MDM (wk 52)
2 HDM (wk 52)
(no corresponding increases in creatinine)

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increase CPK - At week 52, several PPX-treated and control animals had levels that were more than 3x higher than predose levels.

Urinalysis:

Hemoglobin was detected most frequently and in relatively greater amounts in HDF at most time points. However, at week 52 no Hb was detected in samples from this group.

Cardiovascular Measurements:

The most significant cardiovascular effect was bradycardia with a corresponding increase in R-R interval. The effect was most evident in animals of the mid-dose group. During week 29/30, heart rate was reduced at hrs post-dose in MDM, but the effect was statistically significant only at 6 hr. Significant bradycardia occurred at 1.5 hr in MDM during week 36/37 and 47/48, and 6 hr post-dose in MDF during week 36/37.

Significant effects on blood pressure were decreases in systolic, diastolic, and mean arterial pressures at 6 hr postdose in HDF during weeks 29/30, and an increase in mean arterial pressure in LDF at 1.5 hr postdose during weeks 47/48. Significant pressure elevations were detected in females of all dosage groups at 24 hrs postdose in weeks 36/37, but this may have been the result of subnormal pressures in control animals.

Other significant effects on ECG recordings were:

increase Q-T -	MDM, 3 hr	(wk 29/30)
	MDM, 1.5 hr	(wk 36/37)
	L,M&HDM, 1.5 hr	(wk 47/48)
decrease QRS -	HDF, 3 hr	(wk 29/30)
	HDM, 6 hr	(wk 47/48)

Although predose recordings were not taken, the noted cardiovascular effects appeared to be drug-related since readings were normal 24 hrs postdose.

Organ Weights:

No clear drug-related changes occurred. There was a nearly significant increase in testes weight in MDM, and a nearly significant decrease in adrenal weights in HDF.

Histopathology:

Findings observed only in drug-treated animals were:

testes:	reduced spermiogenesis	-	1 LDM
			2 HDM
epididymis:	reduced sperm number	-	2 LDM
			2 HDM
spleen:	focal fibrosis	-	1 MDM
	reduced follicle size	-	1 LDM

The male reproductive effects were attributed to sexual immaturity.

Myelogram:

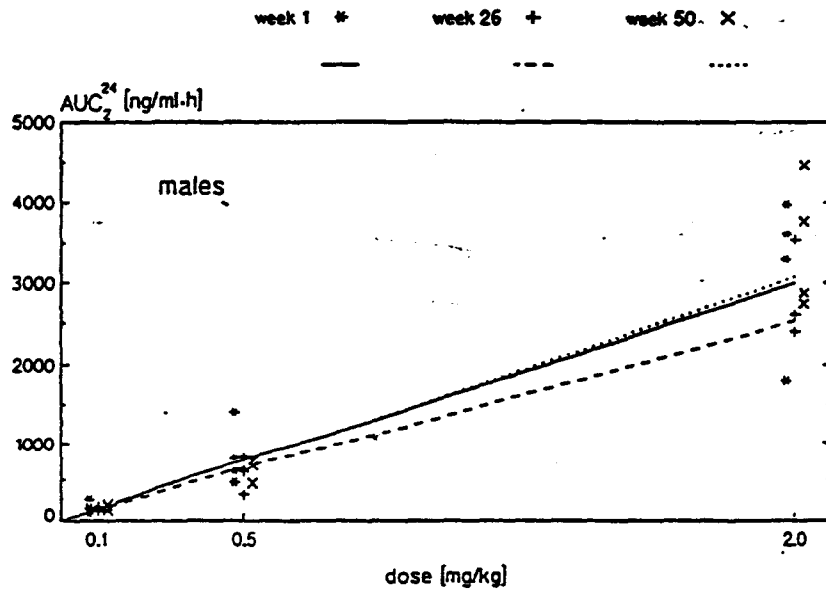
No drug-related changes in the erythropoietic or granulopoietic system were evident.

Plasma Concentrations:

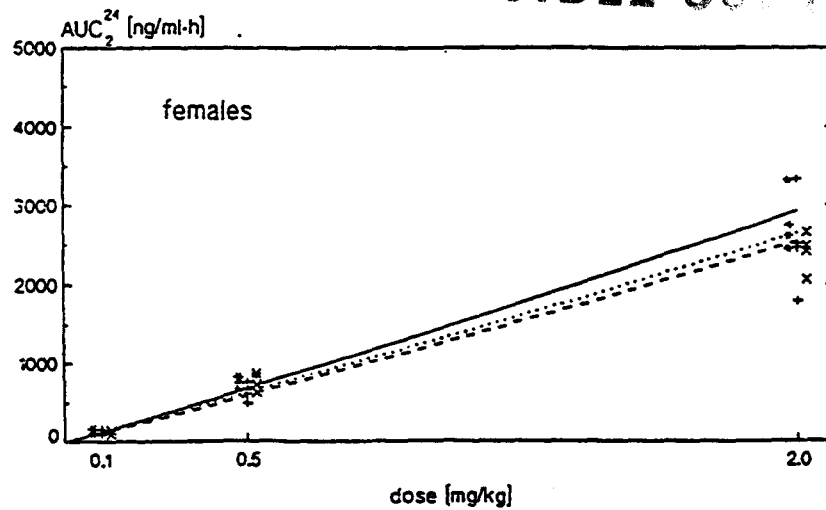
PRAM concentrations in monkey plasma were determined by RIA at 2, 4, 6 and 24 hrs postdose during weeks 1, 26 and 50. Increases in plasma concentrations and AUCs were approximately dose-proportional. ANOVA indicated that significantly higher concentrations were present in males at the 6 and 24 hr time points, and also according to AUC. There were no suggestions of drug accumulation (Fig. C.2.b.3, Tab. C.2.b.1).

Figure C.2.b.3

Fig.5: SND 919 CL2 Y, 52-week toxicity (gavage) in the monkey
AUC HLD project no. 059-018



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Tab. ④: 919 CL 2 Y / rhesus monkey / 52-week oral toxicity / project no. 059-018

Mean plasma concentrations [ng/ml]

HOURS	SEX	DOSE	WEEK			MEAN
			1	26	50	
2	Female	0.1	12.325	15.525	10.963	12.938
		0.5	60.613	98.746	73.575	77.644
		2	199.100	397.000	235.237	277.112
	MALE	0.1	8.637	19.450	9.250	12.446
		0.5	66.258	85.096	55.213	68.856
		2	209.375	421.800	316.875	316.017
4	FEMALE	0.1	11.212	10.088	9.000	10.100
		0.5	68.563	64.150	63.350	65.354
		2	221.517	275.062	208.700	235.093
	MALE	0.1	12.633	15.075	15.238	14.315
		0.5	66.138	62.100	58.325	62.188
		2	223.000	288.437	297.312	269.583
6	FEMALE	0.1	8.000	6.762	7.112	7.292
		0.5	53.058	37.721	52.338	47.706
		2	202.500	146.562	159.187	169.417
	MALE	0.1	11.450	9.200	11.875	10.842
		0.5	54.183	35.638	43.754	44.525
		2	238.042	161.250	238.538	212.610
24	FEMALE	0.1	0.775	0.637	1.087	0.833
		0.5	3.900	3.238	4.058	3.732
		2	12.563	12.400	18.042	14.335
	MALE	0.1	2.325	1.187	1.212	1.575
		0.5	8.575	3.175	4.262	5.337
		2	14.896	19.904	18.800	17.867

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Plasma
Concs

Tab. ⑤: 919 CL 2 Y / rhesus monkey / 52-week oral toxicity / proj. no. 059-018

Mean AUC (2 - 24 hours) data [ng/ml·h]

SEX	DOSE	WEEK			Mean
		1	26	50	
Female	0.1	121.725	109.063	109.875	113.554
	0.5	763.421	633.392	760.175	718.996
	2	2780.195	2524.350	2406.887	2570.478
Male	0.1	169.329	152.287	169.387	163.668
	0.5	817.542	594.246	647.767	686.518
	2	3159.855	2790.717	2466.075	2818.215

AUC

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C.3 Reproductive Toxicology

Conducted by : Boehringer Ingelheim KG
Department of Experimental Pathology and Toxicology
D-6507 Ingelheim am Rhein
West Germany

These studies complied with GLP

C.3.a. Segment I in Rats: Fertility and Reproduction

Document #(s): BI Document U89-0232
Upjohn TR 7219-94-077

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Sponsor Volume: 1.42

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 2.5 mg/kg/day to Wistar (Chbb:THOM) rats (24/sex/dose). Males were treated for 70 days prior to mating, and sacrificed after mating. Females were treated for 14 days prior to mating. One half of the females were treated through gestation, and sacrificed on day 22 for delivery of pups by Caesarean section. The remaining females littered spontaneously and drug treatment was continued through the weaning period (21 days).

Overt drug-related changes were restlessness and agitation with the middle and high doses, and decreased body weight gain and food intake at the high dose. No reproductive toxicities (abnormalities in mating, pregnancy or pup development) were apparent in animals of the low-dose group, or the mid-dose animals (dams and pups) delivered by Caesarean section. Significant toxicities were evident in the high-dose treatment group. Irregular estrus (prolongation by 1-2 days) occurred in about one-half of the HDF; hence, a longer mating period was required for successful insemination. In addition, the numbers of corpora lutea, implantations, pregnant females and females that successfully delivered were markedly reduced. Teratogenic effects of pramipexole were not evident, but one case of micrognathia inferior occurred in an MD pup. The teratogenicity data are limited by the low number of evaluable pups. Body weight development was impaired in pups from the mid- and high dose dams, but statistical evaluation of the high dose pup data was not possible due to the low number of reared pups. The sponsor suggests this impairment may have been due to drug-induced CNS stimulation in the dams resulting in reduced suckling opportunities. An alternative possibility is that inhibition of prolactin secretion by PPX reduced milk production in dams. Other developmental parameters, including fertility, were not affected by PPX. Histopathological findings in F₀ animals were prostate edema in one male subject from each dosage group, and hydronephrosis in one MD and one HD dam. The analysis of the testes may be considered inadequate since tissue fixation was in formalin rather than Bouin's solution. Plasma concentrations were not measured in this study. Thus, pramipexole produces significant reproductive toxicity, most evident as a reduction in successful pregnancies at a dose of 2.5 mg/kg. In view of the established role of prolactin in the

maintenance of pregnancy in the rat, and the probability that this dopamine agonist inhibits prolactin secretion, it is likely that the infertility is due to effects in the dam. However, additional studies are necessary to determine the source of infertility.

Methods:

Dosages: 0.1, 0.5, 2.5 mg/kg/day (Drug Lot: Batch III; prepared in distilled water)

Low dose is five times the expected human dose (at the time of study initiation). The high dose was selected as the highest tolerable dose based on a range-finding study.

Route of Administration: oral (gavage)

Species/Number: 96 males and 96 nulliparous females

Mean initial weights/age:

males: 218 g / 8 weeks
females: 209 g / 11 weeks

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Parameters monitored/Intervals:

Clinical - daily
Body weight - weekly in males; daily in females
Food consumption - weekly

At Termination -

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Males: Testes and epididymis were weighed, fixed in 7.5% formalin, and stored.

Females: Gross pathology, numbers of fetuses (viable and dead), corpora lutea, and resorptions. Non-pregnant females were excluded from mean calculations.

Fetuses: (C-section group) Live/dead, sex, external, skeletal (2/3 of subjects), and visceral (1/3 of subjects) abnormalities.

Pups: (rearing group) Live/dead, body weight, sex, gross abnormalities, functional/maturational parameters (erection of pinnae, fur growth, eye opening, etc.). At weaning, four pups (2 male, 2 female) were retained for additional developmental tests (simming, Preyer reflex, pupillary reflex, water T-maze), and fertility testing at 10 weeks. All pups were examined for pathological changes.

Statistics

Statistical comparisons were made by Bartlett test, one-way ANOVA, Newman-Keuls or Dunnett's test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects in Males:

Mortality: none

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Clinical Signs:

Dose-dependent increases in the severity and duration of restlessness and agitation were evident in MD and HD males.

Body Weight Gain:

Significantly decreased in the HD groups during weeks 1-10 (Fig. C.3.a.1).

Food Intake:

Significantly decreased in the HD groups during week 1, and increased during weeks 2-3 (Fig. C.3.a.2).

Copulation:

One control and one MD male did not copulate.

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Necropsy:

Prostate edema occurred in one male from each dose group (LD, MD, HD). One control male had unilateral testicular hypoplasia, but there were no significant differences in testicular weights among treatment groups.

Effects in Females:

Mortality: none

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Clinical Signs:

Dose-dependent increases in the severity and duration of restlessness were evident MD and HD during the entire treatment period.

Body Weight Gain:

Mean body weight was significantly reduced in the HD group during week 1 of treatment. After mating, the only significant effect on body weight was a slight decrease in the HD C-section group (Fig. C.3.a.3).

Food Intake:

Decreased in the HD group during week 1, and in the LD group during week 2.

Estrous Cycle:

A dose-dependent increase in estrous cycle irregularities was evident (2 LDF, 3 MDF, 13 HDF). For 4 HD females, two estrous cycles were required for successful insemination (Tab. C.3.a.1).

Gestation (Tab. C.3.a.2):

C-section group: Of 12 rats per dose group, 1 MD and 10 HD animals were not pregnant. Body weight and food consumption did not differ among groups.

Spontaneous delivery group: Seven of 12 dams in the HD group did not become pregnant. Body weight did not differ significantly among groups. Food consumption was significantly reduced throughout lactation in the HD group, and during week 1 of lactation in the LD group.

Necropsy: One MD and 1 HD dam had unilateral hydronephrosis.

Effects on fetuses and pups:

C-section group: Only 2 of 12 HD dams were pregnant, and only one had viable fetuses. There were no statistical variations among control, LD and MD litters; the HD group was not included in the analyses because of the low survivor number. The number of implantations in the HD group is clearly lower than in other groups. There were no dose-related trends in the incidence of malformations or skeletal and visceral variations, although one case of micrognathia inferior was found in an MD pup (Tables C.3.a.3-5).

Spontaneous delivery group: Significant reductions in weight were recorded in HD pups at birth, day 4 and day 21, and in MD pups at day 21. Body weight gain from days 1-4 and days 4-21 was also significantly reduced in MD and HD pups (Tables C.3.a.6-7; Fig. C.3.a.4).

The only other notable difference in tests of pup maturation and behavior was a slight (insignificant) delay in eye-opening in MD and HD pups. No drug-related pathological changes were identified in pups (Table C.3.a.8). In fertility studies of the F₁ generation, no overt fertility impairments were apparent. Body weights of the F₁ MD and HD dams were reduced during their gestational period, but body weight gain during gestation did not differ among groups of F₁ offspring (Fig. C.3.a.5).

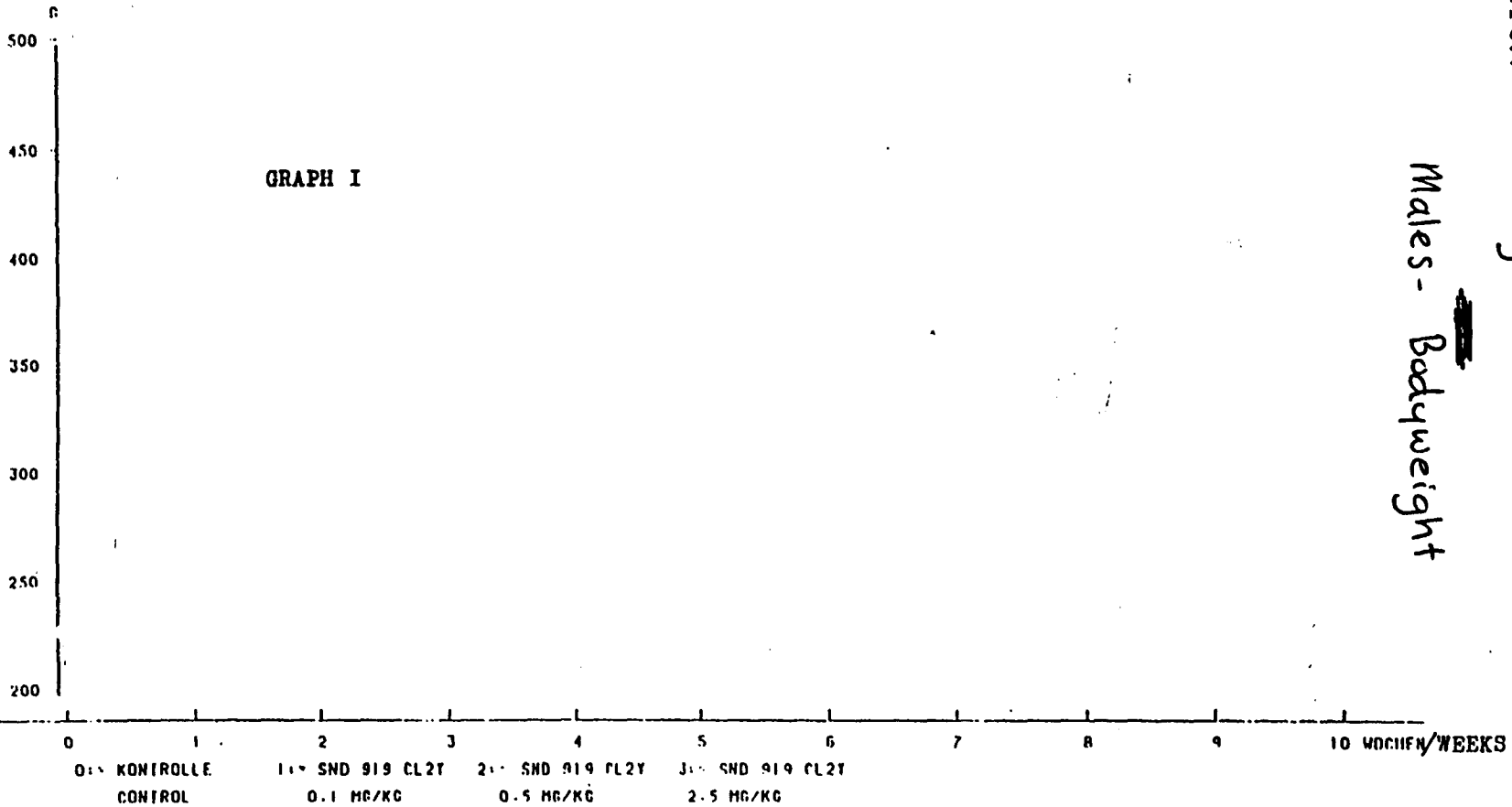
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Fig. C.3.a.1

Males - ~~Bodyweight~~
Bodyweight

SND 919 CL2Y	ROZ P.O.	SEGM. 1	VERSUCH MIT	MAENNL.RATTEN	TERATOLOGIE KOERPERGEW.	VOR VERPAARUNG
SND 919 CL2Y	P.O.		STUDY IN	MALE RATS	TERATOLOGY BODYWEIGHT	BEFORE MATING

49

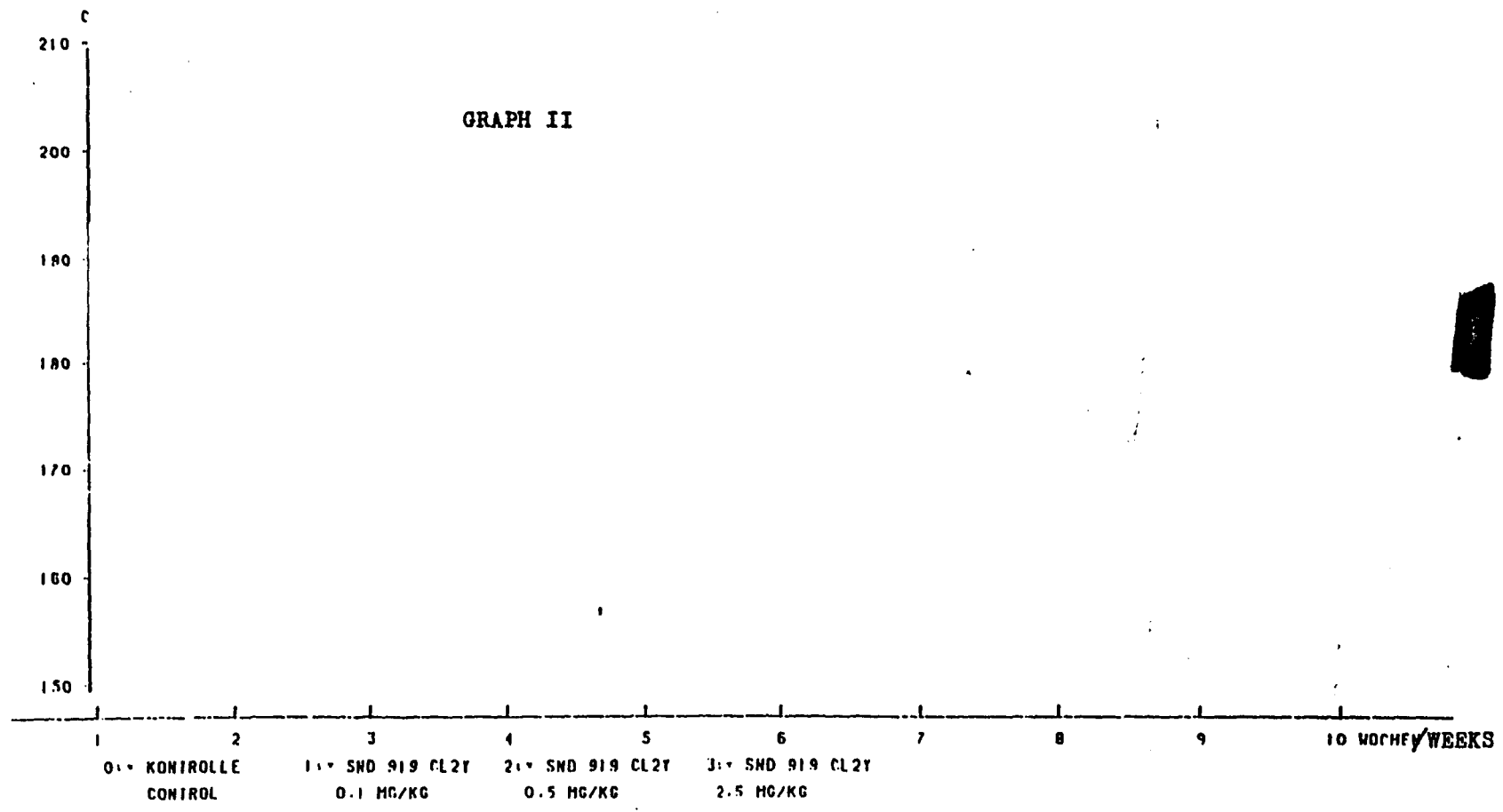


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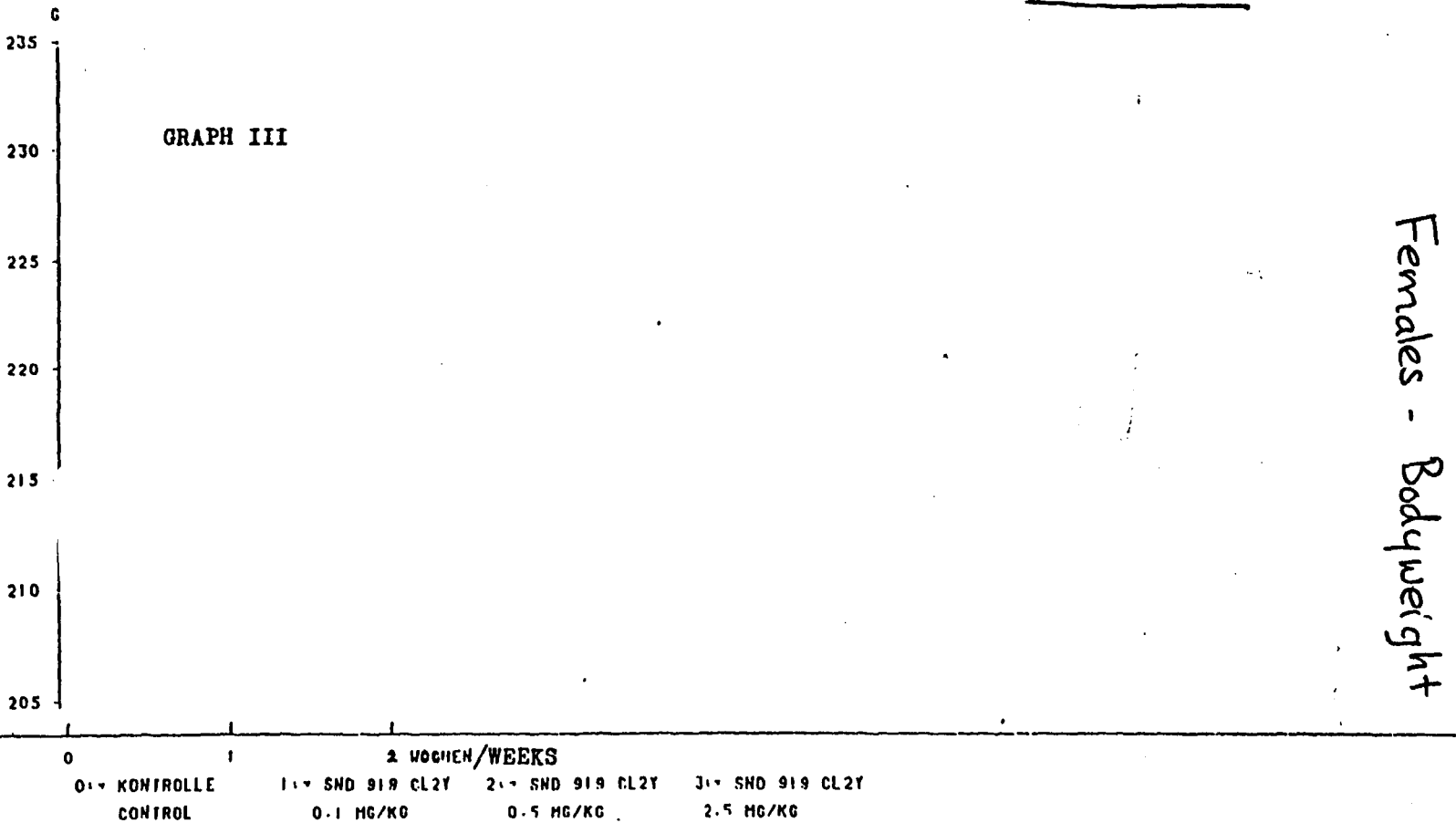
Figure C.3.a.2.
Males - Food Consumption

SND 919 CL2T R02 P.O. SEG. 1 VERSUCH MIT HAENNL. RATTEN TERATOLOGIE. FUTTERVERBR. VOR VERPAARUNG
SND 919 CL2T P.O. STUDY IN MALE RATS TERATOLOGY FEED CONS. BEFORE MATING

50



SND 919 CL2Y R02 P.O. SEGM. 1 VERSUCH MIT WEIBL. RATTEN TERATOLOGIE KOERPERGEW. VOR VERPAARUNG
 SND 919 CL2Y P.O. STUDY IN FEMALE RATS TERATOLOGY BODYWEIGHT BEFORE MATING



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Females - Bodyweight

Fig. C.3.a.3

TR No.: 7219-94-077

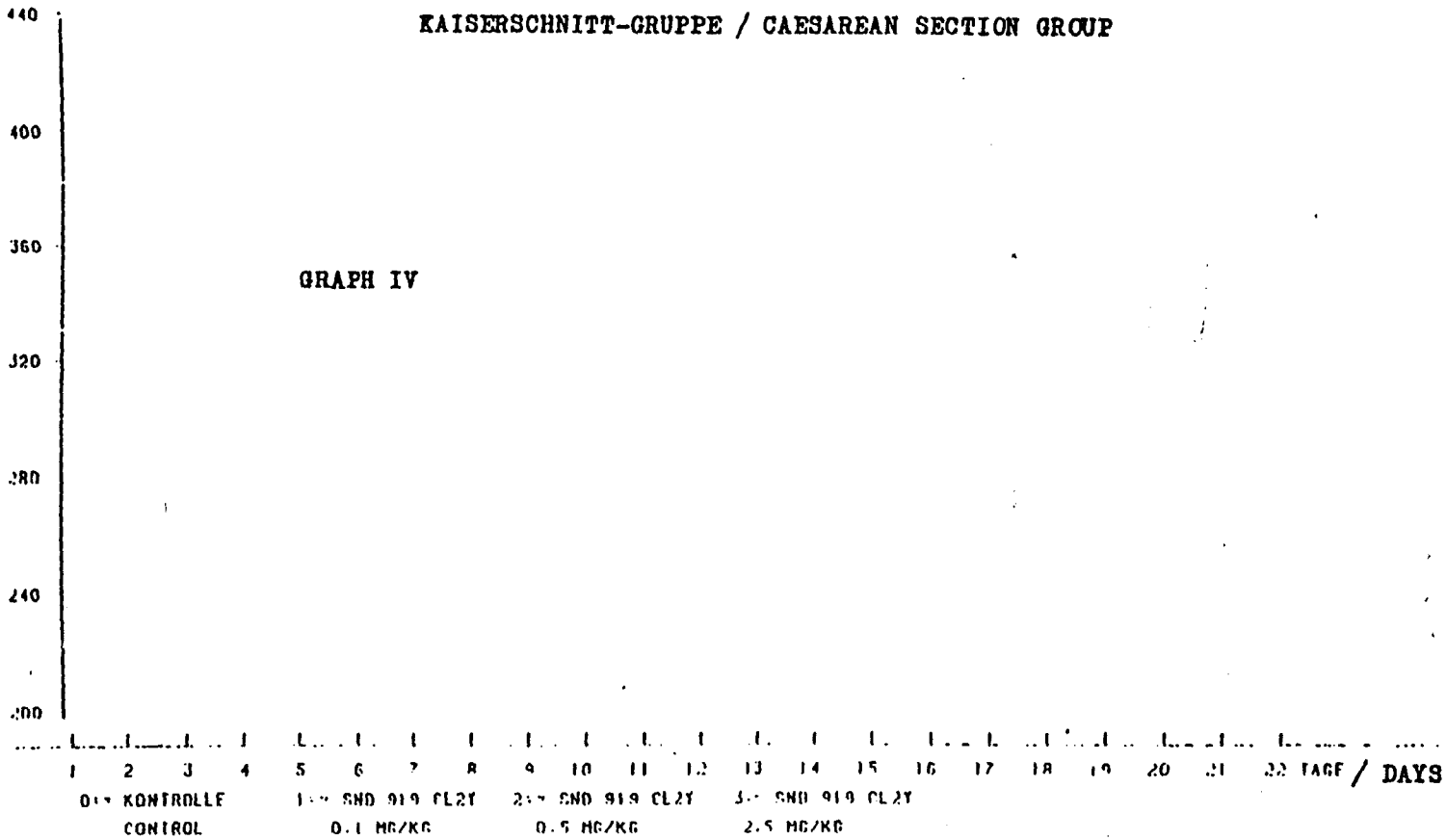
SND 919 CL2Y R02 P.O. SEGM. 1 VERSUCH MIT WEIBL. RATTEN TERATOLOGIE KÖRPERGEW. WAHREND DER GRAVIDITÄET
SND 919 CL2Y P.O. STUDY IN FEMALE RATS TERATOLOGY BODYWEIGHT DURING GESTATION PERIOD

KAISERSCHNITT-GRUPPE / CAESAREAN SECTION GROUP

Females - Bodyweight

Fig. C.3.a.3. (cont.)

GRAPH IV



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SND 919 CL2Y R02 P.O.
SND 919 CL2Y P.O.

VERSUCH MIT WEIBL. RATTEN TERATOLOGIE KOERPERGEW.
STUDY IN FEMALE RATS TERATOLOGY BODYWEIGHT

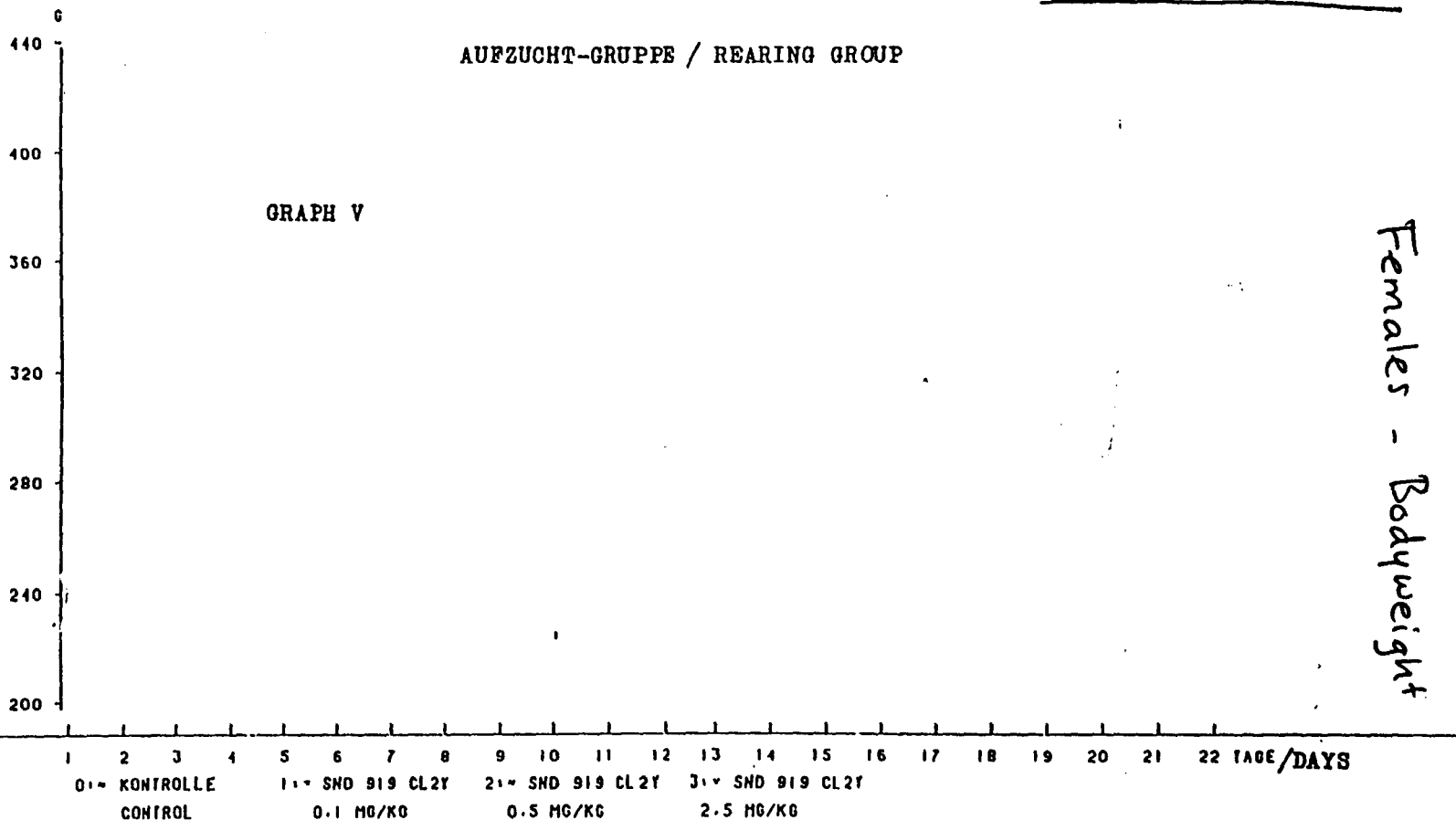
WAEHREND DER GRAVIDITAET
DURING GESTATION PERIOD

AUFZUCHT-GRUPPE / REARING GROUP

GRAPH V

Females - Bodyweight

Fig. C.3. a. 3. (cont.)



53

TR No.: 7219-94-077

Fig. C.3.a.3. (cont.)

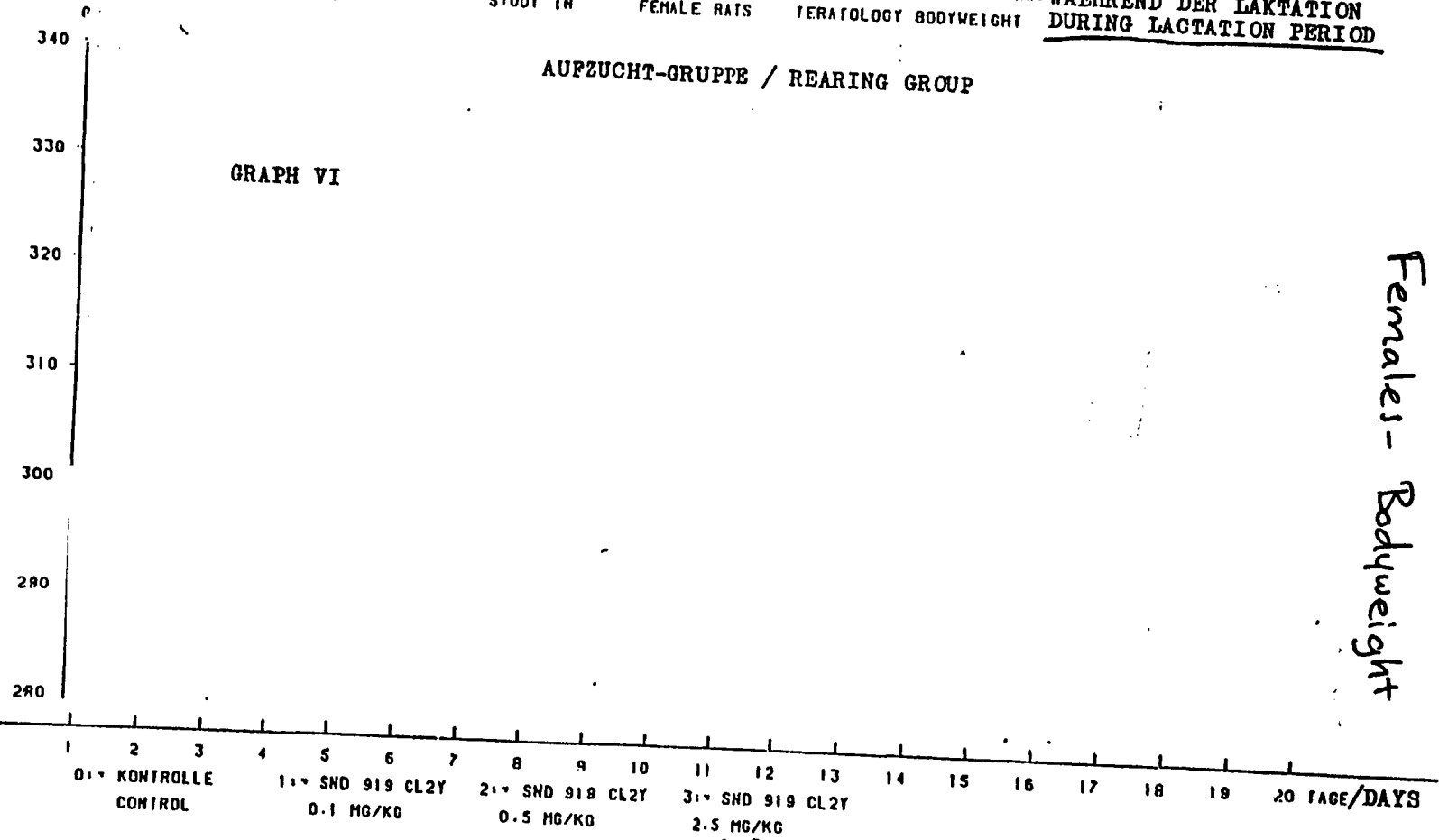
Females - Bodyweight

SND 919 CL2Y R02 P.O. SEG. 1 VERSUCH MIT WEIBL. RATTEN TERATOLOGIE KOERPERGEW. WAEHREND DER LAKTATION
SND 919 CL2Y P.O. STUDY IN FEMALE RATS TERATOLOGY BODYWEIGHT DURING LACTATION PERIOD

AUFZUCHT-GRUPPE / REARING GROUP

GRAPH VI

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Tab. ■ C.3.a.1

SND 919 CL 2 Y

APPEARS THIS WAY
ON ORIGINAL

RATTEN/RATS

DAUER DES OESTRUSZYKLUS WÄHREND DER APPLIKATIONSPERIODE
LENGTH OF ESTROUS CYCLE DURING ADMINISTRATION PERIOD

DOSIS DOSE	ANZAHL TIERE NO. OF ANIM.	REGELMÄSSIG (4 TAGE) REGULAR (4 DAYS)	UNREGELMÄSSIG / IRREGULAR		
			< 4 DAYS	> 4 DAYS	< AND > 4 DAYS
CONTROL	24	24	0	0	0
0.1 MG/KG	24	22	0	2	0
0.5 MG/KG	24	21	0	3	0
2.5 MG/KG	24	11	0	12	1

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

SND 919 CL 2 Y

Tab. C. 3. a. 2.

RATTEN/RATS

VERPAARUNGSERFOLG / MATING PERFORMANCE

ANZAHL DER RATTEN MIT POS. ABSTRICH "n" - TAGE NACH DER PAARUNG
NO. OF RATS WITH POSITIVE SMEARS AT "n" - DAYS AFTER PAIRING

GRUPPE GROUP	ANZAHL DER RATTEN MIT POS. ABSTRICH "n" - TAGE NACH DER PAARUNG NO. OF RATS WITH POSITIVE SMEARS AT "n" - DAYS AFTER PAIRING												ANZAHL TRAECHTIGER TIERE NO. OF PREGNANT ANIMALS			
	n=1	2	3	4	5	6	7	8	9	10	11	12	GESAMT TOTAL	TÖTUNG 22. TAG SACRIFICED AT DAY 22	TIERE DIE WERFEN ALLOWED TO PRODUCE	GESAMT TOTAL
KONTROLLE	1	6	7	9									23	12	11	23
0.1 MG/KG	8	6	4	6									24	12	12	24
0.5 MG/KG	4	7	8	4									23	11	11	22
2.5 MG/KG	7	6	5	2	2		1		1				24	2	5	7

APPEARS THIS WAY
ON ORIGINAL

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TR No.: 7219-94-077

C.3.a.3

Tab. 

BOEHRINGER INGELHEIM KG

REPRODUCTION TOXICOLOGY

SUBST./COMP. : SHD 919 CL2 Y
TIERART/SPEC. : RATTEN / RATS

VERS.NR./STUDY NO. : R02
SEGM. 1

	WURFDATEN / LITTER DATA		KAISERSCHNITT-GRUPPE	
	SUMMENWERTE /	SUM VALUES	CAESAREAN SECTION GROUP	
	KONTROLLE	0.1	0.5	2.5
	CONTROL	MG/KG	MG/KG	MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	12	12	12	12
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	0
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	12	12	11	2
GELBKOEPPER CORPORA LUTEA	191	186	171	34
IMPLANTATIONEN IMPLANTATIONS	185	172	157	24
LEBENDE FETEN VIABLE FETUSES	174	162	146	10
MAEHNLICH IN % MALE IN %	47	48	51	50
WEIBLICH IN % FEMALE IN %	53	52	49	50
TOTE FETEN DEAD FETUSES	0	0	0	0
RESORPTIONEN RESORPTIONS	11	10	11	13
FRUEH IN % EARLY IN %	64	70	55	93
SPAET IN % LATE IN %	36	30	45	7
MISSBILDUNGEN MALFORMATIONS	1	0	1	0
VARIATIONEN VARIATIONS	15	15	8	0

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TR No.: 7219-94-077

C.3.a.4.

BOEHRINGER INGELHEIM KG

Tab. 1

REPRODUCTION TOXICOLOGY

SUBST./COMP. : SHD 919 CL2Y
 TIERART/SPEC. : RATTEN / RATS

VERS.NR./STUDY NO. : R02
 SEGM. 1

	WURFDATEN / LITTER DATA MITTELWERTE / MEAN VALUES		KAISERSCHNITT-GRUPPE CAESAREAN SECTION GROUP		
		KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GEWICHT / FET (G) WEIGHT / FETUS (G)	MW SD	5.01 0.19	5.25 0.22	5.26 0.30	5.25 0.00
PLAZ.GEW. / FET (G) PLAC. WEIGHT / FETUS (G)	MW SD	0.44 0.08	0.41 0.02	0.40 0.04	0.44 0.00
CORPORA LUTEA / MUTTERT. CORPORA LUTEA / DAM	MW SD	15.9 1.6	15.5 1.6	15.5 1.4	23.0 0.0
IMPLANTATIONEN / MUTTERT. IMPLANTATIONS / DAM	MW SD	15.4 1.7	14.3 1.9	14.3 1.6	13.0 0.0
LEBENDE FETEN / MUTTERT. VIABLE FETUSES / DAM	MW SD	14.5 1.7	13.5 1.7	13.3 1.7	10.0 0.0
TOTE FETEN / MUTTERT. DEAD FETUSES / DAM	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
RESORPTIONEN / MUTTERT. RESORPTIONS / DAM	MW SD	0.9 1.1	0.8 0.9	1.0 0.8	3.0 0.0
MISSBILDUNGEN / MUTTERT. MALFORMATIONS / DAM	MW SD	0.1 0.3	0.0 0.0	0.1 0.3	0.0 0.0
VARIATIONEN / MUTTERT. VARIATIONS / DAM	MW SD	1.3 1.5	1.3 1.5	0.7 1.3	0.0 0.0
LEB. FETEN IN % IMPL. VIABLE FET. IN % IMPL.	MW SD	97.2 3.4	96.9 2.8	94.9 2.3	76.9 0.0
RESORPTIONEN IN % IMPL. RESORPTIONS IN % IMPL.	MW SD	2.8 3.4	3.1 2.8	5.1 2.3	23.1 0.0
PRAEIMPLANTAT.-VERLUST PRE IMPLANTAT. LOSS %	MW SD	1.6 1.8	3.7 4.4	4.1 4.6	43.5 0.0
POSTIMPLANTAT.-VERLUST POST IMPLANTAT. LOSS %	MW SD	2.8 3.4	3.1 2.8	5.1 2.3	23.1 0.0
MISSB. IN % LEB. FET. MALFORM. IN % VIAB. FET.	MW SD	0.1 0.6	0.0 0.0	0.1 0.7	0.0 0.0
VARIAT. IN % LEB. FET. VARIAT. IN % VIAB. FET.	MW SD	10.7 10.4	9.8 10.0	3.7 8.8	0.0 0.0

APPEARS THIS WAY
ON ORIGINAL

PROZENTWERTBERECHNUNG UEBER ARCSIN-TRANSFORMATIONEN
 CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

APPEARS THIS WAY
ON ORIGINAL

TR No.: 7219-94-077

Boehringer Ingelheim KG

Study No.: R 02

Tab. C.3.a.5.

SND 919 CL 2 Y

RATTEN/RATS

BEFUNDE AN FETEN FINDINGS IN FETUSES	KAISERSCHNITT-GRUPPE CAESAREAN SECTION GROUP			
	Contr.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TOTAL NO. OF FETUSES EXAMINED	174	162	146	10
FOR SKELETAL DIAGNOSIS	115	108	105	7
FOR VISCERAL DIAGNOSIS	59	54	41	3
<u>EXTERNAL</u>				
POLYDACTYLIA RIGHT FOREPAW	1	0	0	0
MICROGNATHIA INFERIOR	0	0	1	0
<u>SKELETAL</u>				
RUDIMENTARY 13TH RIB	7	9	4	0
ADDITIONAL 14TH RIB	2	1	0	0
GENERAL INCOMPLETENESS OF OSSIFICATION	0	0	1	0
<u>VISCERAL</u>				
DILATATION OF RENAL PELVIS (UNI- OR BILATERAL)	6	5	3	0
<u>RUNTS</u>	0	0	1	0
<u>ADDITIONAL FINDINGS IN STERNEBRAE</u>				
POORLY OSSIFIED STERNEBRA V	8	4	3	0
POORLY OSSIFIED STERNEBRAE II, IV, V	1	0	0	0
POORLY OSSIFIED STERNEBRAE I, II, V	0	1	0	0
POORLY OSSIFIED STERNEBRAE II, III, IV, V	0	0	1	0

APPEARS THIS WAY
ON ORIGINAL

117-10

TR No.: 7219-94-077

Tab. C.3.a.6.

- BOEHRINGER INGELHEIM KG -

VERS.NR./STUDY.NO.: R02 SEGM. 1

SND 919CL2Y

WURFDATEN / LITTER DATA
SUMMENWERTE / SUM VALUES

RATTEN/RATS
AUFZUCHT-GRUPPE
REARING GROUP

	KONTR. /CONTR.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GESAMTZAHL TIERE TOTAL NUMBER ANIMALS	11	12	11	12
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
FEHLWUERFE ABORTIONS	0	0	0	0
TRAECHTIGE TIERE PREGNANT ANIMALS	11	12	11	5
TOTE JUNGTIERE STILLBIRTHS	1	0	1	0
JUNGTIERE 1. TAG VIABLE PUPS DAY 1	158	160	157	75
MAENNLICH IN % MALE IN %	51.27	46.25	51.59	48.00
WEIBLICH IN % FEMALE IN %	48.73	53.75	48.41	52.00
JUNGTIERE 4. TAG VIABLE PUPS DAY 4	156	157	156	75
JUNGTIERE 4*. TAG VIABLE PUPS DAY 4*	88	96	88	40
JUNGTIERE 7. TAG VIABLE PUPS DAY 7	88	96	88	40
JUNGTIERE 14. TAG VIABLE PUPS DAY 14	88	96	88	40
JUNGTIERE 21. TAG VIABLE PUPS DAY 21	88	96	88	40
VERENDETE JUNGTIERE MORT. IN PUPS 1 - 4	2	3	1	0
VERENDETE JUNGTIERE MORT. IN PUPS 4* -21	0	0	0	0
MISSBILDUNGEN MALFORMATIONS	0	1	0	0
VARIATIONEN VARIATIONS	0	0	0	0

* NACH WURFREDUZIERUNG/AFTER LITTER REDUCTION

TR No.: 7219-94-077

Tab. C.3.a.7.

- BOEHRINGER-INGELHEIM KG -

VERS.NR./STUDY.NO.: R02 SEGM. 1

SMD 919CL2Y

RATTEN/RATS

WURFDATEN / LITTER-DATA
MITTELWERTE / MEAN-VALUES

AUFZUCHT-GRUPPE
REARING GROUP

	KONTR. /CONTR.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TRAGEZEIT DER MUTTERTIERE MW	22.00	22.00	22.00	22.00
GESTATION PERIOD OF DAMS SD	0.00	0.00	0.00	0.00
ANZ. TIERE / NUMB. OF ANIM. N	11.00	12.00	11.00	5.00
GEWICHT/JUNGTIER (G) TAG 1 MW	6.12	6.05	6.04	(*) 5.77
WEIGHT/PUP AT (G) DAY 1 SD	0.18	0.30	0.30	0.19
GEWICHT/JUNGTIER (G) TAG 4 MW	7.74	7.72	7.42	** 6.62
WEIGHT/PUP (G) DAY 4 SD	0.26	0.39	0.75	0.35
GEWICHT/JUNGTIER (G) TAG 4* MW	7.90	7.91	7.57	** 6.90
WEIGHT/PUP (G) DAY 4* SD	0.26	0.30	0.75	0.33
GEWICHT/JUNGTIER (G) TAG 21 MW	42.63	40.59	*** 36.60	*** 20.91
WEIGHT/PUP (G) DAY 21 SD	2.18	3.15	2.62	5.14
GEWICHTSZUN. (G) TAG 1-4 MW	1.62	1.61	** 1.28	*** 0.84
BODYW. INCR. (G) DAY 1-4 SD	0.36	0.47	0.51	0.38
GEWICHTSZUN. (G) TAG 4*-21 MW	34.72	32.68	** 29.03	*** 14.01
BODYW. INCR. (G) DAY 4*-21 SD	2.67	4.00	2.48	4.49
LEB. JUNGT./MUTTERT. TAG 1 MW	14.36	13.33	14.27	15.00
VIABLE PUPS/ DAM DAY 1 SD	1.03	2.27	3.04	1.41
TOTE JUNGT./MUTTERT. TAG 1 MW	0.09	0.00	0.09	0.00
DEAD PUPS / DAM DAY 1 SD	0.30	0.00	0.30	0.00
LEB. JUNGT./MUTTERT. TAG 4 MW	14.18	13.08	14.18	15.00
VIABLE PUPS/ DAM DAY 4 SD	0.98	2.23	3.03	1.41
LEB. JUNGT./MUTTERT. TAG 4* MW	8.00	8.00	8.00	8.00
VIABLE PUPS/ DAM DAY 4* SD	0.00	0.00	0.00	0.00
LEB. JUNGT./MUTTERT. TAG 21 MW	8.00	8.00	8.00	8.00
VIABLE PUPS/ DAM DAY 21 SD	0.00	0.00	0.00	0.00
JUNGTIERVER. % TAG 1-4 MW	1.23	1.80	0.61	0.00
PUPS LOSS % DAY 1-4 SD	2.78	3.28	2.01	0.00
JUNGTIERVERL. % TAG 4*-21 MW	0.00	0.00	0.00	0.00
PUPS LOSS % DAY 4*-21 SD	0.00	0.00	0.00	0.00
MISSBILDUNGEN / MUTTERTIER MW	0.00	0.08	0.00	0.00
MALFORMATIONS / DAM SD	0.00	0.29	0.00	0.00
VARIATIONEN / MUTTERTIER MW	0.00	0.00	0.00	0.00
VARIATIONS / DAM SD	0.00	0.00	0.00	0.00
MISSB. % LEB. JUNGT./TAG 1 MW	0.00	0.64	0.00	0.00
MALF. % VIAB. PUPS / DAY 1 SD	0.00	2.22	0.00	0.00
VARIAT. % LEB. JUNGT./TAG 1 MW	0.00	0.00	0.00	0.00
VARIAT. % VIAB. PUPS/ DAY 1 SD	0.00	0.00	0.00	0.00

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** = $p < 0.01$

*** = $p < 0.001$

PROZENTWERTBERECHNUNG UEBER ARCSIN-TRANSFORMATIONEN
CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS
* NACH WURFREDUZIERUNG/AFTER LITTER REDUCTION

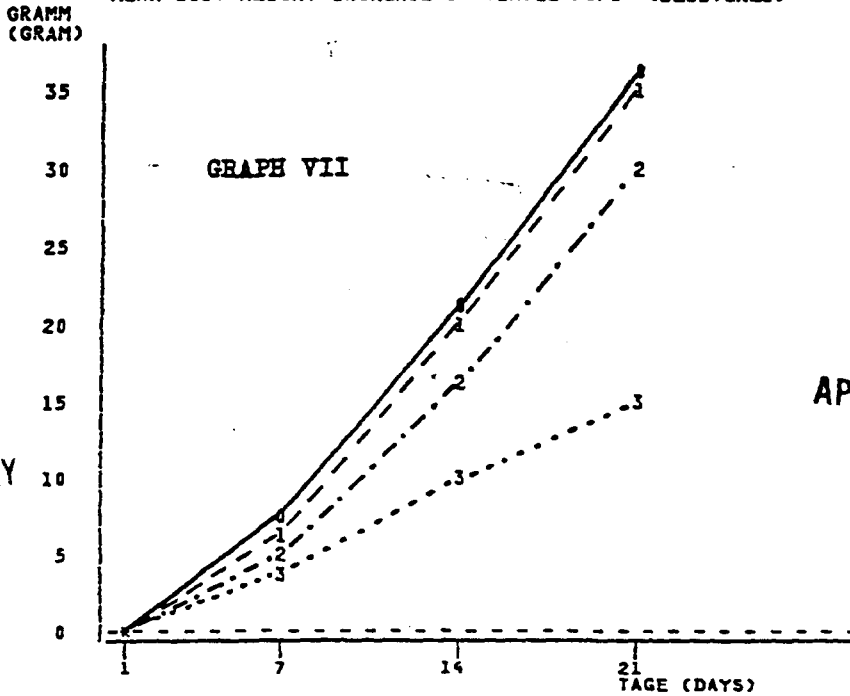
TR No.: 7219-94-077

.Fig. C.3.a.4.

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

SUBST./COMP. : SND 919 CL2Y TIERART/SPEC. : RATTEN / RATS
VERS.NR./STUDY NO. : R02 SEGM. 1

MITTLERE GEWICHTSZUNAHME LEBENDER JUNGTIERE (G) (GEWORFEN)
MEAN BODY WEIGHT INCREASE OF VIABLE PUPS (DELIVERED)



APPEARS THIS WAY

APPEARS THIS WAY
ON ORIGINAL

*: MEHRFACHBELEGUNG - MULTIPLE POINTS
0: KONTR - CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 2.5 MG/KG

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TR No.: 7219-94-077

Study No.: R 02

SND 919 CL 2 Y

Tab.

C.3.a.8.

RATTEN/RATS

SEGM. 1

BEOBACHTUNGEN DER F₁-GENERATION DER GRUPPE DER SPONTANGEBURTEN

OBSERVATIONS OF F₁-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

ERGEBNISSE IN PROZENT / RESULTS IN PER CENT

63

DOSIS DOSE	AUSGEWERTETE MÜRFE EVALUATED LITTERS	AUFSTELLEN DER OHREN		FELLWACHSTUM		LAUFEN MIT ANGE- HOBENEM BAUCH		DURCHBRECHEN DER OBEREN SCHNEIDEZÄHNE		AUGENÖFFNUNG		
		ERECTION OF PINNAE		FUR GROWTH		RUNNING WITH RAISED VENTER		ERUPTION OF MAXIL- LARY INCISORS		EYE OPENING		
		TAG 4	DAY 5	TAG 6	DAY 7	TAG 12	DAY 13	TAG 12	DAY 13	TAG 15	DAY 16	DAY 17
KONTROLLE/ CONTROL	11	3.4	93.2	-	100.0	100.0	100.0	100.0	100.0	28.4	80.7	100.0
0.1 MG/KG	12	3.1	95.8	-	100.0	100.0	100.0	100.0	100.0	17.7	74.0	98.0
0.5 MG/KG	11	9.1	98.9	-	100.0	100.0	100.0	100.0	100.0	2.3	67.0	100.0
2.5 MG/KG	5	2.5	100.0	-	100.0	100.0	100.0	100.0	100.0	10.0	57.5	100.0

APPEARS THIS WAY
ON ORIGINAL

Fig. C.3.a.5.

TR No.: 7219-94-077

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

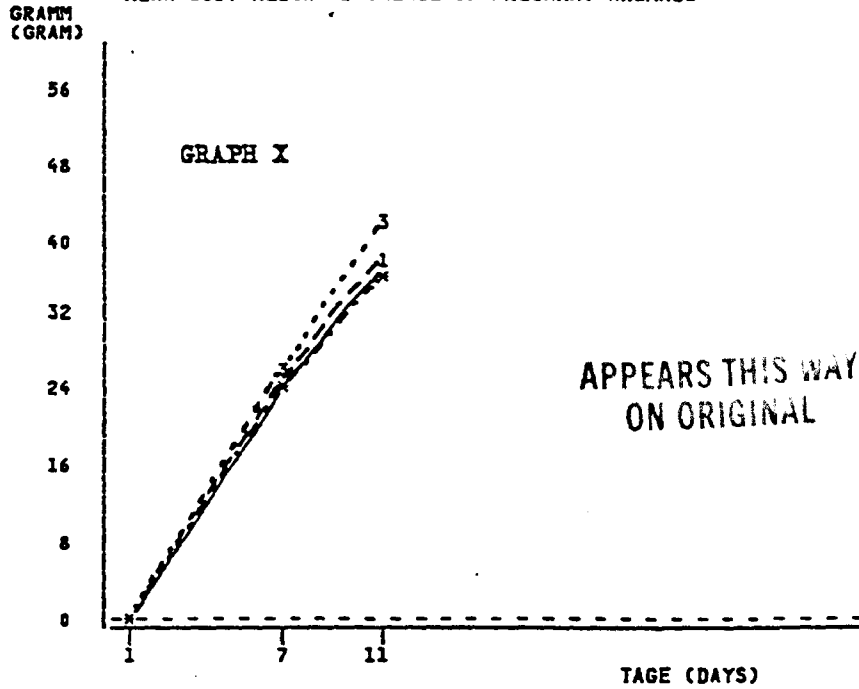
SUBST./COMP. : SHD 919CL2Y TIERART/SPEC. : RATTEN / RATS
 VERS.NR./STUDY NO. : R03 SEGM. 1

KOERPERGEWICHT TRAECHTIGER MUTTERTIERE (G) (TAG 1, 7, 11)
 BODY WEIGHT OF PREGNANT ANIMALS (G)(DAYS 1, 7, 11) F₁-GENERATION
 MITTELWERTE / MEAN VALUES

		N	1	7	11	
KONTROLLE CONTROL	MW	10	238.2	261.8	274.4	
	SD		13.0	12.1	9.3	
0.1 MG/KG	MW	11	228.5	252.8	267.4	
	SD		12.8	18.9	24.2	
0.5 MG/KG	MW	11	216.8*	240.8*	253.1(*)	* p < 0.05
	SD		17.1	19.1	20.4	** p < 0.01
2.5 MG/KG	MW	4	196.8***	223.3**	237.8*	*** p < 0.001
	SD		25.9	27.0	36.6	

APPEARS THIS WAY
ON ORIGINAL

MITTLERE GEWICHTSZUNAHME TRAECHTIGER MUTTERTIERE
 MEAN BODY WEIGHT INCREASE OF PREGNANT ANIMALS



APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

N: MEHRFACHBELEGUNG - MULTIPLE POINTS
 0: KONTR - CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 2.5 MG/KG

APPEARS THIS WAY
ON ORIGINAL

TR No.: 7219-94-077

Tab. C.3.a.9

BOEHRINGER INGELHEIM KG

REPRODUKTIONSTOXIKOLOGIE

SUBST./COMP. : SND 919CL2Y
VERS.NR./STUDY NO. : R03

TIERART/SPEC. : RATTEN / RATS
SEGM. 1

WURFDATEN / LITTER DATA F₁-GENERATION
SUMMENWERTE / SUM VALUES
(GETOETET 14.-16. TAG / SACRIFICED DAY 14-16)

	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	11	12	11	5
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	0
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	10	11	11	6
GELBKOEPPER CORPORA LUTEA	155	171	163	60
IMPLANTATIONEN IMPLANTATIONS	129	160	149	57
LEBENDE FETEN VIABLE FETUSES	122	146	139	54
RESORPTIONEN RESORPTIONS	7	14	10	3

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TR No.: 7219-94-077

Tab. C.3.a.10

BOEHRINGER INGELHEIM KG

REPRODUKTIONSTOXIKOLOGIE

SUBST./COMP. : SND 919CL2Y
VERS.NR./STUDY NO. : R03

TIERART/SPEC. : RATTEN / RATS
SEGM. 1

WURFDATEN / LITTER DATA F₁-GENERATION
MITTELWERTE / MEAN VALUES
(GETOETET 14.-16. TAG / SACRIFICED DAY 14-16)

		KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
CORPORA LUTEA / MUTTERT.	MW	15.5	15.5	14.8	15.8
CORPORA LUTEA / DAM	SD	2.0	1.9	1.3	1.4
IMPLANTATIONEN / MUTTERT.	MW	12.9	14.5	13.5	14.3
IMPLANTATIONS / DAM	SD	4.1	2.9	3.1	1.5
LEBENDE KEIME / MUTTERT.	MW	12.2	13.3	12.6	13.5
LIFE EMBRYOS / DAM	SD	4.2	3.1	3.4	1.3
RESORPTIONEN / MUTTERT.	MW	8.7	1.3	0.9	0.8
RESORPTIONS / DAM	SD	1.3	1.9	1.0	1.0
LEBENDE KEIME IN % IMPL.	MW	98.4	96.3	95.9	97.5
LIFE EMBRYOS IN % IMPL.	SD	4.4	5.9	4.2	3.5
RESORPTIONEN IN % IMPL.	MW	1.6	3.7	4.1	2.5
RESORPTIONS IN % IMPL.	SD	4.4	5.9	4.2	3.5
PRAEIMPLANTAT.-VERLUST	MW	10.9	1.5	3.8	3.8
PRE IMPLANTAT. LOSS %	SD	10.1	6.2	7.8	1.7

PROZENTWERTBERECHNUNG UEBER ARCSIN-TRANSFORMATIONEN
CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

C.3.b. Segment I in Rats: Fertility and Reproduction (Follow-up Study)

Document #(s): BI Document U92-0374
Upjohn TR 7219-94-078

Sponsor Volume: 1.43

Summary:

In the previous Segment I study in rats, daily treatment of females with 2.5 mg/kg PPX before and during gestation, and of males for 10 weeks before copulation significantly reduced the pregnancy rate. These studies did not determine the source of this impairment (i.e., male or female). Because of the well-established role of prolactin in the maintenance of rat pregnancy, and the ability of dopamine agonists to inhibit prolactin, it is reasonable to suspect that the female is the source of impairment. The present study was designed to provide evidence of this phenomenon by mating PPX-treated males with untreated females, and PPX-treated females with untreated males. A control group of untreated males and females, and a positive control group of treated males and females were also evaluated. PPX (2.5 mg/kg) was administered according to a schedule similar to that of the initial study. Males were sacrificed after copulation, and females were sacrificed on day 22 of gestation. In addition to the reproductive assessments, toxicokinetics and prolactin levels were also determined.

The main finding of the study was that the number and percentage of pregnant rats were significantly reduced in treated females regardless of whether the male partners had been treated. As in the preceding Segment I study, estrus was prolonged, and the total number of implantations in PPX-treated females was markedly reduced. Thus, the fertility impairment appears to result from an effect in the females rather than males. These findings were anticipated since pramipexole lowers serum prolactin as demonstrated in this study. The toxicokinetic analysis indicated that exposures in the pregnant rats at 2 hrs after dosing were higher than anticipated steady-state human levels (ng/ml). No adverse effects on litter parameters, and no teratogenic effects of PPX were evident. However, as in the preceding study, a low number of viable offspring from the treated groups limited the teratology information.

Methods:

Dosages: 2.5 mg/kg/day (Drug Lot: Batch VI; prepared in distilled water)

Route of Administration: oral (gavage)

Species/Number: 96 male and 96 nulliparous females

Allocated to four groups (24/sex):

Group 0: control male; control female
1: treated male; treated female
2: treated male; untreated female
3: treated female; untreated male

Mean initial weights/age:

males: 269g / 8 weeks
females: 203 g / 11 weeks

Parameters monitored/Intervals:

Clinical - daily
Body weight - weekly in males; daily in females
Food consumption - weekly

At Termination -

Males: Sacrificed after successful mating. Testes and epididymis were weighed, fixed in 7.5% formalin, and stored.

Females: Sacrificed on day 22 of gestation. Gross pathology, numbers of fetuses (viable and dead), corpora lutea, and resorptions. Ovaries were fixed in 7.5% formalin, and stored.

Fetuses: Live/dead; sex; one-half were examined for skeletal abnormalities, and one-half were examined for visceral and cephalic abnormalities.

Histopathology:

Fixed organs were embedded in paraplast. Sections were stained with hematoxylin-eosin.

Toxicokinetics:

Plasma levels were determined at sacrifice two hours after the last dose in 10/sex treated animals from the test groups (1-3), and in 5/sex control animals (group 0).

Prolactin determinations:

Serum prolactin levels were measured at sacrifice two hours after the last dose in 10 treated and 10 untreated animals per sex.

Statistics

Litter data were statistically evaluated using the Bartlett test, one-way ANOVA, Newman-Keuls test, Fisher's exact test, and the exact Wilcoxon test. Serum prolactin levels were evaluated using the Wilcoxon Rank Sum Test.

Results:

Effects in Males

Mortality: none

Clinical Signs:

Restlessness was observed from hrs after treatment.

Body Weight Gain:

Slight significant decrease in PPX-treated groups during week 2 (Fig. C.3.b.1).

Food Intake:

Significantly decreased in treated groups during week 1; significantly increased at later time points.

Necropsy:

No gross pathological changes were evident in any male rats. No significant differences in testicular weights among treatment groups were apparent.

Effects in Females

Mortality: none

Clinical Signs:

Restlessness was observed from hrs after treatment.

Body Weight Gain:

Body weight and body weight gain was significantly reduced in the PPX-treated groups during the first 2 weeks of treatment. No consistent effects on body weight in the treated animals occurred during gestation (Fig. C.3.b.2).

Food Intake:

Significantly increased in treated groups during week 2 prior to mating and during week 1 of gestation. During weeks 2 and 3, intake was significantly increased only in group 1.

TR No.: 7219-94-078

Fig. C.3.b.1.

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Male - Bodyweight

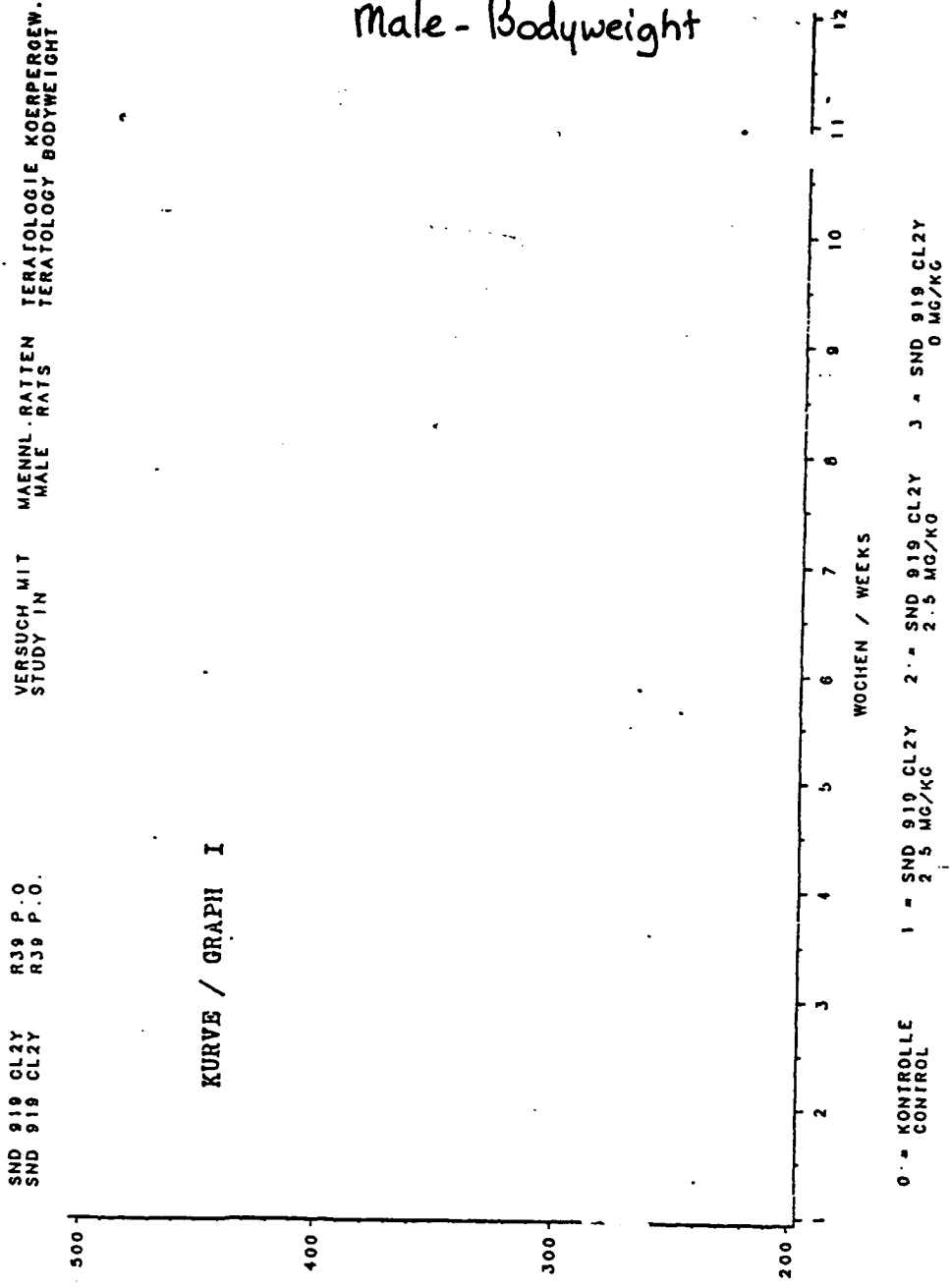
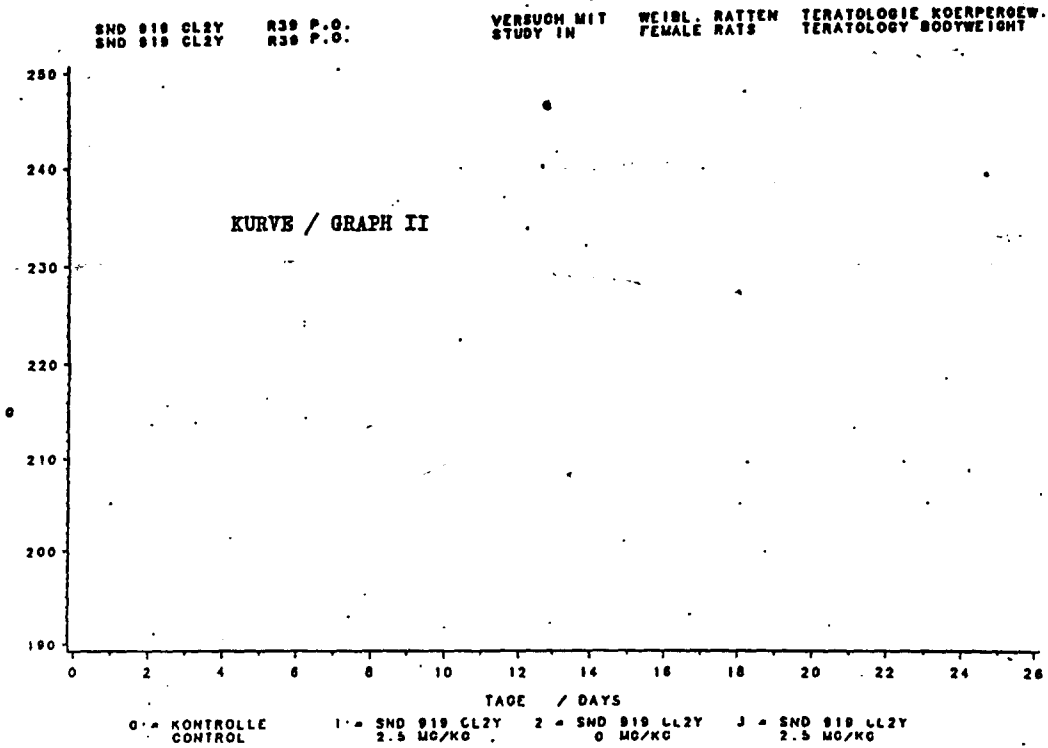
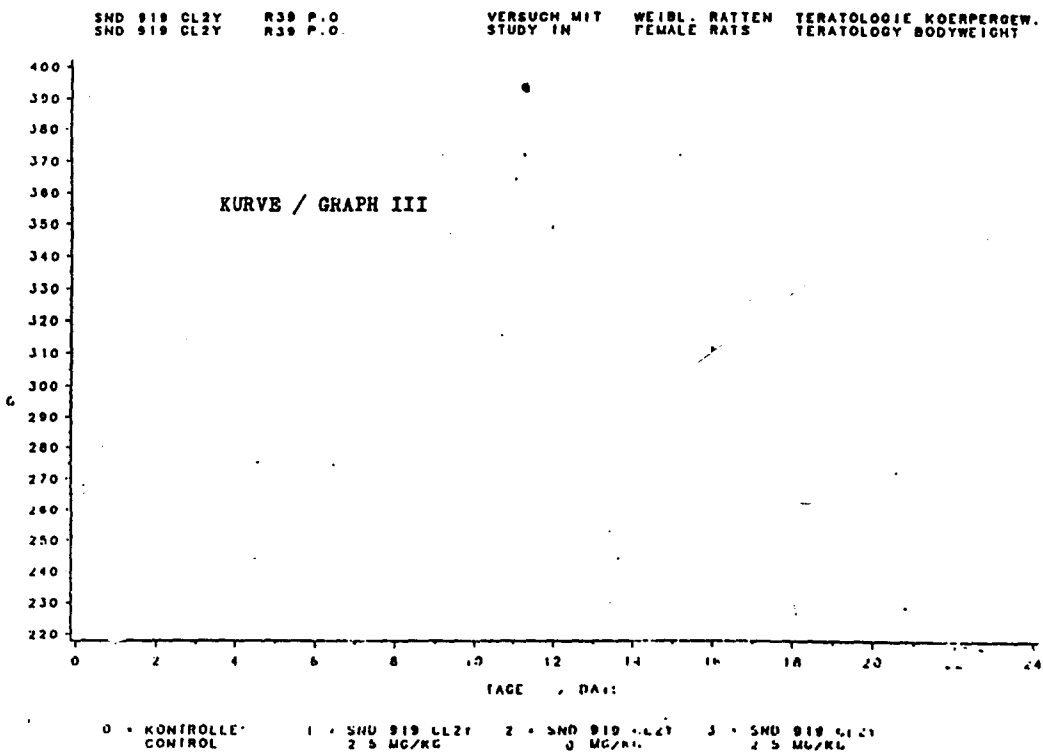


Fig. C.3.b.2.
Female - Bodyweight

Premating



Gestation



Estrous Cycle:

The estrus cycle was prolonged by 1 or 2 days in 13 of 24 females from each of the two drug-treated groups.

Conception:

Successful matings occurred in most groups within the first four days of mating. An additional cycle was required in 5 of 48 treated pairs. Two treated pairs did not successfully mate.

Fertility:

Successful pregnancies were recorded in 46 of 48 females of the untreated groups, and in 7 of 47 females of the treated groups.

Necropsy:

No gross pathological changes were found in any female rats, and there were no significant differences in ovary weights among treatment groups.

Effects on litter parameters

One group 3 female had a total resorption. The total number of implantations and pregnant dams in the PPX-treated groups was significantly reduced compared to controls (Tab. C.3.b.1). There were no significant differences among groups in the number of corpora lutea, fetuses (viable or dead), or resorptions per dam (Tab. C.3.b.2). Some differences in group means occurred when the dam with the total resorption was included in the calculation.

Effects on fetuses

The low pregnancy rate in PPX-treated animals provided a small number of fetuses for this assessment. No drug-related skeletal or visceral abnormalities were identified by the sponsor. The incidence of an additional rib in fetuses of PPX-treated dams (4/25 = 16% in Group 3 fetuses; 4/40 = 10% if PPX-treated fetuses are pooled; Tab. C.3.b.3) appears elevated relative to historical control data compiled by MARTA (Mid-Atlantic Reproduction and Teratology Association; Tab.C.3.b.4).

Histopathology

No drug-related lesions of the testes or epididymis were identified. Treated females (33/48) had an abnormally high number of corpora lutea and low number of follicles.

TR No.: 7219-94-078

Tab. C.3.b.1

BOEHRINGER INGELHEIM KG

REPORT/STUDY NO. : R39

(SND 919 CL2Y , P.O. , RATTE / RAT , SEGMENT I)

WURFDATEN SUMMENWERTE / LITTER DATA SUM VALUES
KAISERSCHNITT / CAESAREAN SECTION

	KONTROLLE CONTROL	2.5 MG/KG	0 MG/KG	2.5 MG/KG	2.5 MG/KG
				a)	b)
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	24	24	24	24	24
TODESFAELLE MATERNAL MORTALITY	0	0	0	0	0
RESORPTIONEN TOTAL RESORPTIONS	0	0	0	1	0
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	23	2	23	4	5
GELBKOEPPER CORPORA LUTEA	355	32	345	65	87
IMPLANTATIONEN IMPLANTATIONS	339	31	333	56	70
LEBENDE FETEN VIABLE FETUSES	330	31	308	53	53
MAENNlich IN % MALE IN %	51	55	50	45	45
WEIBlich IN % FEMALE IN %	49	45	50	55	55
TOTE FETEN DEAD FETUSES	0	0	0	0	0
RESORPTIONEN RESORPTIONS	9	0	25	3	17
FRUEH IN % EARLY IN %	89	0	68	100	100
SPAET IN % LATE IN %	11	0	32	0	0
MISSBILDUNGEN MALFORMATIONS	1	0	0	0	0
VARIATIONEN VARIATIONS	42	3	38	8	8

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a) = excluding, b) = including dam no.317 with total resorptions

TR No.: 7219-94-078

Tab. C.3.b.2

BOEHRINGER INGELHEIM KG

REPORT/STUDY NO. : R39

(SND 919 CL2Y , P.O. , RATTE / RAT , SEGMENT I)

WURFDATEN MITTELWERTE / LITTER DATA MEAN VALUES
KAISERSCHNITT / CAESAREAN SECTION

		KONTROLLE CONTROL	2.5 MG/KG	0 MG/KG	2.5 a) MG/KG	2.5 b) MG/KG
GEWICHT / FET (G) WEIGHT / FETUS (G)	MW SD	5.20 0.22	4.93 0.44	5.24 0.24	5.07 0.34	5.07 0.34
PLAZ.GEW. / FET (G) PLAC. WEIGHT / FETUS (G)	MW SD	0.42 0.04	0.40 0.02	0.41 0.05	0.43 0.07	0.43 0.07
CORPORA LUTEA / MUTTERT. CORPORA LUTEA / DAM	MW SD	15.4 1.5	16.0 2.8	15.0 2.4	16.3 1.0	17.4 2.7
IMPLANTATIONEN / MUTTERT. IMPLANTATIONS / DAM	MW SD	14.7 1.7	15.5 3.5	14.5 2.3	14.0 4.8	14.0 4.1
LEBENDE FETEN / MUTTERT. VIABLE FETUSES / DAM	MW SD	14.3 1.7	15.5 3.5	13.4 2.7	13.3 4.3	10.6 7.0
TOTE FETEN / MUTTERT. DEAD FETUSES / DAM	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
RESORPTIONEN / MUTTERT. RESORPTIONS / DAM	MW SD	0.4 0.7	0.0 0.0	1.1 1.3	0.8 1.5	3.4 6.1
MISSBILDUNGEN / MUTTERT. MALFORMATIONS / DAM	MW SD	0.1 0.2	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
VARIATIONEN / MUTTERT. VARIATIONS / DAM	MW SD	1.8 2.2	1.5 0.7	1.7 1.2	2.0 2.4	~~2.0~~ 2.4
LEB. FETEN IN % IMPL. VIABLE FET. IN % IMPL.	MW SD	99.3 2.1	100.0 0.0	95.6 4.2	98.8 4.6	84.8 39.6
RESORPTIONEN IN % IMPL. RESORPTIONS IN % IMPL.	MW SD	0.7 2.1	0.0 0.0	4.4 4.2	1.2 4.6	15.2 39.6
PRAEIMPLANTAT.-VERLUST PRE IMPLANTAT. LOSS %	MW SD	2.0 2.7	1.8 3.6	0.9 2.9	7.0 14.2	11.4 13.4
POSTIMPLANTAT.-VERLUST POST IMPLANTAT. LOSS %	MW SD	0.7 2.1	0.0 0.0	4.4 4.2	1.2 4.6	15.2 39.6
MISSB. IN % LEB. FET. MALFORM. IN % VIAB. FET.	MW SD	0.1 0.8	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
VARIAT. IN % LEB. FET. VARIAT. IN % VIAB. FET.	MW SD	17.2 13.0	18.1 0.5	22.0 11.0	14.5 20.1	14.5 20.1

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CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

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a) = excluding, b) = including dam no.317 with total resorptions

TR No.: 7219-94-078

Tab. C.3.b.3

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Report/Study No.: R 39

No. 15

	SND 919 CL 2 Y BEFUNDE AN FETEN		RATTE	
	SND 919 CL 2 Y EFFECTS ON FETUSES		RATS	
SUMMENWERTE / SUM VALUES				
	KONTR.	2.5	0	2.5
	CONTR.	MG/KG	MG/KG	MG/KG
<u>SKELETAL EXAMINATION</u>				
NO. OF FETUSES EXAMINED	160	15	147	25
NO. OF FETUSES WITH MALFORMATIONS	1	0	0	0
NO. OF FETUSES WITH VARIATIONS	22	0	13	5
<u>VISCERAL EXAMINATION</u>				
NO. OF FETUSES EXAMINED	170	16	161	28
NO. OF FETUSES WITH MALFORMATIONS	0	0	0	0
NO. OF FETUSES WITH VARIATIONS	20	3	25	3
<u>TYPE OF MALFORMATIONS</u>				
CLEFT VERTEBRAE	1	0	0	0
<u>TYPE OF VARIATIONS</u>				
DUMB-BELL SHAPED VERTEBRAE	5	0	0	0
SHORT 13TH RIB (UNI- OR BILAT.)	16	0	13	1
ADDITIONAL 14TH RIB (PUNCTUAL)	0	0	0	4
GENERAL INCOMPLETENESS OF OSSIFICATION	1	0	0	0
DILATATION OF RENAL PELVIS (UNI- OR BILATERAL)	20	3	25	3
<u>RUNTS</u>				
	0	1	0	0
<u>ADDITIONAL SKELETAL FINDINGS</u>				
UNOSSIFIED STERNEBRA V	0	1	2	1
POORLY OSSIFIED STERNEBRA V	27	2	15	0
POORLY OSSIFIED STERNEBRAE IV+V	1	0	0	0

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Tab. C.3.b.4.

SKELETAL ANOMALIES ALL STUDIES

	FETAL INCIDENCE (%)			LITTER INCIDENCE (%)			
	AVG	S.D.	MAX	AVG	S.D.	MAX	
STERNEBRAE							
1st fused to Manubrium	0.002	0.03	0.47	0.018	0.27	4.00	
Multiple fusions	0.031	0.17	1.71	0.259	1.19	9.09	
Agnesis	0.004	0.04	0.58	0.041	0.43	4.76	
Split	0.128	0.51	5.88	0.540	2.19	21.74	
Misaligned	0.471	1.44	10.19	2.890	7.37	47.37	
Asymmetric	0.027	0.17	2.04	0.282	1.78	22.73	
Duplicated	0.004	0.06	0.88	0.030	0.45	6.67	
Misshapen	0.064	0.40	4.78	0.439	2.54	27.78	
RIBS							
Agnesis	0.056	0.28	2.98	0.422	1.60	12.00	
Branched/split	0.002	0.03	0.40	0.002	0.03	0.40	
Cervical	0.394	0.75	5.00	2.814	4.80	25.00	
Fused	0.034	0.13	0.68	0.287	1.11	5.88	
Hypoplastic	0.826	2.81	21.64	2.778	8.53	61.90	
Intercostal	0.004	0.06	0.84	0.025	0.37	5.56	
Misshapen	0.270	0.96	7.50	1.628	5.42	42.11	
* Supernumerary	3.199	6.30	25.14	14.776	22.97	77.78	
Wavy	0.409	2.00	28.40	1.461	3.18	20.00	
Bent	0.050	0.31	3.49	0.332	2.31	29.41	
PELVIC GIRDLE							
Pelvic bone:	Agnesis	0.003	0.05	0.72	0.023	0.33	5.00
	Misaligned	0.002	0.02	0.26	0.037	0.39	4.17
Ilium:	Misshapen	0.003	0.05	0.72	0.025	0.37	5.56
Ischium:	Hypoplastic	0.013	0.10	1.20	0.110	0.87	10.00
SHOULDER GIRDLE							
Scapula:	Misshapen	0.008	0.07	0.82	0.076	0.66	6.67
APPENDICULAR SKELETON							
Forelimb							
	Long bone: Hypoplastic	0.006	0.09	1.41	0.041	0.61	9.09
	Misshapen	0.001	0.02	0.28	0.020	0.29	4.35
	Metacarpal: Agnesis	0.012	0.11	1.37	0.090	0.82	10.00
	Hypoplastic	0.021	0.14	1.36	0.136	0.95	10.00
	Phalanx: Misaligned	0.002	0.04	0.54	0.023	0.33	5.00
	Agnesis	0.003	0.04	0.59	0.019	0.28	4.17
	Clubbed	0.006	0.09	1.41	0.041	0.61	9.09
	Fused	0.004	0.05	0.82	0.030	0.45	6.67
Hindlimb							
	Long bone: Small	0.006	0.09	1.41	0.041	0.61	9.09
	Hypoplastic	0.002	0.03	0.47	0.002	0.03	0.47
	Misshapen	0.005	0.04	0.47	0.041	0.41	4.35
	Metacarpal: Agnesis	0.004	0.06	0.88	0.030	0.45	6.67
	Phalanx: Agnesis	0.024	0.22	2.37	0.158	1.43	16.00
	Clubbed	0.006	0.09	1.41	0.041	0.61	9.09
	Supernumerary	0.005	0.07	1.03	0.018	0.27	4.00
	Misaligned	0.044	0.65	9.73	0.169	2.51	37.50
	Talus: Advanced	0.013	0.16	2.35	0.039	0.41	4.55

Serum Prolactin levels

A marked lowering of serum prolactin was recorded in most PPX-treated rats (Tab. C.3.b.5).

Influence of SND 919 Cl2 on Serum Prolactin Levels in Rats

Groups	Dose	Sex	Animal-No.	Prolactin (ng/ml)
0/3	Control	m	054	120.87
			059	123.72
			065	99.95
			068	28.11
			069	34.57
			351	31.30
			355	77.08
			357	357.44
			358	53.22
			362	103.99
			Median	88.52
			NI	10
1/2	2.5 mg/kg SND 919 Cl2	m	154	< 0.39
			156	< 0.39
			263	0.71
			265	0.72
			268	< 0.39
			269	< 0.39
			270	1.43
			271	3.01
			272	10.37
			274	2.19
			Median	0.71 ***
			NI	10
0/2	Control	f	009	252.09
			015	186.42
			019	15.35
			021	409.13
			205	272.42
			207	294.12
			209	287.99
			215	238.15
			218	91.73
			223	195.20
			Median	245.12
			NI	10
1/3	2.5 mg/kg SND 919 Cl2	f	112	< 0.39
			113	< 0.39
			114	< 0.39
			115	< 0.39
			118	236.64
			119	< 0.39
			312	< 0.39
			316	< 0.39
			317	72.26
			318	< 0.39
			Median	< 0.39 ***
			NI	10

*** = p < 0.001

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Toxicokinetics

Plasma concentrations of PPX were determined 2 hrs after dosing. Levels were higher in females than in males (Tab. C.3.b.6).

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group no.	mean $\pm$ SD	
	females	males
1	158.3 $\pm$ 47.18	74.7 $\pm$ 23.74
2	-	85.0 $\pm$ 34.83
3	164.1 $\pm$ 40.95	-

The plasma concentrations of SND 919 CL 2 Y in female animals were clearly higher than in males.

For both sexes, there was no relevant difference between the results from different groups (females: group no. 1 vs. no 3, males: group no. 1 vs. no. 2).

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C.3.c. Segment II in Rats: Reproduction and Teratogenicity

	<u>Main Study</u>	<u>PK Study</u>
Document #(s):	BI Document U88-0068 Upjohn TR 7219-94-074	BI Document U94-0004 Upjohn TR 7256-94-027
Sponsor Volume:	1.43	1.59

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 1.5 mg/kg/day to Wistar rats (36/dose) from day 7 to 16 of gestation. Twenty-four rats per group were sacrificed on day 22 for delivery of pups by Caesarean section. The remaining females (12/dose) littered spontaneously and raised the pups to weaning (21 days). A supplementary toxicokinetic study was conducted in 6 pregnant females/dose. Animals were treated on days 7-12, and plasma samples collected at 1, 2, 4 and 24 hrs post-treatment on day 12.

Overt drug-related changes were restlessness and agitation with the middle and high doses, and decreased body weight gain and food intake at the high dose. With respect to reproductive toxicities, a very clear threshold effect was apparent; the MD group was virtually devoid of toxicities, and very pronounced toxicities were evident at the HD. Significant embryoletality occurred with the high dose as only 7 of 32 pregnant females had viable offspring. The other 25 pregnancies were classified as complete "early" resorptions. No clear drug-related effects on fetal maturation and development, or skeletal/visceral abnormalities were apparent. As in the previous studies, the teratology information is limited by the low number of evaluable pups. One case each of anal atresia (LD), sirenomelia (LD), and cleft vertebra (MD) were noted in pups from PPX-treated dams. Since impairment of body weight development and delayed eye-opening in pups from drug-treated dams did not occur in this study, as they had in the previous Segment I study, it is reasonable to conclude that these impairments were due to drug administration during lactation. Drug exposure in the LD group approximated exposure of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d.

Methods:

Dosages: 0.1, 0.5, 1.5 mg/kg/day (Drug Lot: Batch I - main study, Batch IV - PK study; prepared in distilled water) from day 7 to day 16 (inclusive) of gestation in main study, and day 7-12 in PK study.

Low dose is 10 times the expected human dose (at the time of study initiation). The high dose was somewhat lower than the dose used in a pilot study, in which significant signs of CNS toxicity were observed in dams administered 2.5 mg/kg.

Route of Administration: oral (gavage)

Species/Number: 144 inseminated females for main study, 24 for PK study

Approximate initial weight/age: 230 g / 12 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	days 1, 7-16, and 22 of gestation, and days 1, 6, 13, and 20 of lactation
Food consumption	-	weekly
Plasma Concs	-	1, 2, 4, 24 hrs postdose on day 12

Termination:

Caesarean Section: 24 dams/group were sacrificed on day 22 of gestation. Non-pregnant females were excluded from mean calculations. The number of corpora lutea, fetal viability/loss, and implantation sites were determined. Dams were autopsied. Fetuses were sexed, and examined for skeletal or visceral and cephalic abnormalities.

Spont. delivery: 12 dams/group delivered pups and raised them to weaning. Litter parameters (size, live/still births, gross abnormalities) were recorded, and functional/behavioral/maturational tests were conducted. Pups were sacrificed and autopsied during the fourth week.

Statistics

Statistical comparisons were made by Bartlett's test, one-way ANOVA, Newman-Keuls test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects on Dams

Mortality: One MD dam died apparently from choking on bedding

Clinical signs:

In the main study, restlessness and agitation at MD and HD, and one HD dam had vaginal bleeding. In the TK study, sedation was noted at the HD, and 5/6 HD dams had vaginal bleeding.

Body Weight Gain:

Significantly decreased in the HD groups from beginning of treatment through gestation (Fig. C.3.c.1).

Food Intake:

Significantly decreased in HD group during week 2 and 3 of gestation. No differences among groups occurred during the lactation period.

Gestation:

21 of 144 females were not pregnant (CON: 7; LD: 3; MD: 8; HD: 3). 25 of 32 pregnant HD dams (18 C-section, 7 spontaneous delivery) had complete resorptions.

In the PK study, all HD dams had complete resorptions.

Necropsy: No pathologies were found in the dams.

Effects on fetuses and pups

C-section group: The total litter resorption by 18 of 22 pregnant dams in the HD group resulted in some significant differences in mean litter values. There were no significant differences in mean fetal or placental weights, or in the incidence of external, skeletal, visceral or cephalic abnormalities (Tab. C.3.c.1-3), although some rare malformations were noted in pups of PPX-treated dams (one case of anal atresia at LD, one case of sirenomelia with gastroschisis at LD, and one case of cleft vertebra at MD).

Spontaneous delivery group: The mean number of live pups per dam was significantly reduced in the HD group because 7 of 10 pregnant animals had total resorptions (Tab. C.3.c.4-5). There was a dose-dependent trend, but no significant increase in pup body weight development through weaning (Fig. C.3.c.2). No functional, behavioral or maturational impairments, or structural abnormalities were evident in the pups (Tab. C.3.c.6-7).

Plasma Concentrations (Satellite Study)

Except for 24 hrs after the 0.1 mg/kg dose, PPX was detectable in plasma. The highest concentrations were noted 1 hr after dosing. Increases in AUC were generally dose proportional. PK parameters ($C_{1\text{ hr}}$, AUC_{1-24}) associated with the lowest test dose approximated those of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d. ($C_{\text{max}_{ss}} =$ ng/ml, $AUC_{0-8} =$)

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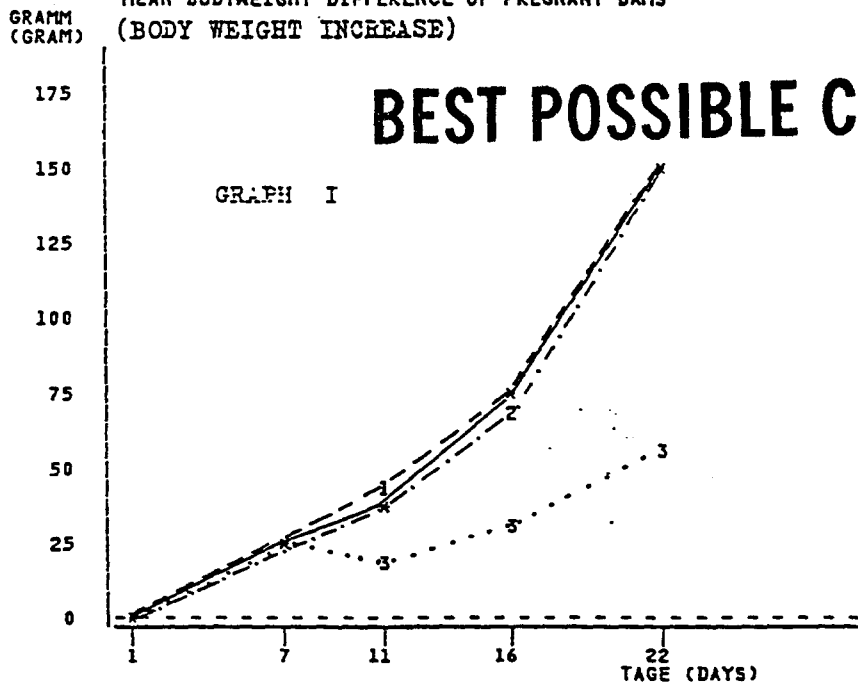
SND 919 CL2Y RATTEN / RATS

SEGM. 2

KOERPERGEWICHT TRAECHTIGER MUTTERTIERE (G) ~~V. I. S. P. S. C. H. I. M. - G. R. I. E. P. P.~~
 BODYWEIGHTS OF PREGNANT DAMS (G) **CAESAREAN SECTION GROUP**
 MITTELWERTE / MEAN VALUES

		N	1	7	11	16	22
KONTROLLE CONTROL	MW	19	222.4	246.8	262.7	296.1	373.8
	SD		10.7	12.9	13.3	15.7	27.3
0.1 MG/KG	MW	21	224.3	250.6	267.7	300.5	376.3
	SD		8.2	9.5	10.0	12.3	24.7
0.5 MG/KG	MW	18	222.7	247.1	257.4	291.1	373.2
	SD		8.6	13.3	14.6	13.9	21.7
1.5 MG/KG	MW	22	222.6	246.6	238.8	254.1	280.5
	SD		8.9	14.2	16.0	22.9	50.0

MITTLERE GEWICHTSDIFFERENZ TRAECHTIGER MUTTERTIERE
 MEAN BODYWEIGHT DIFFERENCE OF PREGNANT DAMS
 (BODY WEIGHT INCREASE)



*: MEHRFACHBELEGUNG - MULTIPLE POINTS
 0: KONTR - CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 1.5 MG/KG

*** p < 0.001

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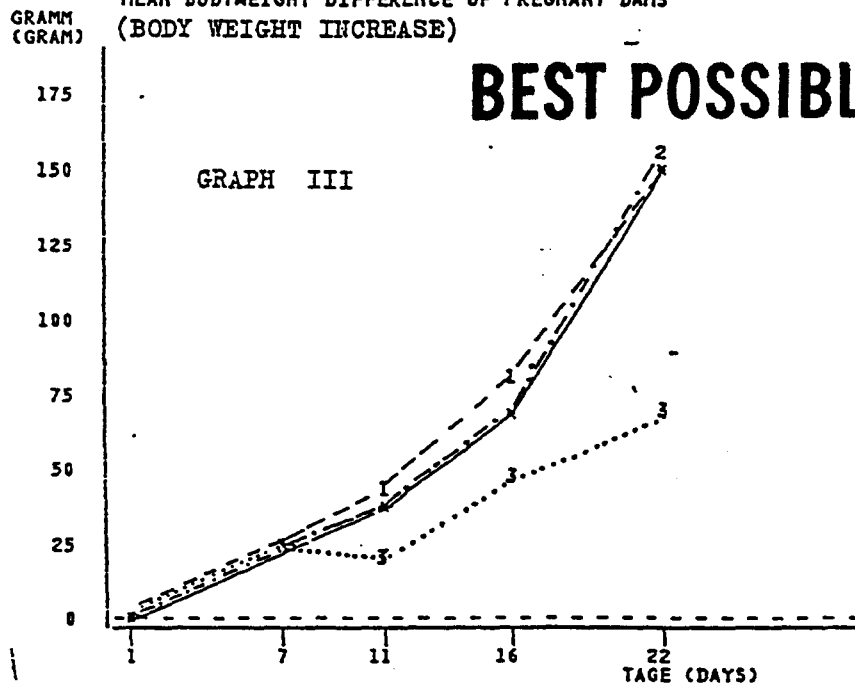
SND 919 CL2Y RATTEN / RATS

SEGM. 2

KOERPERGEWICHT TRAECHTIGER MUTTERTIERE (G) ~~AUFZUCHT GRUPPE~~
 BODYWEIGHTS OF PREGNANT DAMS (G) **SPONTANEOUS DELIVERY GROUP**
 MITTELWERTE / MEAN VALUES

		N	1	7	11	16	22
KONTR - KONTR CONTROL	MW	10	237.9	259.9	275.2	308.2	388.7
	SD		9.9	10.8	14.4	14.6	24.1
0.1 MG/KG	MW	12	236.0	263.8	281.7	316.2	387.8
	SD		15.4	16.3	18.8	21.8	30.8
0.5 MG/KG	MW	10	237.8	261.7	275.2	308.1	394.1
	SD		9.8	8.6	8.0	8.9	16.6
1.5 MG/KG	MW	10	234.6	261.8	255.0***	275.9***	308.6***
	SD		7.5	8.8	8.6	16.8	52.9

MITTLERE GEWICHTSDIFFERENZ TRAECHTIGER MUTTERTIERE
 MEAN BODYWEIGHT DIFFERENCE OF PREGNANT DAMS
 (BODY WEIGHT INCREASE)



K: MEHRFACHBELEGUNG - MULTIPLE POINTS
 0: KONTR - KONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 1.5 MG/KG

*** p < 0.001

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RATTEN / RATS

SEGM. 2

	WURFDATEN / LITTER DATA SUMMENWERTE / SUM VALUES		KESCHNITTGRUPPEN CAESAREAN SECTION GROUP	
	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	24	24	24	24
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	18
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	19	21	18	4
GELBKOEPPER CORPORA LUTEA	261	294	247	312
IMPLANTATIONEN IMPLANTATIONS	240	267	233	311
LEBENDE FETEN VIABLE FETUSES	232	250	222	51
MAENNLICH IN % MALE IN %	51	54	58	55
WEIBLICH IN % FEMALE IN %	49	46	42	45
TOTE FETEN DEAD FETUSES	0	0	0	0
RESORPTIONEN RESORPTIONS	8	17	11	260
FRUEH IN % EARLY IN %	50	76	73	100
SPAET IN % LATE IN %	50	24	27	0
MISSBILDUNGEN MALFORMATIONS	0	2	1	0
VARIATIONEN VARIATIONS	1	6	5	0

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RATTEN / RATS

SEGM. 2

	WURFDATEN / LITTER DATA MITTELWERTE / MEAN VALUES		KAISERSCHNITT-GRUPPE CAESAREAN SECTION GROUP		
		KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GEWICHT / FET (G) WEIGHT / FETUS (G)	MW SD	5.31 0.23	5.45 0.30	5.38 0.22	5.41 0.32
PLAZ.GEW. / FET (G) WEIGHT PLAC. / FETUS (G)	MW SD	0.45 0.05	0.49 0.10	0.46 0.06	0.46 0.03
CORPORA LUTEA / MUTTERT. CORPORA LUTEA / DAM	MW SD	13.7 1.3	14.0 2.4	13.7 0.6	14.2 1.5
IMPLANTATIONEN / MUTTERT. IMPLANTATIONS / DAM	MW SD	12.6 3.0	12.7 4.1	12.9 2.0	14.1 1.5
LEBENDE FETEN / MUTTERT. VIABLE FETUSES / DAM	MW SD	12.2 3.0	11.9 3.9	12.3 2.1	2.3 5.1
TOTE FETEN / MUTTERT. DEAD FETUSES / DAM	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
RESORPTIONEN / MUTTERT. RESORPTIONS / DAM	MW SD	0.4 0.6	0.8 1.2	0.6 1.1	11.8 5.4
MISSBILDUNGEN / MUTTERT. MALFORMATIONS / DAM	MW SD	0.0 0.0	0.1 0.3	0.1 0.2	0.0 0.0
VARIATIONEN / MUTTERT. VARIATIONS / DAM	MW SD	0.1 0.2	0.3 0.5	0.3 0.6	0.0 0.0
LEB. FETEN IN % IMPL. VIABLE FET. IN % IMPL.	MW SD	98.8 2.2	97.6 3.8	98.5 3.5	6.0 26.9
RESORPTIONEN IN % IMPL. RESORPTIONS IN % IMPL.	MW SD	1.2 2.2	2.4 3.8	1.5 3.5	94.0 26.9
PRAEIMPLANTAT.-VERLUST PRE IMPLANTAT. LOSS %	MW SD	2.5 8.2	5.1 11.0	1.5 5.3	0.1 0.3
POSTIMPLANTAT.-VERLUST POST IMPLANTAT. LOSS %	MW SD	1.2 2.2	2.4 3.8	1.5 3.5	94.0 26.9
MISSB. IN % LEB. FET. MALFORM. IN % VIAB. FET.	MW SD	0.0 0.0	0.1 0.7	0.1 0.6	0.0 0.0
VARIAT. IN % LEB. FET. VARIAT. IN % VIAB. FET.	MW SD	0.1 1.4	2.1 5.5	1.7 6.5	0.0 0.0

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Tab. C.3.c.3.

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RATTEN/RATS

SND 919 CL 2 Y

SEGM. 2

BEFUNDE AN FETEN
FINDINGS IN FETUSES

KAISERSCHNITT-GRUPPE
CAESAREAN SECTION GROUP

	KONTR. CONTOL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
<u>EXTERNAL</u>				
ATRESIA ANI	0	1 ^a	0	0
SIRENIFORM MALFORM.. OEDEMA, GASTROSCHISIS	0	1 ^b	0	0
<u>SKELETAL</u>				
BENT AND SHORTENED LONG BONES, SYNOSTOSIS OF VERTEBRAE AND RIBS	0	1 ^b	0	0
SPLIT VERTEBRAL BODY	0	0	1 ^c	0
"HOUR-GLASS" SHAPED VERTEBRA	0	1 ^d	0	0
<u>VISCERAL</u>				
DILATATION OF RENAL PELVIS	1 ^e	5 ^f	4 ^g	0
DISPLACEMENT OF LEFT KIDNEY	0	0	1 ^h	0
<u>ADDITIONAL SKELETAL FINDINGS</u>				
UNOSSIFIED 5TH STERNEBRA	3	3	4	0
REDUCED OSSIFIED 5TH STERNEBRA	2	1	6	0

a FETUS NO 101/14
b FETUS NO 116/2
c FETUS NO 213/5
d FETUS NO 107/7
e FETUS NO 017/3

f FETUS NO 101/4, 106/2, 114/15, 119/12, 124/16
g FETUS NO 210/10, 216/9, 216/11, 219/7
h FETUS NO 209/9

117-10

SND 919 CL2Y RATTEN / RATS

SEGM. 2

	WURFDATEN / LITTER DATA SUMMENWERTE / SUM VALUES		AUFZUCHT-GRUPPE SPONTANEOUS DELIVERY GROUP	
	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	12	12	12	12
TODESFÄLLE MATERNAL MORTALITY	0	0	0	1
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	7
TRAECHTIGE TIERE PREGNANT ANIMALS	10	12	10	10
LEBENDE JUNGTIERE VIABLE YOUNG	134	133	138	39
MAENNLICH IN % MALE IN %	46	49	41	49
WEIBLICH IN % FEMALE IN %	54	51	59	51
TOTE JUNGTIERE DEAD PUPS	0	1	0	0
MISSBILDUNGEN MALFORMATIONS	0	0	0	0
VARIATIONEN VARIATIONS	0	0	0	0
JUNGTIERE 7. TAG PUPS DAY 7	131	130	133	38
JUNGTIERE 14. TAG PUPS DAY 14	131	130	132	38
JUNGTIERE 21. TAG PUPS DAY 21	131	130	132	38
VERENDETE JUNGTIERE MORTALITY IN OFFSPRING	3	3	6	1

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RATTEN / RATS

SEGM. 2

		WURFDATEN / LITTER DATA MITTELWERTE / MEAN VALUES		AUFZUCHT-GRUPPE SPONTANEOUS DELIVERY GROUP		
		KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG	
TRAGEZEIT DER MUTTERTIERE GESTATION PERIOD OF DAMS	MW SD N	22.0 0.0 10	22.1 0.3 12	22.0 0.0 10	22.0 0.0 10	
GEWICHT / JUNGTIER 1.TAG WEIGHT / PUP AT DAY 1	MW SD	5.88 0.15	6.24 0.34	5.95 0.26	6.04 0.47	
GEWICHT / JUNGTIER 21.TAG WEIGHT / PUP AT DAY 21	MW SD	29.58 2.59	34.76 6.98	31.14 4.83	32.82 4.01	
GEWICHTSZUNAHME 1.-21.TAG BODYW. INCR. DAY 1-21	MW SD	23.69 2.56	28.51 6.80	25.19 4.79	26.78 3.88	
LEB. JUNGT./MUTTERT.1.TAG VIABLE PUPS / DAM DAY 1	MW SD	13.4 1.4	11.1 3.3	13.8 2.0	3.0 6.3	***
TOTE JUNGT./MUTTERT.1.TAG DEAD PUPS / DAM DAY 1	MW SD	0.0 0.0	0.1 0.3	0.0 0.0	0.0 0.0	
LEB. JUNGT./MUTTERT.7.TAG VIABLE PUPS / DAM DAY 7	MW SD	13.1 1.2	10.8 3.5	13.3 2.3	3.8 6.1	***
LEB. JUNGT./MUTTERT.21.TAG VIABLE PUPS / DAM DAY 21	MW SD	13.1 1.2	10.8 3.5	13.2 2.2	3.8 6.1	***
JUNGTIERVERLUST % 1.-21.T. PUPS LOSS % DAY 1-21	MW SD	0.6 1.6	0.5 3.0	2.2 2.7	0.1 0.3	
MISSBILDUNGEN / MUTTERT. MALFORMATIONS / DAM	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	
VARIATIONEN / MUTTERTIER VARIATIONS / DAM	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	
MISSBILDUNGEN % LEB. JUNGT. MALFORMATIONS IN % VIAB.P.	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	
VARIATIONEN % LEB. JUNGT. VARIATIONS IN % VIAB.PUPS	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0	

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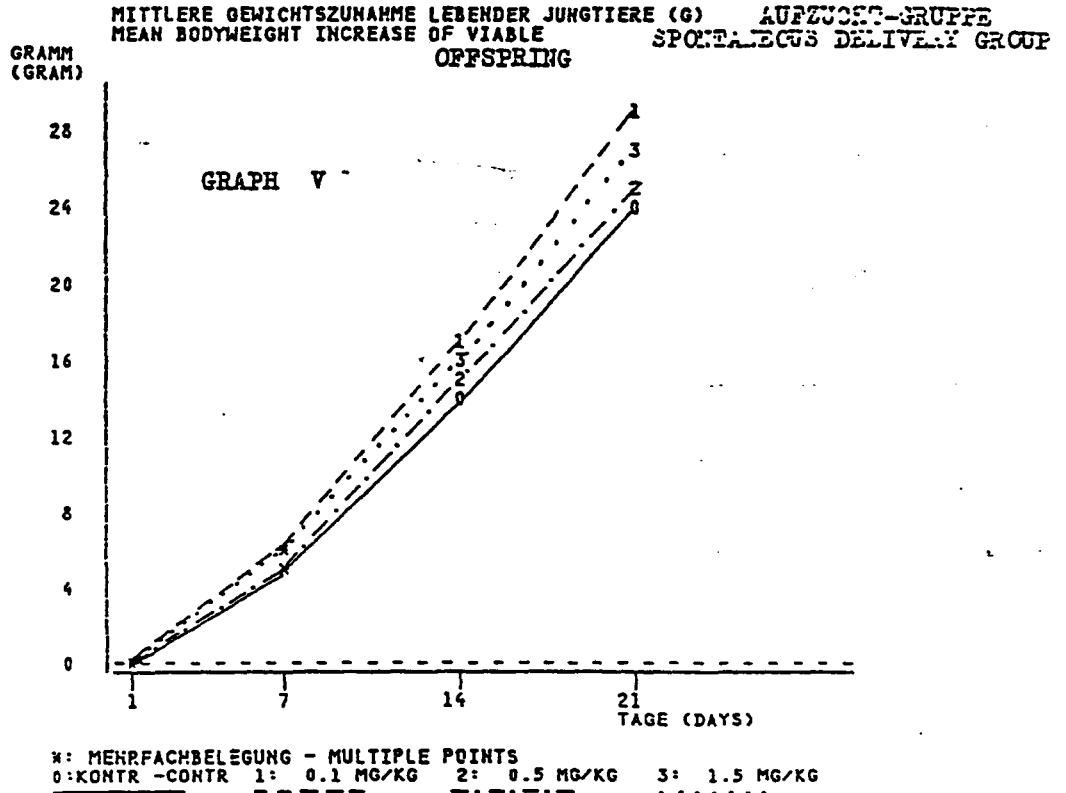
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Fig. C.3.c.2.

SND 919 CL2Y RATTEN / RATS

SEGM. 2



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Tab. C.3.c.6

SND 919 CL 2 Y

RATTEN/RATS

SEGM. 2

BEOBSACHTUNGEN DER F₁-GENERATION DER GRUPPE DER SPONTANGEBURTEN

OBSERVATIONS OF F₁-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

ERGEBNISSE IN PROZENT / RESULTS IN PER CENT

DOSIS DOSE	AUSGEWERTETE WÜRFE EVALUATED LITTERS	AUFSTELLEN DER OHREN		FELLWACHSTUM		LAUFEN MIT ANGE- HOBENEM BAUCH		DURCHBRECHEN DER OBEREN SCHNEIDEZÄHNE		AUGENÖFFNUNG	
		ERECTION OF PINNAE		FUR GROWTH		RUNNING WITH RAISED VENTER		ERUPTION OF MAXIL- LARY INCISORS		EYE OPENING	
		TAG 4	DAY 5	TAG 6	DAY 7	TAG 12	DAY 13	TAG 12	DAY 13	TAG 15	DAY 16
KONTROLLE/ CONTROL	10	-	96.2	-	100.0	98.5	100.0	95.4	100.0	10.7	67.2
0.1 MG/KG	12	7.6	99.2	6.2	100.0	99.2	100.0	96.2	100.0	22.3	76.9
0.5 MG/KG	10	-	97.0	-	100.0	99.2	100.0	96.2	100.0	12.1	55.3
1.5 MG/KG	3	2.6	100.0	-	100.0	100.0	100.0	97.4	100.0	18.4	81.6

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Tab. C.3.c.7

SND 919 CL 2 Y

RATTEN/RATS

SEGM. 2

ERGEBNISSE VON FUNKTIONS- UND VERHALTENSTESTE DER F₁-GENERATION

RESULTS OF FUNCTION AND BEHAVIOUR TESTS IN F₁-OFFSPRING

TR No.: 7219-94-074

DOSIS DOSE	ANZAHL WÜRFE No. OF LITTERS	ANZAHL TIERE No. OF ANIMALS	AUF RICHTE-REFLEX RIGHTING-REFLEX %	SEHTEST PUPILLARY REACTION %	HÖRTEST HEARING-TEST %		
					80 Hz	4000 Hz	16000 Hz
KONTROLLE CONTROL	10	131	100.0	100.0	100.0	100.0	100.0
0.1 MG/KG	12	130	100.0	100.0	100.0	100.0	100.0
0.5 MG/KG	10	132	100.0	100.0	100.0	100.0	100.0
1.5 MG/KG	3	38	100.0	100.0	100.0	100.0	100.0

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DESTROY UPON DISPOSAL

TR No.: 7256-94-027

Boehringer Ingelheim KG

Report/Study No.: R 49

C.3.c.8

Table 1: Geometric mean values and ranges of plasma concentrations [ng/ml] and AUC [1-24 h] of SND 919 CL 2 Y in rats on day 12 of gestation after multiple administration by gavage

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dose [mg/kg]	hours				AUC [ng/ml-h]
	1	2	4	24	
0.1	7.32	5.98	2.92	0.00	44.78
0.5	33.25	26.75	13.27	0.63	213.20
1.5	77.74	68.95	40.10	1.84	620.01

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C.3.d. Segment II in Rabbits: Reproduction and Teratogenicity

	<u>Main Study</u>	<u>PK Study</u>
Document #(s):	BI Document U87-0805 Upjohn TR 7219-94-073	BI Document U94-0020 Upjohn TR 7256-94-026
Sponsor Volume:	1.44	1.59

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 1.0 and 10.0 mg/kg/day to pregnant Himalayan rabbits (/dose) from day 6 to 18 of gestation. Fetuses were delivered by Caesarean section on day 29, and maintained in an incubator for 24 hrs. After sacrifice, the offspring were examined for skeletal and visceral abnormalities. A supplemental toxicokinetic study was conducted in 4 rabbits/dose on day 12 of gestation.

Overt drug-related changes were restlessness and agitation with the high dose, and dose-dependent decreases in body weight gain and fecal output. One animal died after the third drug treatment due to cardiovascular collapse. Drug exposure in the LD group was at least equivalent to, and generally exceeded, the exposure of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d. Pathological findings in other dams at sacrifice were considered spontaneous findings for this strain. No embryotoxic or fetotoxic effects of pramipexole were identified. Increases in the rate of resorption, which occurred at a very high rate in rats, did not occur in rabbits. No dose-related trends in the incidence of malformations were observed in newborns. Thus, pramipexole appears to be devoid of reproductive toxicities in rabbits at doses up to 10 mg/kg, and at exposures that are well-above expected human exposures.

Methods:

Dosages: 0.1, 1.0, 10.0 mg/kg/day (Drug Lot: Batch I - main study, Batch IV - PK study; prepared in distilled water) from day 6 to day 18 (inclusive) of gestation in the main study, and day 6 to 12 in the TK study.

Low dose is 10 times the expected human dose (at the time of study initiation).
The high dose was selected based on a pilot study, in which a reduction in body weight was produced by this dose.

Route of Administration: oral (gavage)

Species/Number: Main Study - 72 mated females
TK Study - 16 mated females

Mean initial weight/age: 2317 g / 5-6 months

Parameters monitored/Intervals:

Clinical - daily

Body weight - days 1, 6-18, and 29 of gestation, and days 1, 6, 13, and 20 of lactation
Food consumption - not measured
Plasma Concs - day 12 (0, 2, 4, 8 and 24 hrs postdose)

Termination:

Dams were sacrificed on day 29 of gestation. Routine pathological examinations of the dams were done, and the number of corpora lutea, fetal viability/loss, and implantations and resorptions were determined. Viable newborns were maintained in an incubator for 24 hrs, at which point they were weighed, examined for malformations and skeletal variations, and necropsied.

Statistics:

Statistical comparisons were made by one-way ANOVA followed by Newman-Keuls test for multiple comparisons, or Fisher's exact test.

Results:

Effects on Dams (Main Study)

Mortality: Three deaths occurred during the study, but only one was likely drug-related; an HD dam died on day 3 apparently because of circulatory collapse.

Clinical Signs:

Restlessness and agitation in HD animals between days 10-18.
Reduced fecal output on several days in 8 LD, 16 MD, and 17 HD.

Body Weight Gain:

Dose-dependent, significant decreases in all 3 groups on day 7, in MD and HD groups from days 8-12, and in HD group on days 13-14. The effect waned with increasing duration of treatment (Fig. C.3.d.1).

Gestation:

One control and one LD dam were not pregnant at the end of the study. Dams with no living offspring were excluded from statistical analyses. No miscarriages occurred during the study.

Necropsy:

None of the identified pathologies appeared to be drug-related.

Fig. C.3.d.1.

SND 919 CL2Y. KANINCHEN- / RABBITS

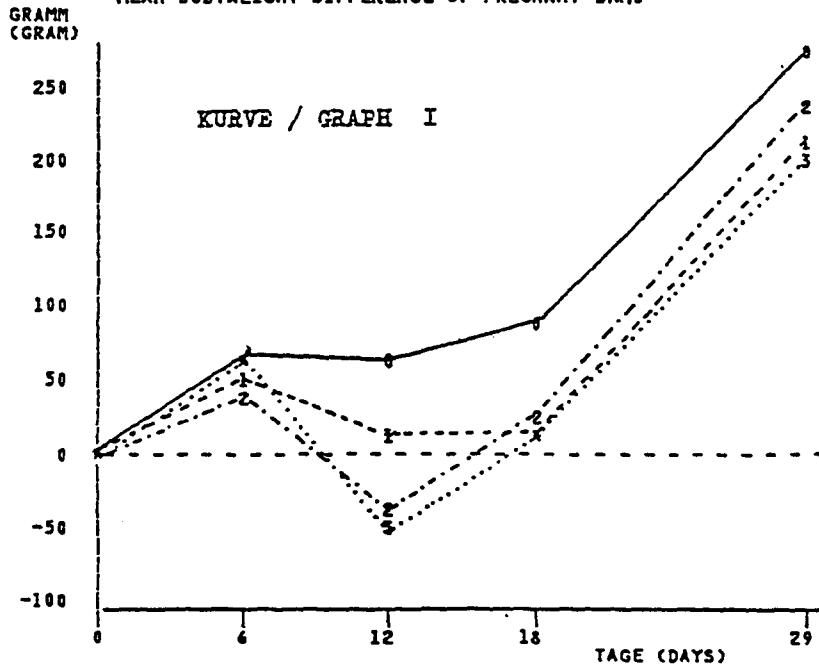
SEGM. 2

KOERPERGEWICHT TRAECHTIGER MUTTERTIERE (G)
 BODYWEIGHTS OF PREGNANT DAMS (G)
 MITTELWERTE / MEAN VALUES

		N	0	6	12	18	29
KONTROLLE CONTROL	MW	17	2284.1	2351.8	2350.6	2370.6	2558.8
	SD		148.7	160.3	180.2	180.5	170.1
0.1 MG/KG	MW	15	2304.7	2349.3	2318.0	2316.0	2515.3
	SD		158.1	155.3	161.6	181.1	198.2
1 MG/KG	MW	18	2310.6	2345.0	2271.1	2336.1	2549.4
	SD		135.3	165.7	154.8	201.2	164.5
10 MG/KG	MW	17	2336.5	2397.6	2287.6	2354.7	2542.4
	SD		138.1	174.0	172.5	152.2	149.8

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MITTLERE GEWICHTSDIFFERENZ TRAECHTIGER MUTTERTIERE
 MEAN BODYWEIGHT DIFFERENCE OF PREGNANT DAMS



*: MEHRFACHBELEGUNG - MULTIPLE POINTS
 0: KONTR -CONTR 1: 0.1 MG/KG 2: 1 MG/KG 3: 10 MG/KG

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Autopsy findings in the dams

At the autopsy of the dams after the ovario-hysterectomy (or after death) the following findings were obtained:

Animal no. 006: Approx. bean-sized subcapsular pale area on the liver.
(Histological finding: subcapsular focal, small- to large droplet fatty infiltration).

Animal no. 008: Right uterine horn segmented and empty.

Animal no. 102: Fracture in the region of the 4th lumbar vertebra.

Animal no. 105: Right uterine horn segmented and empty.

Animal no. 111: Agenesis of the accessory lobe of the lung.

Animal no. 118: Foamy contents in the bronchi, multiple haemorrhages in all lobes of the lung.

Animal no. 208: Agenesis of the left uterine horn.

Animal no. 304: Severe lung congestion with oedema. Extensive haemorrhages in the tissue of the mammary gland (Histopathological finding: recent haemorrhages in the subcutis and in the intra- and inter-lobular mammary tissue).

Animal no. 310: Pyometra of right uterine horn.

Further random findings were parovarian cysts and necroses of the fatty tissue in the retroperitoneal adeps renis with the following incidence:

	Contr.	0.1 mg/kg	1 mg/kg	10 mg/kg
parovarian cysts	5	5	2	1
necroses of fatty tissue	1	3	0	3

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Effects on Litters

No significant differences were evident among groups in mean litter values of number of corpora lutea, implantations, viable/dead fetuses, and resorptions. Mean fetal birth weights and placental weights also did not differ among groups. There were no drug-related trends in the distribution of "runts" (<65% mean fetal weight; 4 Con, 8 LD, 2 HD) and fetal deaths between 0-24 hrs after birth (5 Con, 6 LD 4 MD) (Tab. C.3.d.1-2).

Tab. C.3.d.1. **BEST POSSIBLE COPY**

SEGM. 2

WURFDATEN / LITTER DATA
SUMMENWERTE / SUM VALUES

	KONTROLLE CONTROL	0.1 MG/KG	1 MG/KG	10 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	18	18	18	18
TODESFAELLE MATERNAL MORTALITIES	0	2	0	1
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	0
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	17	15	18	17
GELBKOEPPER CORPORA LUTEA	179	157	183	192
IMPLANTATIONEN IMPLANTATIONS	133	114	124	127
LEBENDE FETEN VIABLE FETUSES	113	99	115	104
MAENNlich IN % MALE IN %	44	49	47	60
WEIBlich IN % FEMALE IN %	56	51	53	40
TOTE FETEN DEAD FETUSES	0	0	0	0
RESORPTIONEN RESORPTIONS	20	15	9	23
FRUEH IN % EARLY IN %	60	60	89	70
SPAET IN % LATE IN %	40	40	11	30
MISSBILDUNGEN MALFORMATIONS	1	1	1	2
VARIATIONEN VARIATIONS	6	2	6	5

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SND 919 CL2Y KANINCHEN / RABBITS

SEGM. 2

BEST POSSIBLE COPYWURFDATEN / LITTER DATA
MITTELWERTE / MEAN VALUES

		KONTROLLE CONTROL	0.1 MG/KG	1 MG/KG	10 MG/KG
GEWICHT / FET (G) WEIGHT / FETUS (G)	MW SD	38.93 5.13	35.80 5.08	38.65 4.41	38.07 4.75
PLAZ.GEW. / FET (G) WEIGHT PLAC. / FETUS (G)	MW SD	4.92 0.86	4.55 0.72	4.62 0.66	4.63 0.90
CORPORA LUTEA / MUTTERT. CORPORA LUTEA / DAM	MW SD	10.5 2.4	10.5 2.1	10.2 2.0	11.3 1.9
IMPLANTATIONEN / MUTTERT. IMPLANTATIONS / DAM	MW SD	7.8 2.2	7.6 1.4	6.9 1.5	7.5 1.8
LEBENDE FETEN / MUTTERT. VIABLE FETUSES / DAM	MW SD	6.6 2.0	6.6 1.7	6.4 1.8	6.1 2.1
TOTE FETEN / MUTTERT. DEAD FETUSES / DAM	MW SD	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
RESORPTIONEN / MUTTERT. RESORPTIONS / DAM	MW SD	1.2 1.3	1.0 0.9	0.5 0.8	1.4 1.7
MISSBILDUNGEN / MUTTERT. MALFORMATIONS / DAM	MW SD	0.1 0.2	0.1 0.3	0.1 0.2	0.1 0.3
VARIATIONEN / MUTTERT. VARIATIONS / DAM	MW SD	0.4 0.6	0.1 0.4	0.3 0.8	0.3 0.7
LEB. FETEN IN X IMPL. VIABLE FET. IN X IMPL.	MW SD	91.0 6.5	90.8 6.6	96.8 6.5	89.8 9.9
RESORPTIONEN IN X IMPL. RESORPTIONS IN X IMPL.	MW SD	9.0 6.5	9.2 6.6	3.2 6.5	10.2 9.9
PRAEIMPLANTAT.-VERLUST PRE IMPLANTAT. LOSS X	MW SD	23.4 4.1	25.2 2.5	31.1 1.4	32.5 2.7
POSTIMPLANTAT.-VERLUST POST IMPLANTAT. LOSS X	MW SD	9.0 6.5	9.2 6.6	3.2 6.5	10.2 9.9
MISSB. IN X LEB. FET. MALFORM. IN X VIAB. FET.	MW SD	0.1 1.3	0.1 1.9	0.1 0.8	0.2 1.9
VARIAT. IN X LEB. FET. VARIAT. IN X VIAB. FET.	MW SD	1.8 5.6	0.3 1.8	1.1 6.6	0.9 4.6

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Fetal Necropsies

A relatively even distribution was evident in the incidence of malformations and variations among fetuses from different treatment groups (Tab. C.3.d.3). The distribution of anomalies compared favorably to historical data. Deficient ossification of the 5th sternal anlage was noted with a slightly higher frequency in fetuses of the MD group (40% vs. 27.9-29.2% in the other 3 treatment groups).

Tab. C.3.d.3.

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SEGM. 2

MISSBILDUNGEN UND VARIATIONEN
MALFORMATIONS AND VARIATIONS

SUMMENWERTE / COLLECTIVE VALUES

B E F U N D E F I N D I N G S	KONTR. CONTR.	0.1 MG/KG	1 MG/KG	10 MG/KG
<u>MALFORMATIONS</u>				
MULTIPLE MISSBILDUNGEN MULTIPLE MALFORMATIONS	0	1	0	0
STERNEBRA-SYNOSTOSEN SYNOSTOSIS OF STERNABRAE	1	0	0	1
AGENESIE DER GALLENBLASE ABSENCE OF GALLBLADDER	0	0	1	0
AGENESIE EINES WIRBELKÖRPERS MISSING OF ONE VERTEBRA	0	0	0	1
<u>VARIATIONS</u>				
FLEXUR DER VORDERPFOTE(N) FLEXURAE OF FORE PAW(S)	5	1	4	4
13. RIPPE 13TH RIB	1	0	0	0
AGENESIE 12. RIPPE MISSING OF 12TH RIB	0	1	0	0
HYPOPLASIE 12. RIPPE SHORTENED 12TH RIB	0	0	0	1
AGENESIE LUNGENANHANGSLAPPEN MISSING OF ACCESSORIUS LOBE OF THE LUNG	1	1	3	0

RUNTS	4	8	0	2

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Plasma Concentrations (Satellite Study)

PPX was detectable in all plasma samples. The highest concentrations were noted 2 hr after dosing. Increases in AUC were generally dose proportional. PK parameters ($C_{2\text{hr}}$, AUC_{1-24}) associated with the lowest test dose were equivalent to or slightly greater than those of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d. (C_{max} = ng/ml, AUC_{0-8} =)

Table 7: Geometric mean value and ranges of plasma concentrations [ng/ml] after oral administration of SND 919 CL 2 Y in pregnant rabbits

hours	dose [mg/kg]		
	0.1*	1.0	10.0
0	0.49	12.23	104.38
2	8.66	92.16	886.99
4	6.36	89.93	788.86
8	4.03	52.26	506.26
24	0.44	10.40	102.38

Table 8: AUC (0 - 24 hours) values [ng/ml-h] with geometric means and ranges

animal	Dose [mg/kg]		
	0.1	1	10
1	(72.81)*	1120.41	10370.14
2	69.89	1094.90	8047.06
3	75.00	1228.85	11726.36
4	104.70	905.50	10935.35
geometric - mean - range	81.87	1080.90	10170.79

C.3.e. Segment III in Rats: Perinatal and Postnatal Toxicity

Document #(s): BI Document U89-0091
Upjohn TR 7219-94-076

Sponsor Volume: 1.44

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 1.5 mg/kg/day to female Wistar rats (24/dose) from day 16 of gestation to day 21 of the rearing phase (lactation). Overt drug-related changes were agitation and increased activity in the MD and HD dams during lactation. Food-intake was also decreased at the high dose. No *in utero* toxicities were apparent. The major toxicity observed was an impairment of pup development reflected by a decreased body weight gain during the lactation/rearing phase, and a slight (insignificant) delay in eye-opening in pups of the MD and HD dams. The sponsor suggests that the basis of this effect is CNS activation in the dams leading to an inability of the pups to suckle; no evidence to support this hypothesis was presented. An alternative explanation is the inhibitory effect of PPX on prolactin release impairs milk-production in the dams. Despite the reduced body weight development, fertility of the F1 offspring was not impaired. No remarkable drug-related changes in litter parameters or at necropsy of the pups were evident. Since the development and maintenance of pregnancies of HD rats were comparable to the other groups, in contrast to the Segment I and II studies where PPX dramatically impaired pregnancy, it may be concluded that the deleterious effects of PPX on rat reproduction occur at the early, prolactin-dependent implantation stage of pregnancy (circa days 6-8).

Methods:

Dosages: 0.1, 0.5, 1.5 mg/kg/day (Drug Lot: Batch III; prepared in distilled water) from day 16 of gestation to day 21 of rearing.

Low dose is 5 times the expected human dose (at the time of study initiation).
The high dose was selected based on a previous Segment II study, in which signs of maternal and fetal toxicity were apparent.

Route of Administration: oral (gavage)

Species/Number: 96 inseminated females (24/group)

Approximate initial weight/age: 218 g / 10 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	days 1, 7, 11, 16, and 22 of gestation, and daily during lactation

Food consumption - weekly
Litter parameters - Size, live/still births, and gross abnormalities were recorded. Non-pregnant females were excluded from mean calculations. Litters were reduced to 8 pups (4/sex) at day 4 post-partum. Functional, maturational and behavioral tests were conducted on the pups. At day 21, dams were necropsied, and half the offspring were examined for visceral abnormalities. The remaining weanlings were tested for swimming ability, Preyer reflex, pupillary reflex, water T-maze, and fertility (1 male and 1 female per litter).

Statistics

Statistical comparisons were made by Bartlett's test, one-way ANOVA, Newman-Keuls test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects on Dams

Mortality: One control dam died from maladministration.

Clinical Signs:

Restlessness and agitation at MD and HD during lactation.

Body Weight Gain:

No significant effects during gestation, but significantly increased in the LD group on day 3 and 4 of lactation (Fig. C.3.e.1).

Food Intake:

Non-significant decrease in HD group (%) during week 3 of gestation and the 3 week lactation period.

Gestation:

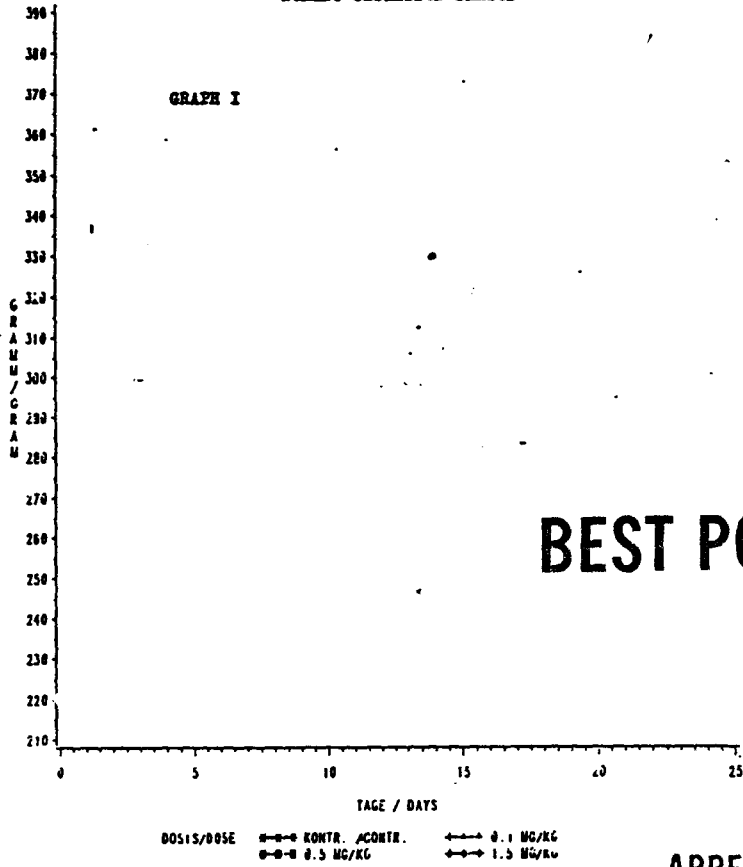
Nine of 96 females were not pregnant (1 CON, 3 LD, 2 MD, 3 HD). All except 1 HD dam delivered on day 23.

Necropsy:

No significant drug-related pathologies were found. One control dam had pulmonary edema, and MD dam had blood and calculi in the urinary tract.

Fig. C.3e.1.

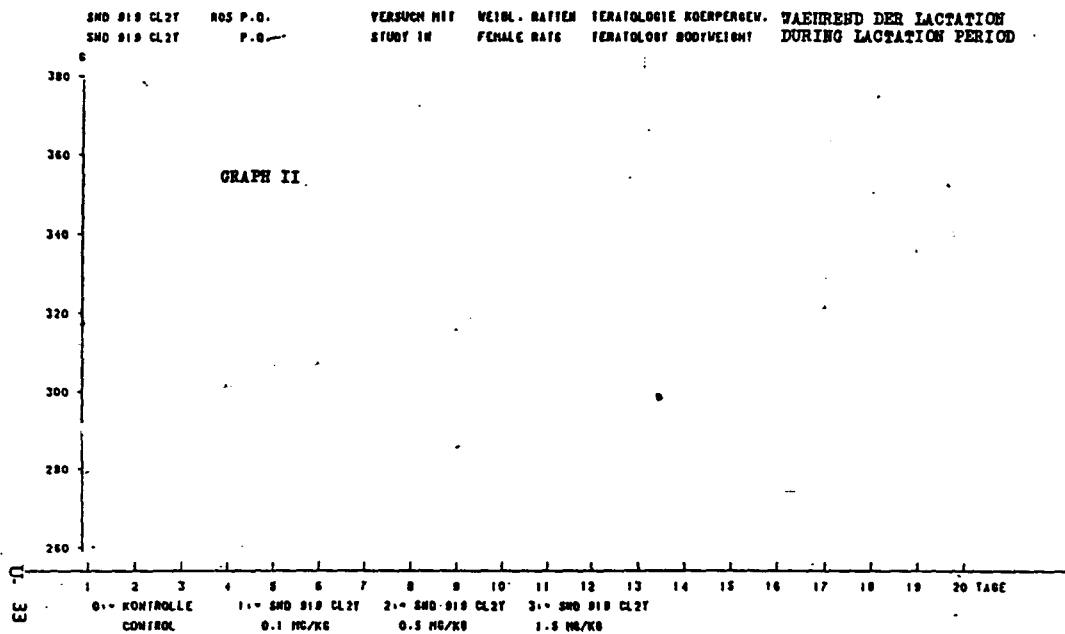
DURING GESTATION PERIOD



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Effects on fetuses and pups

The most notable effects of PPX in the offspring were significant reductions in body weight at days 4 and 21, and body weight gain between days 1-4 and 4-21 in pups from MD and HD dams (Fig. C.3.e.2). Mortality in pups during rearing was due to cannibalism (1 CON, 1 LD, and 1 HD litter) (Tables C.3.e.1-2). With respect to maturational parameters, a slight (insignificant) delay in eye-opening was noted. There were no impairments in swimming, visual, auditory or memory tests (Tab. C.3.e.3). At autopsy, 2 LD and 1 MD weanling had hydronephrosis.

Fertility in Offspring

All females were inseminated within a 10 day mating period except for 1 control, 1 LD, and 1 MD offspring. Three of 80 inseminated females did not become pregnant (1 control, 1 LD, and 1 MD). Mean body weight of the HD group was significantly reduced during gestation, although body weight gain was increased (Tab. C.3.e.4). There were no differences among groups in corpora lutea number, implantations, viable embryos, or resorptions (Tab. C.3.e.5). At autopsy, one dam was diagnosed with hepatocellular necrosis.

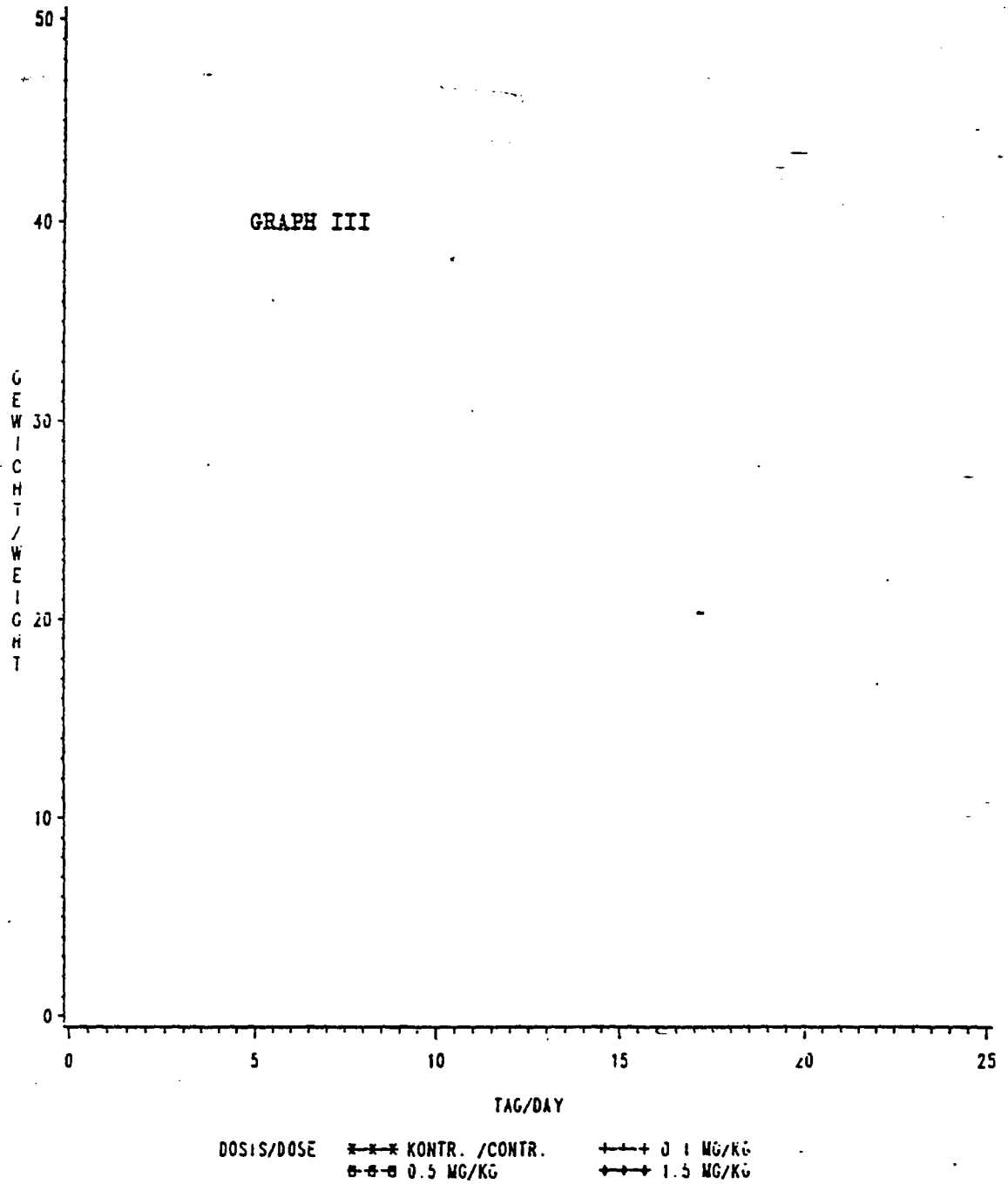
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Fig. C.3.e.2.

— BOEHRINGER INGELHEIM KG —

SNO 919CL2Y VERS.NR./STUDY.NO. R05 SEGM. J RATTEN/RATS
JUNGTIERGEWICHT / WEIGHT OF PUP (G)



TR No.: 7219-94-076

Tab. C.3.e.t

- BOEHRINGER INGELHEIM KG -

VERS.NR./STUDY.NO.: R05 SEGM. 3

SND 919CL2Y

RATTEN/RATS

WURFDATEN / LITTER DATA
SUMMENWERTE / SUM VALUES

	KONTR. /CONTR.	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GESAMTZAHL TIERE TOTAL NUMBER ANIMALS	24	24	24	24
TODESFAELLE MATERNAL MORTALITY	0	0	1	0
FEHLWUERFE ABORTIONS	0	0	0	0
TRAECHTIGE TIERE PREGNANT ANIMALS	23	21	21	21
TOTE JUNGTIERE STILLBIRTHS	1	1	0	1
JUNGTIERE 1. TAG VIABLE PUPS DAY 1	279	276	278	272
MAENNLICH IN % MALE IN %	53.05	46.74	52.52	54.04
WEIBLICH IN % FEMALE IN %	46.95	53.26	47.48	45.96
JUNGTIERE 4. TAG VIABLE PUPS DAY 4	261	273	276	255
JUNGTIERE 4*. TAG VIABLE PUPS DAY 4*	174	165	168	160
JUNGTIERE 7. TAG VIABLE PUPS DAY 7	173	157	168	158
JUNGTIERE 14. TAG VIABLE PUPS DAY 14	173	157	167	158
JUNGTIERE 21. TAG VIABLE PUPS DAY 21	173	157	167	158
VERENDETE JUNGTIERE MORT. IN PUPS 1 - 4	18	3	2	17
VERENDETE JUNGTIERE MORT. IN PUPS 4* - 21	1	8	1	2
MISSBILDUNGEN MALFORMATIONS	0	2	1	0
VARIATIONEN VARIATIONS	0	0	0	0

* NACH WURFREDUZIERUNG/AFTER LITTER REDUCTION

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- BOEHRINGER INGELHEIM KG -

VERS.NR./STUDY.NO.: R05 SEGM. 3

SMD 919CL2Y

RATTEN/RATS

WURFDATEN / LITTER-DATA
MITTELWERTE / MEAN-VALUES

		KONTR. /CONTR.	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
TRAGEZEIT DER MUTTERTIERE	MW	22.00	22.00	22.00	22.05
GESTATION PERIOD OF DAMS	SD	0.00	0.00	0.00	0.22
ANZ. TIERE / NUMB. OF ANIM.	N	23.00	21.00	21.00	21.00
GEWICHT/JUNGTIER (G) TAG 1	MW	6.12	6.12	6.06	5.94
WEIGHT/PUP AT (G) DAY 1	SD	0.29	0.24	0.23	0.29
GEWICHT/JUNGTIER (G) TAG 4	MW	7.95	7.82	** 7.41	*** 7.00
WEIGHT/PUP (G) DAY 4	SD	0.46	0.52	0.49	0.52
GEWICHT/JUNGTIER (G) TAG 4*	MW	8.00	7.94	** 7.53	*** 7.11
WEIGHT/PUP (G) DAY 4*	SD	0.48	0.46	0.44	0.52
GEWICHT/JUNGTIER (G) TAG 21	MW	41.19	41.99	***36.03	***26.03
WEIGHT/PUP (G) DAY 21	SD	3.90	2.37	2.66	6.52
GEWICHTSZUM. (G) TAG 1-4	MW	1.76	1.63	*** 1.32	*** 1.02
BODYW. INCR. (G) DAY 1-4	SD	0.46	0.46	0.40	0.45
WICHTSZUM. (G) TAG 4*-21	MW	33.19	34.07	***28.48	***18.88
BODYW. INCR. (G) DAY 4*-21	SD	4.04	2.78	2.70	6.17
LEB. JUNGT./MUTTERT. TAG 1	MW	12.13	13.14	13.24	12.95
VIALE PUPS/ DAM DAY 1	SD	2.40	2.89	1.81	2.20
TOTE JUNGT./MUTTERT. TAG 1	MW	0.04	0.05	0.00	0.05
DEAD PUPS / DAM DAY 1	SD	0.21	0.22	0.00	0.22
LEB. JUNGT./MUTTERT. TAG 4	MW	11.86	13.00	13.14	12.75
VIALE PUPS/ DAM DAY 4	SD	2.36	2.90	1.85	2.10
LEB. JUNGT./MUTTERT. TAG 4*	MW	7.91	7.86	8.00	8.00
VIALE PUPS/ DAM DAY 4*	SD	0.43	0.48	0.00	0.00
LEB. JUNGT./MUTTERT. TAG 21	MW	7.86	7.85	7.95	7.90
VIALE PUPS/ DAM DAY 21	SD	0.47	0.49	0.22	0.31
JUNGTIERVER. % TAG 1-4	MW	6.31	1.09	0.81	8.52
PUPS LOSS % DAY 1-4	SD	20.70	2.77	2.69	22.16
JUNGTIERVERL. % TAG 4*-21	MW	0.57	4.76	0.60	1.25
PUPS LOSS % DAY 4*-21	SD	2.67	21.82	2.73	3.85
MISSBILDUNGEN / MUTTERTIER	MW	0.00	0.10	0.05	0.00
MALFORMATIONS / DAM	SD	0.00	0.44	0.22	0.00
RIATIONEN / MUTTERTIER	MW	0.00	0.00	0.00	0.00
RIATIONS / DAM	SD	0.00	0.00	0.00	0.00
MISSB. % LEB. JUNGT./TAG 1	MW	0.00	0.68	0.34	0.00
MALF. % VIAB. PUPS / DAY 1	SD	0.00	3.12	1.56	0.00
VARIAT. % LEB. JUNGT./TAG 1	MW	0.00	0.00	0.00	0.00
VARIAT. % VIAB. PUPS/ DAY 1	SD	0.00	0.00	0.00	0.00

** p < 0.01

*** p < 0.001

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 CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS
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TR No.: 7219-94-076

SND 919 CL 2 Y

Tab. ■ C.3.e.3.

RATTEN/RATS

BEOBACHTUNGEN DER F₁-GENERATION DER GRUPPE DER SPONTANGEBURTEN

OBSERVATIONS OF F₁-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

SEGM. 3

ERGEBNISSE IN PROZENT / RESULTS IN PER CENT

VERS.NR./STUDY NO. R 05

DOSIS DOSE	AUSGEWERTETE MÜRFE EVALUATED LITTERS	AUFSTELLEN DER OHREN		FELLWACHSTUM		LAUFEN MIT ANGE- HOBENEM BAUCH			DURCHBRECHEN DER OBEREN SCHNEIDEZÄHNE			AUGENÖFFNUNG		
		ERECTION OF PINNAE		FUR GROWTH		RUNNING WITH RAISED VENTER			ERUPTION OF MAXIL- LARY INCISORS			EYE OPENING		
		TAG 4	DAY 5	TAG 6	DAY 7	TAG 12	DAY 13	TAG 12	DAY 13	TAG 12	DAY 13	TAG 15	DAY 16	DAY 17
KONTROLLE/ CONTROL	22	8.0	98.9	-	100.0	100.0	100.0	100.0	100.0	100.0	20.8	75.1	98.8	
0.1 MG/KG	20	8.9	100.0	-	100.0	100.0	100.0	100.0	100.0	100.0	17.8	79.0	100.0	
0.5 MG/KG	21	22.6	100.0	-	100.0	100.0	100.0	100.0	100.0	100.0	6.0	57.5	99.4	
1.5 MG/KG	20	17.0	98.7	-	100.0	83.5	99.4	100.0	100.0	100.0	8.9	41.1	89.2	

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Tab. C.3.e.4.

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

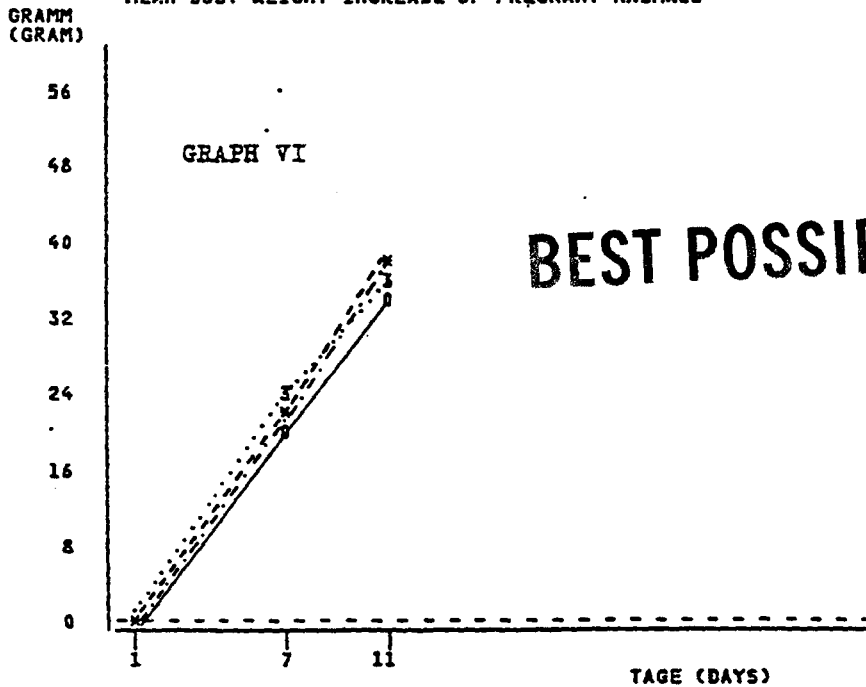
SUBST./COMP. : SNO 919CL2Y TIERART/SPEC. : RATTEN / RATS
 VERS.NR./STUDY NO. : R 05 SEGM. 3

KOERPERGEWICHT TRAECHTIGER MUTTERTIERE (G) (TAG 1, 7, 11)
 BODY WEIGHT OF PREGNANT ANIMALS (G)(DAYS 1, 7, 11)
 MITTELWERTE / MEAN VALUES F₁-GENERATION

		N	1	7	11
KONTROLLE CONTROL	MW	20	246.1	266.1 ²⁰	279.4 ³¹
	SD		18.0	18.9	17.7
0.1 MG/KG	MW	18	239.1	260.5 ²¹	277.1 ³¹
	SD		18.6	18.9	19.0
0.5 MG/KG	MW	19	233.6	256.6 ²³	271.8 ³¹
	SD		18.2	19.3	20.5
1.5 MG/KG	MW	20	213.3 ^{***}	237.6 ⁴¹	250.1 ³⁷
	SD		19.2	20.1	20.6

*** p < 0.001

MITTLERE GEWICHTSZUNAHME TRAECHTIGER MUTTERTIERE
 MEAN BODY WEIGHT INCREASE OF PREGNANT ANIMALS



N: MEHRFACHBELEGUNG - MULTIPLE POINTS
 0: KONTR - CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 1.5 MG/KG

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Tab. C.3.e.5.

MURFDATEN / LITTER DATA F₁-GENERATION
 SUMMENWERTE / SUM VALUES
 (GETOETET 14.-16. TAG / SACRIFICED DAY 14-16)

	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	21	19	20	20
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	0
SPONTANKUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	20	18	19	20
GELBKOEPPER CORPORA LUTEA	313	291	300	313
IMPLANTATIONEN IMPLANTATIONS	304	277	290	309
LEBENDE FETEN VIABLE FETUSES	278	249	264	289
RESORPTIONEN RESORPTIONS	26	28	26	20

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MURFDATEN / LITTER DATA F₁-GENERATION
 MITTELWERTE / MEAN VALUES
 (GETOETET 14.-16. TAG / SACRIFICED DAY 14-16)

	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
CORPORA LUTEA / MUTTERT.	MW	15.6	16.2	15.8
CORPORA LUTEA / DAM	SD	2.0	2.3	1.4
IMPLANTATIONEN / MUTTERT.	MW	15.2	15.4	15.3
IMPLANTATIONS / DAM	SD	2.8	3.3	2.4
LEBENDE KEIME / MUTTERT.	MW	13.9	13.4	13.9
LIFE EMBRYOS / DAM	SD	3.8	4.2	2.3
RESORPTIONEN / MUTTERT.	MW	1.3	2.0	1.4
RESORPTIONS / DAM	SD	2.5	2.7	1.7
LEBENDE KEIME IN % IMPL.	MW	96.4	90.8	95.4
LIFE EMBRYOS IN % IMPL.	SD	6.9	7.7	4.6
RESORPTIONEN IN % IMPL.	MW	3.6	7.6	4.6
RESORPTIONS IN % IMPL.	SD	6.9	6.5	4.6
PRAEIMPLANTAT.-VERLUST	MW	0.6	1.2	0.6
PRE IMPLANTAT. LOSS %	SD	3.6	5.6	3.7

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C.4. Genotoxicity

- a. Testing for Point Mutagenic Activity of PPX (dihydrochloride) with *Salmonella typhimurium*
- b. Testing for Point Mutagenic Activity of PPX (free base) with *Salmonella typhimurium*
- c. Cell Transformation Assay in Syrian Hamster Embryo Cells
- d. Induction of Chromosome Aberrations in Chinese Hamster Ovary Cells
- e. V79 Gene Mutation Assay for HGPRT Mutants
- f. *In vivo* Mouse Micronucleus Test

Studies were conducted by: Boehringer Ingelheim KG
Department of Experimental Pathology and Toxicology
D-6507 Ingelheim am Rhein
West Germany

except for studies *d* (Cytotest) and *e* (NOTOX) (see text for addresses).

All studies complied with GLP.

C.4.a. Testing for Point Mutagenic Activity of PPX dihydrochloride with *Salmonella typhimurium*

Document #(s): BI Document U85-0554
Upjohn TR 7219-94-079
Sponsor Volume: 1.44

Summary:

Pramipexole was not mutagenic under the conditions employed in this study. The highest dose tested was appropriate. The strains employed for conferring of his-independence are not sensitive to A-T substitutions. A second study (C.4.b.) was conducted to meet this criterion.

Methods:

Drug concentrations: 10, 100, 500, 1000, 5000 µg/plate (Batch C of PPX dihydrochloride prepared in distilled water)

Positive controls/vehicles: 1-methyl-3-nitro-1-nitrosoguanidine/DMSO (dil. w. 50% DMSO)
2-nitrofluorene/DMSO
4-nitroquinoline-1-oxide/20%DMSO (dil. w. PBS)
9-aminoacridine/water
2-aminoanthracene/DMSO
benzo(a)pyrene/DMSO
emodin/DMSO

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Bacterial Tester Strains:

Strain	Genetic characteristics
TA1535	hisG46, ΔuvrB, rfa
TA1537	hisC3076, ΔuvrB, rfa
TA100	hisG46, ΔuvrB, rfa, R fact.
TA98	hisD3052, ΔuvrB, rfa, R fact.

Base-pair (G-C) substitutions or frameshift mutations in the *his* operon confer *his*-independence; *uvrB* gene deletion confers defective excision repair system; *rfa* mutation increases permeability to chemical mutagens; **R factor** increases sensitivity to mutagens.

Metabolizing System: S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Test Conditions: Test system components (agar, bacteria, test substance, +/- S9) mixed and poured onto plates (triplicate samples). Plates were incubated for two days at 37° and the number of revertants determined.

Results:

Spontaneous reversion frequencies on control plates were within historical control. Pramipexole did not increase mutation frequency above control values in any tester strain at any dose in the presence or absence of S9. PPX was not toxic to indicator cells. The positive controls produced the expected increases in mutation frequency (Tables C.4.a.1-4).

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Tab. C.4.a.1

Table 1: Induction of His⁺ mutations in *S. typhimurium* by SMO 919 CL 2 in the absence of a metabolizing system (Experimental part No. MUT 0074/01)

Substance ^a	Concentration (µg/plate)	S9 ^b	Number of His ⁺ revertants per plate ^{c,d}							
			TA1535		TA1537		TA100		TA98	
			n	̄	n	̄	n	̄	n	̄
Control		-	6	11	8	10	108	129	23	24
			16		16		151		20	
			11		8		127		30	
SMO 919 CL 2	10	-	8	11	6	6	148	147	22	26
			11		7		154		27	
			13		5		139		28	
	100	-	8	10	4	6	118	131	22	21
			11		9		119		18	
			11		6		157		24	
	500	-	6	5	6	7	116	130	23	23
			6		7		153		26	
			4		9		122		20	
1000	-	7	7	4	7	120	139	28	23	
		8		7		152		17		
		5		9		144		23		
5000	-	5	6	9	6	160	140	30	22	
		8		6		140		18		
		4		4		121		17		
MNNG	2.5	-	>2000		16	22	>2000		19	21
			>2000		20		>2000		22	
			>2000		29		>2000		23	
2-HF	10	-	13	9	116	126	>2000		>2000	
			6		131		>2000		>2000	
			8		132		>2000		>2000	

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Tab. C.4.a.2.

Table 2: Induction of His⁺ mutations in *S. typhimurium* by SMO 919 CL 2 in the absence of a metabolizing system - repeat study (Experimental part No. MUT 0074/05)

Substance ^a	Concentration (µg/plate)	S9 ^b	Number of His ⁺ revertants per plate ^{c,d}							
			TA1535		TA1537		TA100		TA98	
			n	̄	n	̄	n	̄	n	̄
Control		-	27	24	6	7	154	162	27	27
			18		9		C		23	
			28		7		170		31	
SMO 919 CL 2	10	-	28	26	5	6	171	158	29	26
			25		8		170		30	
			24		6		133		19	
	100	-	30	34	10	8	131	141	19	23
			38		6		166		31	
			34		8		127		19	
	500	-	14	14	4	7	142	151	26	23
			14		8		143		18	
			14		8		167		26	
1000	-	18	21	8	8	161	161	27	24	
		20		6		160		25		
		24		11		162		20		
5000	-	20	18	7	7	139	144	17	20	
		10		7		151		27		
		24		8		142		17		
4-MQO	1	-	98	81	29	28	>2000		549	532
			88		29		>2000		515	
			58		25		>2000		C	
9-AA	100	-	36	25	489	358	156	139	8	9
			14		280		126		9	
			26		305		135		11	

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Tab. C.4.a.3

Table 3: Induction of His⁺ mutations in *S. typhimurium* by SMO 919 CL 2 in the presence of a metabolizing system (Experimental parts No. MUT 0074/02 and /03)

Substance ^a	Concentration (ug/plate)	S9 ^b	Number of His ⁺ revertants per plate ^{c,d}							
			TA1535		TA1537		TA100		TA98	
			n	̄	n	̄	n	̄	n	̄
Control		+	9	11	9	8	167	177	31	41
			13		7		190		49	
			12		7		174		44	
SMO 919 CL 2	10	+	16	12	14	12	149	158	40	44
			8		11		170		42	
			11		12		156		50	
	100	+	4	10	6	7	177	176	53	44
			9		8		182		42	
			17		7		168		36	
	500	+	12	9	6	9	173	171	50	54
			8		9		172		52	
			7		11		167		59	
	1000	+	5	9	6	8	173	166	55	54
			7		5		163		46	
			14		12		163		60	
5000	+	6	13	8	8	171	182	85	78	
		17		11		198		88		
		16		6		176		61		
2-AA	0.5	+					279	427		
							535			
							468			
	2.5	+	375	388	351	364			1118	1065
			406		372				1268	
			384		368				808	
0.5	-					157	159			
						151				
						168				
2.5	-	13	9	4	11			41	33	
		5		20				31		
		9		9				28		

Tab. C.4.a.4. BEST POSSIBLE COPY

Table 4: Induction of His⁺ mutations in *S. typhimurium* by SMO 919 CL 2 in the presence of a metabolizing system - repeat study (Experimental part No. MUT 0074/04)

Substance ^a	Concentration (ug/plate)	S9 ^b	Number of His ⁺ revertants per plate ^{c,d}							
			TA1535		TA1537		TA100		TA98	
			n	̄	n	̄	n	̄	n	̄
Control		+	4	9	3	8	159	154	37	36
			14		13		151		35	
			10		7		153		35	
SMO 919 CL 2	10	+	14	13	7	8	149	150	50	42
			10		7		148		42	
			14		9		152		33	
	100	+	15	8	6	8	153	154	37	39
			7		8		159		41	
			2		11		149		38	
	500	+	18	15	8	10	132	140	35	37
			10		11		142		36	
			16		11		145		41	
	1000	+	10	12	6	9	159	166	45	46
			20		15		C		44	
			16		8		173		48	
5000	+	13	16	7	8	175	164	58	45	
		16		C		162		35		
		19		9		156		42		
B(a)P	5	+	14	14	164	167	953	925	592	546
			9		156		6		498	
			18		120		896		549	
Emodin	10	+	11	10	498	494	274	312	36	37
			10		509		314		36	
			8		475		349		40	

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C.4.b. Testing for Point Mutagenic Activity of PPX (free base) with *Salmonella typhimurium*

Document #(s): BI Document U90-0639
Upjohn TR 7219-94-084

Sponsor Volume: 1.44

Summary:

This experiment confirms the previous study that PPX is not mutagenic in *S. typhimurium* strains sensitive to mutations that affect G-C sites. The absence of mutagenicity in the *E. Coli* strains suggests that PPX does not induce mutations by affecting A-T base pairs. The highest dose tested was appropriate, and positive controls produced the expected results.

Methods:

Drug concentrations: 10, 100, 500, 1000, 5000 µg/plate (Batch III of PPX free base prepared in DMSO)

Positive Controls/vehicles: 1-methyl-3-nitro-1-nitrosoguanidine/DMSO
1-ethyl-3-nitro-1-nitrosoguanidine/DMSO
2-nitrofluorene/DMSO
2-aminoanthracene/DMSO

Bacterial Tester Strains:

Strain	Genetic characteristics
TA1535	hisG46, ΔuvrB, rfa
TA1537	hisC3076, ΔuvrB, rfa
TA1538	hisD3052, ΔuvrB, rfa
TA100	hisG46, ΔuvrB, rfa, R fact.
TA98	hisD3052, ΔuvrB, rfa, R fact.

Base-pair (G-C) substitutions or frameshift mutations in the **his** operon confer **his**-independence; **uvrB** gene deletion confers defective excision repair system; **rfa** mutation increases permeability to chemical mutagens; **R factor** increases sensitivity to mutagens.

In addition, the WP2uvrA strain of *E. Coli* was used. Point mutations in the **trp** operon of this strain confer **trp**-independence. It is sensitive to the base-pair substituting (A-T) activity of alkylating agents.

Metabolizing System: S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Test Conditions: Test system components (agar, bacteria, test substance, +/- S9) mixed and poured onto plates (triplicate samples). Plates were incubated for two days at 37° and the number of revertants determined.

Results:

Spontaneous reversion frequencies on control plates were within historical control. PPX did not increase mutation frequency above control values in any tester strain at any dose in the presence or absence of S9. PPX was not toxic to indicator cells. The positive controls produced the expected increases in mutation frequency (Tables C.4.b.1-4).

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Table 1. Induction of mutations in the absence of a metabolizing system

Experiment 1 (MUT 0193/01 and /05)

Substance ^a	Conc. (ng/pl.)	S ^b	Number of revertants per plate ^c				TA98	WP2uvra
			TA1535	TA1537	TA1538	TA100		
Solvent control (DMSO, 100 µl/pl.)		-	3	29	13	103	19	14
			15	18	13	91	19	27
			5	25	14	104	20	25
			8	24	13	99	19	22
SND 919 BSY	10	-	6	34	11	107	25	20
			5	23	15	93	23	15
			5	23	20	95	29	13
			5	27	15	98	26	16
	100	-	2	24	14	107	15	13
			7	13	11	108	20	13
			3	22	13	96	22	15
			4	26	13	94	19	14
	500	-	3	23	17	83	26	16
			6	23	19	95	15	15
			2	23	13	81	19	16
			4	23	16	86	20	16
1000	-	4	36	13	86	9	18	
		3	36	14	99	28	12	
		4	21	19	78	17	15	
		4	34	15	88	16	15	
5000	-	5	20	11	81	18	17	
		4	40	14	81	19	15	
		4	26	9	62	13	14	
		4	29	11	75	17	15	
MNG (1)	2.5	-	>2000	165	>2000	>2000	>2000	1006
ZNF (2-2-4-2)	10	-	>2000	160	>2000	>2000	>2000	798
ENG (3)	2.5	-	>2000	168	>2000	>2000	>2000	728
				164				845
Titer of the bacterial suspension (x10 ⁸ /ml)			3.2 (338, 298, 327) ^d	2.2 (249, 196, 215) ^d	2.5 (235, 233, 274) ^d	0.6 (60, 49, 62) ^d	1.9 (205, 198, 162) ^d	1.9 (196, 196, 182) ^d

Tab.
C.4.b.1

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Table 2. Induction of mutations in the absence of a metabolizing system

Experiment 2 (MUT 0193/02 and /05)

Substance ^a	Conc. (ng/pl.)	S ^b	Number of revertants per plate ^c				TA98	WP2uvra
			TA1535	TA1537	TA1538	TA100		
Solvent control (DMSO, 100 µl/pl.)		-	9	9	15	107	31	23
			19	7	19	129	20	23
			24	9	14	95	30	19
			17	8	16	110	27	22
SND 919 BSY	10	-	8	26	C	126	28	8
			3	22	11	133	31	18
			4	3	29	104	15	17
			5	17	20	121	25	14
	100	-	7	11	15	115	27	16
			14	3	12	116	30	13
			4	10	13	117	27	15
			8	8	13	116	28	15
	500	-	8	7	20	89	14	14
			5	4	19	104	23	10
			6	21	15	137	14	12
			6	11	18	110	17	12
1000	-	3	18	18	96	35	14	
		7	9	16	82	28	15	
		2	5	18	105	16	14	
		6	11	17	94	26	14	
5000	-	3	3	11	86	11	17	
		5	8	20	101	14	11	
		7	7	6	107	10	9	
		5	6	12	98	12	12	
MNG (1)	2	-	1279	145	>2000	>2000	>2000	928
ZNF (2-2-4-2)	10	-	1597	143	>2000	>2000	>2000	994
ENG (3)	2.5	-	1482	183	>2000	>2000	>2000	968
			1453	157				963
Titer of the bacterial suspension (x10 ⁸ /ml)			2.3 (244, 242, 200) ^d	1.8 (194, 181, 171) ^d	3.0 (294, 302, 297) ^d	0.8 (92, 62, 72) ^d	1.8 (185, 170, 174) ^d	1.9 (199, 178, 206) ^d

Tab.
C.4.b.2.

Table 3. Induction of mutations in the presence of a metabolizing system

Experiment 1 (MUT 0193/03 and /05)

Substance ^a	Conc. (µg/pl.)	S ⁹	Number of revertants per plate ^c					WP2avrA
			TA1535	TA1537	TA1538	TA100	TA98	
Solvent control (DMSO, 100 µl/pl.)	•	+	6	6	17	86	34	25
			6	14	16	106	29	11
			4	7	24	105	17	17
			5	9	19	99	33	18
SND 919 BSY	10	+	7	14	30	102	26	16
			5	12	37	100	33	14
			7	14	25	108	18	23
			6	13	31	103	26	18
	100	+	11	7	15	105	30	c
			2	11	26	100	28	15
			5	13	30	94	29	13
			6	10	24	100	29	14
	500	+	7	8	31	124	31	16
			6	12	14	107	42	19
			4	9	24	95	25	14
			6	10	26	109	33	16
1000	+	2	17	17	107	25	11	
		11	9	36	141	23	19	
		6	9	28	129	24	9	
		6	12	26	126	27	13	
5000	+	7	7	23	121	34	17	
		10	4	26	117	34	17	
		7	4	18	118	25	14	
		8	5	22	119	31	16	
2AA (2-4-8) (1-2) (*)	0.5	+	168	239	554	338	275	304
	2.5		207	245	472	358	255	301
	5		218	250	422	396	264	490
			198	245	503	364	265	365
Titer of the bacterial suspension (x10 ⁹ /ml)			2.3 (194, 244, 247) ^d	2.0 (175, 215, 193) ^d	2.9 (292, 318, 244) ^d	0.9 (86, 88, 82) ^d	2.0 (195, 178, 220) ^d	1.9 (196, 196, 182) ^d

Tab. C.4.b.3.

Table 4. Induction of mutations in the presence of a metabolizing system

Experiment 2 (MUT 0193/04 and /05)

Substance ^a	Conc. (µg/pl.)	S ⁹	Number of revertants per plate ^c					WP2avrA
			TA1535	TA1537	TA1538	TA100	TA98	
Solvent control (DMSO, 100 µl/pl.)	•	+	14	5	18	122	41	9
			6	3	27	131	38	19
			9	11	22	126	50	25
			10	6	22	126	43	18
SND 919 BSY	10	+	13	8	24	107	50	16
			11	5	24	123	47	20
			6	4	27	116	50	15
			10	6	25	115	49	17
	100	+	12	9	19	121	46	22
			13	8	26	102	42	23
			7	11	23	119	28	16
			11	9	23	114	39	20
	500	+	5	11	30	110	34	24
			4	6	25	102	31	11
			2	14	23	124	39	18
			6	10	26	115	35	18
1000	+	5	16	30	107	39	18	
		6	7	23	122	45	9	
		8	7	24	105	40	18	
		6	10	26	111	41	15	
5000	+	7	7	28	108	33	16	
		7	4	20	100	27	13	
		7	2	22	128	31	12	
		7	6	23	112	30	14	
2AA (2-4-8) (1-2) (*)	0.5	+	334	177	354	313	319	351
	2.5		367	172	375	346	360	561
	5		341	194	381	332	336	369
			347	181	370	330	338	427
Titer of the bacterial suspension (x10 ⁹ /ml)			2.3 (232, 214, 244) ^d	1.3 (126, 110, 146) ^d	2.0 (200, 198, 194) ^d	0.5 (50, 45, 41) ^d	1.7 (167, 182, 165) ^d	1.9 (199, 178, 206) ^d

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Tab. C.4.b.4.

C.4.c. Cell Transformation Assay in Syrian Hamster Embryo Cells

Document #(s): BI Document U87-1074
Upjohn TR 7219-94-082

Conducted by:

Sponsor Volume: 1.44

Summary:

In this transformation experiment, no reproducible transforming potential of PPX was detected in Syrian Hamster Embryo cells. The dosage range used in this study ($\mu\text{g/ml}$) was limited by cytotoxicity criteria established by the sponsor (minimum desired survival rate of %). This cytotoxicity level is below that established in the newer guidelines (no more than 20% survival), as is the exposure range (desired upper treatment levels for mammalian cells is 5 mg/ml or 10 mM = 2.9 mg/ml for PPX).

Since this assay is not in the core battery for genotoxicity testing, a repetition of the test at higher doses is not required. In view of the relatively low transformation rate with the positive controls, the utility of this test in predicting genotoxic potential is questionable.

Methods:

Drug Concentrations

and Exposures: PPX dihydrochloride (Batch I) prepared in nutrient medium at the following concentrations:

Without S9 activation:

4 hr: 10, 25, 40, 100 $\mu\text{g/ml}$

48 hr: 10, 25, 40, 100 $\mu\text{g/ml}$

With S9 activation:

4 hr: 10, 40, 200, 400 $\mu\text{g/ml}$

Positive Controls/vehicles:

Without S9 activation:

1-methyl-3-nitro-1-nitrosoguanidine/DMSO (0.5 $\mu\text{g/ml}$ medium)

With S9 activation:

Benzo(a)pyrene/DMSO (5 $\mu\text{g/ml}$ medium)

(final concentration of DMSO in medium was 1%)

Test System:

Cultures prepared from 12-14 day Syrian Hamster embryos (decapitated, eviscerated), and propagated in 175 cm² (feeder cells) or 25 cm² (target cells) flasks. Cultures were exposed to the test substance for the indicated times (4 or 48 hr). Cultures were maintained for up to 10 days after the initial seeding, then fixed and stained. Colonies within each flask were examined for morphological transformations:

- criss-cross growth in marginal zones of colonies
- three-dimensional piling up of cells in center of the colony
- reduced cytoplasm to nuclear ratio

One or two thousand colonies per test condition were scored (100 colonies in 10 or 20 flasks). A response was considered positive if two or more transformed colonies occur in flasks treated with test article. Historical control frequency of spontaneous alterations is 0.05 - 0.1%

Metabolizing System:

S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Results:

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Determination of cytotoxicity:

Experimental doses for the main study were selected based on the following survival/toxicity data:

Final concentration µg/ml	% relative survival	
	without S9 mix 48 h	with S9 mix 4 h
0 = medium	100.0	100.0
5.0	89.4	96.0
10.0	87.8	95.6
50.0	54.3	84.9
100.0	43.0	71.6
250.0	0.0	59.6
500.0	0.0	38.7
750.0	0.0	2.2
1000.0	0.0	0.0
2900.0	0.0	0.0

According to these data the concentrations applied in the transformation study were chosen.

PPX was toxic at concentrations above 100 µg/ml in the absence of S9, and above 250 µg/ml in the presence of S9. Doses for the transformation experiment were 100 and 400 µg/ml in the absence and presence of S9, respectively.

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Transformation Experiment I (Tables C.4.c.1-2):

RESULTS WITHOUT S9 MIX

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4 h Treatment Interval

Test groups	number of colonies scored	transf. colonies	% transf. colonies	PE = % survival	absolute relative
untreated cells	1,000	0	0.0	45.7	100.0
MNNG 0.5 µg/ml	1,000	13	1.3	24.9	54.5
test article					
10.0 µg/ml	1,000	1	0.1	45.4	99.3
25.0 µg/ml	1,000	0	0.0	37.8	82.7
40.0 µg/ml	1,000	1	0.1	31.4	68.7
100.0 µg/ml	1,000	0	0.0	22.6	49.5

48 h Treatment Interval

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Test groups	number of colonies scored	transf. colonies	% transf. colonies	PE = % survival	absolute relative
untreated cells	1,000	1	0.1	44.0	100.0
MNNG 0.5 µg/ml	1,000	11	1.1	28.0	63.6
test article					
10.0 µg/ml	1,000	0	0.0	43.4	98.6
25.0 µg/ml	1,000	0	0.0	36.6	83.2
40.0 µg/ml	1,000	1	0.1	26.1	59.3
100.0 µg/ml	1,000	2	0.2	20.7	47.0

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RESULTS WITH S9 MIX

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4 h Treatment Interval

Test groups	number of colonies scored	transf. colonies	% transf. colonies	PE = % survival absolute relative	
untreated cells	1,000	0	0.0	44.9	100.0
B(a)P 5 µg/ml	1,000	12	1.2	30.5	67.9
test article					
4.0 µg/ml	1,000	0	0.0	45.5	101.3
40.0 µg/ml	1,000	0	0.0	36.9	82.2
200.0 µg/ml	1,000	0	0.0	30.0	66.8
400.0 µg/ml	1,000	0	0.0	21.8	48.6

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Similar results were obtained in a repeat experiment in which 2000 colonies per condition were scored, except that no more than 1 transformed colony appeared in PPX-treated cultures at a given concentration.

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C.4.d. Induction of Chromosome Aberrations in Cultured Chinese Hamster Ovary Cells

Document #(s): BI Document U87-0467
Upjohn TR 7219-94-081

Conducted by:

Sponsor Volume: 1.44

Summary:

In this clastogenicity study, no reproducible transforming potential of PPX was detected in the Chinese Hamster Ovary cell line. The dosage range used in this study was appropriate, since it approached desired upper treatment levels for cell lines (5 mg/ml or 10 mM = 2.9 mg/ml for PPX) and caused significant cytotoxicity at the highest concentrations. A small, non-reproducible clastogenic effect was observed with activation at the highest test dose (3300 µg/ml).

Methods:

Drug Concentrations

and Exposures: PPX dihydrochloride (Batch I) dissolved in F10/HEPES at the following concentrations:

Without S9 activation: 100, 500, 1000, 2000 µg/ml

With S9 activation: 100, 333, 1000, 3330 µg/ml

Positive Controls/vehicles:

Without S9 activation: Ethylmethanesulfonate (4 or 6 mM) in DMSO

With S9 activation: Cyclophosphamide (10 or 5 µg/ml) in medium

Test System:

Duplicate monolayer cultures of CHO cells (1×10^6) in 75cm² flasks were exposed to test substance for 2 hr. Incubations were continued for hrs. Cell division was arrested at metaphase by addition of colchicine during the last two hrs of the incubation. Chromosomal material was condensed and fixed on a glass slide, stained with 5% Giemsa, and examined microscopically for aberrations (gaps, breaks, fragments, dicentrics, exchange figures, numerical variations). 100 Metaphase spreads per culture were examined by light microscopy.

Metabolizing System:

S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Statistics: Chi-square analysis, $p < 0.05$ (one-tailed test)

Results:

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Determination of cytotoxicity:

Experimental doses were selected based on the following cytotoxicity data:

4.1 Cytotoxicity test/dosage selection

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TABLE 1 CYTOTOXICITY TEST OF SND 919 C12Y

Test substance concentration ($\mu\text{g/ml}$)	Cells/6 cm ϕ culture dish ($\times 10^5$) ^b	
	Directly after exposure (% of control)	After 18-20 h of growth (% of control)
<u>Without metabolic activation (-S9-mix) -</u>		
Control ^a)	4.61 (100%)	11.57 (100%)
1	*	*
3.3	4.77 (103%)	12.39 (107%)
10	*	*
33	4.99 (108%)	10.14 (88%)
100	4.38 (95%)	12.08 (104%)
333	2.97 (64%)	10.85 (94%)
1000	3.48 (75%)	11.48 (99%)
3330	1.80 (39%)	3.35 (29%)
5000	0.92 (20%)	0
<u>With metabolic activation (+S9-mix)</u>		
Control ^a)	4.41 (100%)	13.25 (100%)
1	*	*
3.3	4.27 (97%)	14.12 (107%)
10	*	*
33	4.57 (104%)	12.05 (91%)
100	4.24 (96%)	*
333	4.35 (99%)	12.20 (92%)
1000	4.57 (104%)	13.40 (101%)
3330	4.48 (102%)	10.17 (77%)
5000	2.71 (61%)	0.50 (4%)

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Cytogenetic Test Results:

In the absence of S9, no increase in the number of chromosomal aberrations was observed in PPX-treated cultures (Table C.4.d.2). However, the positive control (EMS) was only "mildly" clastogenic, so the experiment was repeated. A more robust EMS response was obtained, and PPX appeared clastogenic at a concentration of 500 µg/ml (Table C.4.d.3). Since the effect was rather small and no dose-related trends were observed, it is probably not biologically significant.

In the presence of S9, a significant increase in number of chromosomal aberrations was observed in cultures treated with the high concentration of PPX (3300 µg/ml; Tab. C.4.d.4). The effect was relatively small compared to that of cyclophosphamide, and not reproducible (Tab. C.4.d.5).

The frequency of chromosomal aberrations in control cultures were within historical control range for this laboratory (6.6 ± 3.0).

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C.4.d.2.

TABLE 1 CHROMOSOME ABERRATIONS^{a)}: INDIVIDUAL DATA (WITHOUT METABOLIC ACTIVATION;-S9-mix)

STUDY NUMBER : EC 121 (1) TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y
 PROJECT NUMBER: 0311 SOLVENT : F10-HEPES
 STUDY DIRECTOR: I. Enninga DOSE RANGE : 100-2000 µg/ml

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Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations gaps		g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
			included	excluded											
0	A	100	9	5	4	1			9						14/9
0	B	100	5	5			2		3						5/5
Total	(A + B)	200	14	10											
100	A	100	7	4	2	1		1	3						7/4
100	B	100	5	3	1	1	2		1						5/3
Total	(A + B)	200	12	7											
500	A	100	9	7	2		1		6				sp		10/8
500	B	100	9	5	3	1	1		4						9/5
Total	(A + B)	200	18	12											
1000	A	100	3	2	1				2						3/2
1000	B	100	7	3	2	2	1		2						7/3
Total	(A + B)	200	10	5											
2000	A	100	8	3	5		1		2				poly, endo		8/3
2000	B	100	9	5	4				3	1			sp, endo		9/5
Total	(A + B)	200	17	8											
4 mM EMS	A	100	15	10	5	1	2	1	8				poly		17/11
4 mM EMS	B	100	12	8	3	1	3		5				ma		13/9
Total	(A + B)	200	27*	18											

TR No.: 7219-94-081

a) Abbreviations used for various types of aberrations are listed in Appendix 1.

The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.

Significantly different from control group: Chi-Square Test, *P < 0.05, **P < 0.01, or ***P < 0.001.

C.A.d.3

TABLE # CHROMOSOME ABERRATIONS^a): INDIVIDUAL DATA (WITHOUT METABOLIC ACTIVATION; -S9-III)

TR No.: 7219-94-081

STUDY NUMBER : ECC 121 (2) TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y
 PROJECT NUMBER: 0311 SOLVENT : F10-HEPES
 STUDY DIRECTOR: I. Enninga DOSE RANGE : 100-2000 µg/ml

Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations		g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
			gaps included	gaps excluded											
0	A	100	5	3	2	1	1			2					6/3
0	B	100	11	5	9		4			1				2 poly	14/5
Total	(A + B)	200	16	8											
100	A	100	12	9	3		2			6				sp	12/9
100	B	100	7	5	1	1	2			4				3 poly, endo	8/6
Total	(A + B)	200	19	14											
500	A	100	8	8	1		6			1		1		poly	9/8
500	B	100	12	9	3		3			6				2 poly	12/9
Total	(A + B)	200	20	17*											
1000	A	100	8	1	8		1								9/1
1000	B	100	6	2	3	1	2							poly	6/2
Total	(A + B)	200	14	3											
2000	A	100	5	2	3		1					1		3 poly	5/2
2000	B	100	7	2	5		1			1				poly	7/2
Total	(A + B)	200	12	4											
6 mM EMS	A	100	22	16	8	2	10	1		4				sp, poly	26/16
6 mM EMS	B	100	25	20	7		11			11	3			sp	33/26
Total	(A + B)	200	47***	36***											

a) Abbreviations used for various types of aberrations are listed in Appendix 1.
 The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.
 Significantly different from control group: chi-square test, *P < 0.05, **P < 0.01, or ***P < 0.001

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TABLE 4 CHROMOSOME ABERRATIONS^{a)}: INDIVIDUAL DATA (WITH METABOLIC ACTIVATION; +S9-mix)

TR No.: 7219-94-081

		STUDY NUMBER : EC 121 (1) PROJECT NUMBER: 0311 STUDY DIRECTOR: I. Enninga		TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y SOLVENT : F10-HEPES DOSE RANGE : 100-3330 µg/ml											
Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations		g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
			gaps included	gaps excluded											
0	A	100	11	7	3	1	1			6				endo	11/7
0	B	100	6	3	3		2			2					7/4
Total	(A + B)	200	17	10											
100	A	100	10	5	4	1				4		1			10/5
100	B	100	11	8	4	1	3			4				ma	13/8
Total	(A + B)	200	21	13											
333	A	100	2	1	1					1					2/1
333	B	100	12	7	5		2			4		1		endo	12/7
Total	(A + B)	200	14	8											
1000	A	100	12	10	3		1			7		2		sp	14/11
1000	B	100	8	6	2		1	2		4					9/7
Total	(A + B)	200	20	16											
3330	A	100	19	15	4		3			13				3ma, poly, endo	23/19
3330	B	100	15	12	5		2			4	2			6ma, 3poly, endo, 2sp	21/16
Total	(A + B)	200	34**	27**											
10 µg/ml CP	A	50	42	35	7	1	13			25	20			2ma, endo, 2 sp	70/62
10 µg/ml CP	B	50	40	38	9	4	10			29	10			sp, 6ma	69/56
Total	(A + B)	100	82***	73***											

a) Abbreviations used for various types of aberrations are listed in Appendix 1.
 The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.
 Significantly different from control group: Chi-Square Test, * P<0.05, **P<0.01, or ***P<0.001

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C.A.d.5

TABLE 1. CHROMOSOME ABERRATIONS^a: INDIVIDUAL DATA (WITH METABOLIC ACTIVATION; +S9-mix)

STUDY NUMBER : ECC 121 (2) TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y
 PROJECT NUMBER: 0311 SOLVENT : F10-HEPES
 STUDY DIRECTOR: I. Enninga DOSE RANGE : 333-3330 µg/ml

Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations		g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
			gaps included	gaps excluded											
0	A	100	11	9	3	1	3	1		5				poly, 2 endo	13/9
0	B	100	5	4	2		1			3				2 poly, 4 endo	6/4
Total	(A + B)	200	16	13											
333	A	100	9	3	6		2			1					9/3
333	B	100	14	7	6	3	2			5				2 endo, 1 poly	16/7
Total	(A + B)	200	23	10											
1000	A	100	14	11	4	1	5			6				endo, poly, r	17/12
1000	B	100	9	6	4		4			2				2 endo, poly	10/6
Total	(A + B)	200	23	17											
2500	A	100	10	6	5		4			1		1		4 endo, poly	11/6
2500	B	100	11	7	5		4			3				2 poly	12/7
Total	(A + B)	200	21	13											
3330	A	100	13	10	4		6			4				3 endo	14/10
3330	B	100	9	5	5		3			3				poly, endo	11/6
Total	(A + B)	200	22	15											
5 µg/ml CP	A	50	45	44	7	3	21			14	16	2		14 ma, 4 sp	81/71
5 µg/ml CP	B	50	49	49	8		16			41	23			10 ma, 3 sp	101/93
Total	(A + B)	100	94***	93***											

TR No.: 7219-94-081

a) Abbreviations used for various types of aberrations are listed in Appendix 1.

The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.

Significantly different from control group: chi-square test, *P < 0.05, **P < 0.01, or ***P < 0.001

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C.4.e. V79 Gene Mutation Assay for HGPRT Mutants

Document #(s): BI Document U90-0385
Upjohn TR 7219-94-083

Sponsor Volume: 1.44

Summary:

In this mutagenicity study, PPX did not produce mutations in the HGPRT locus in the Chinese Hamster V79 cell line. The dosage range used in this study was appropriate, since it approached desired upper treatment levels for cell lines (10 mM pramipexole = 2.9 mg/ml for pramipexole). The survival rate at the high concentration of 3000 µg/ml was Positive controls produced the expected mutations.

Methods:

Drug Concentrations
and Exposures: PPX dihydrochloride (Batch III) dissolved in DMEM as follows:

Expt. I:

Without S9 activation: 100, 500, 1000, 2500, 3000 µg/ml

With S9 activation: 100, 1000, 2000, 3000 µg/ml

Expt. II:

Without S9 activation: 100, 1000, 2500, 3000 µg/ml

With S9 activation: 100, 1000, 2000, 3000 µg/ml

Positive Controls/vehicles:

Without S9 activation: Ethylmethanesulfonate (500 µg/ml) dissolved in treatment medium

With S9 activation: DMBA (8 µg/ml) in DMSO (final conc = 1% in medium)

Test System:

The basis of this study is the presence/absence of hypoxanthine-guanine phosphoribosyl transferase in V79 cells. A mutation in the HGPRT locus results in cells which do not convert 6-thioguanine (6-TG) into a toxic metabolite, and thus survive treatment with media containing 6-TG. Mutants arise from base-pair substitutions, frameshifts, deletions, and chromosome rearrangements.

V79 Chinese hamster cells (5×10^5) were cultured in 80 cm² flasks for mutation

studies (1 flask per point). For survival analysis, 220 cells were plated in 58 cm² dishes in triplicate. Cells were exposed to test substance, with and without S9 fraction, for 4 hr. Cells in the survival study were fixed and stained on day 6. Cells in the mutation study were subcultured every 2-3 days. On day 7, cells (5x10⁵) were plated into 58 cm² dishes and medium containing 6-TG was added to cultures for mutant selection. An additional set of 58 cm² dishes were seeded with 220 cells to which complete medium was added for determination of plating efficiency. Incubations were continued with media changes for 6-7 days. Cultures were fixed (ethanol/glacial acetic acid, 3:1) and stained (7% Giemsa) on days 13 and 14 after culture initiation for determination of plating efficiency and mutant selection, respectively. Colonies containing more than 50 cells were counted.

Metabolizing System: S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Results:

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Determination of cytotoxicity:

Significant cytotoxicity occurred with concentrations of 5000 µg/ml in the presence or absence of S9 (Tab. C.4.e.1). Thus, 3000 µg/ml was chosen as the high dose for mutagenicity testing.

Table 1: Results of the preliminary experiment on toxicity

(Experimental parts no. MUT 0127/01 and /02)

Substance	Concentration ^a (µg/ml)	Number of colonies per plate		Survival %
		Individual counts	Mean	
<u>Without S9 mix:</u>				
Negative control		222, 249, 233	235	100
SND 919 CL2Y	10	227, 234, 231	231	98
	100	238, 207, 216	220	94
	1000	106, 127, 105	113	48
	2500	111, 89, 92	97	41
	5000	25, 23, 17	22	9
<u>With S9 mix:</u>				
Negative control		244, 256, 238	246	100
SND 919 CL2Y	10	235, 240, 229	235	96
	100	252, 228, 239	240	98
	1000	230, 248, 249	242	98
	2500	245, 227, 201	224	91
	5000	81, 86, 53	73	30

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Mutagenicity Test Results:

The mutation rate in cultures treated with PPX was approximately equivalent to negative control rates in the presence or absence of S9 in both experiments. The mutation frequency in these cultures were within the normal range of this laboratory. The positive controls EMS and DMBA produced the expected significant increases in mutation rate frequency (Tables C.4.e.2-3). Similar results were obtained in a replicate experiment.

C.4.e.2.

Table 2: Mutagenicity assay; experiment 1; without S9 mix

(Experimental part no. MUT 0127/03)

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Toxicity data

Substance	Concentration ^a (µg/ml)	Number of colonies per plate		Survival %
		Individual counts	Mean	
Negative control		215, 218, 201	211	100
SND 919 CL2Y	100	206, 188, 209	201	95
	500	186, 206, 208	200	95
	1000	199, 188, 177	188	89
	2500	131, 123, 160	138	65
	3000	118, 110, 131	120	57
Positive control with EMS	500	183, 176, 190	183	87

Mutation induction

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Substance	Conc. ^a (µg/ml)	Plating efficiency		Number of cells seeded per flask (B)	Mutant selection ^b		Mutants per 10 ⁶ survivors (D)
		Individual plate counts	Mean (A) ^c		Individual plate counts	Mean (C)	
Negative control		77, 109, 101	96	238806	0, 0, 3	1.0	4.2
SND 919 CL2Y	100	80, 77, 85	81	199507	0, 0, 0	0	0
	500	103, 117, 104	108	259615	1, 6, 1	2.7	10.4
	1000	61, 77, 85	74	184080	0, 1, 0	0.3	1.6
	2500	120, 117, 103	113	278325	0, 0, 1	0.3	1.1
	3000	126, 112, 110	116	287129	0, 0, 0	0	0
Positive control with EMS	500	72, 79, 68	73	180693	129, 144, 123	132.0	730.5

For footnotes and abbreviations see Table 1.

^a Based on number of seeded cells: neg. control, 201; 100 µg/ml, 203; 500 µg/ml, 208; 1000 µg/ml, 201; 2500 µg/ml, 203; 3000 µg/ml, 202; pos. control, 202.

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C.A.e.3.
 Table 2: Mutagenicity assay; experiment 1; with S9 mix
 (Experimental part no. MUT 0127/05)

Toxicity data

Substance	Concentration* (µg/ml)	Number of colonies per plate		Survival %
		Individual counts	Mean	
Negative control		210, 213, 187	203	100
SND 919 CL2Y	100	202, 176, 184	187	92
	1000	174, 145, 178	166	82
	2000	178, 189, 169	179	88
	3000	125, 153, 131	136	67
Positive control with DMBA	8	74, 65, 64	68	33

Mutation induction

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Substance	Conc.* (µg/ml)	Plating efficiency		Number of cells seeded per flask (B)	Mutant selection ^b		Mutants per 10 ⁶ survivors (D)
		Individual plate counts	Mean (A)		Individual plate counts	Mean (C)	
Negative control		167, 165, 179	170	425000	7, 7, 5	6.3	14.8
SND 919 CL2Y	100	174, 171, 176	174	435000	0, 1, 1	0.7	1.6
	1000	173, 182, 190	182	455000	2, 1, 1	1.3	2.9
	2000	175, 180, 179	178	445000	3, 2, 1	2.0	4.5
	3000	194, 186, 187	189	472500	0, 0, 1	0.3	0.6
Positive control with DMBA	8	92, 94, 123	103	257500	250, 295, 221	255.3	991.5

For footnotes and abbreviations see Table 1.

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C.4.f. *In vivo* Mouse Micronucleus Test

Document #(s): BI Document U85-0651
Upjohn TR 7219-94-080

Sponsor Volume: 1.44

Summary:

In this *in vivo* mutagenicity study, a single, high, toxic dose of PPX (1000 mg/kg) did not significantly increase the number of micronucleated polychromatic erythrocytes in the femoral bone marrow of mice at _____ hrs after dosing. The positive control cyclophosphamide produced the expected result.

According to 1994 OECD guidelines, this study is deficient with respect to the number of doses employed (one rather than the recommended three), and the number of polychromatic erythrocytes scored for the presence of micronuclei (1000 vs recommended 2000). Since there was no indication that a single high toxic dose of PPX causes even the slightest increase in the occurrence of micronuclei, and a high rate of lethality would be expected at the recommended 2000 mg/kg dose level, a repetition of this study to conform with guidelines will not be required.

Methods:

Dosage/Route: 1000 mg/kg PPX dihydrochloride (Batch C in 10 ml/kg distilled water) by gavage.

Positive Controls/vehicles: Cyclophosphamide

Animals: Chbb:NMRI mice, 5 g, 10 weeks old.
35 animals (17 M, 18 F) received drug; 2 M and 3 F died within 1 hr of dosing.

Dosing Regimen:

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Group	Dose	Sampling time	Sex	Animal number
0	dist. water	24 h	male female	001 - 005 051 - 055
1	SND 919 CL 2 1000 mg/kg	24 h	male female	101 - 106 151 - 156
2	SND 919 CL 2 1000 mg/kg	48 h	male female	201 - 206 251 - 256
3	SND 919 CL 2 1000 mg/kg	72 h	male female	301 - 305 351 - 356
4	Cyclophosphamide 50 mg/kg	24 h	male female	401 - 405 451 - 455

Note: Failure to comply with OECD guidelines stating that 3 dose levels, or a single dose level of 2000 mg/kg/day should be employed.

Sample Analysis: Femoral marrow smears were fixed on a slide (2 per animal) and stained with Giemsa. At least 1000 polychromatic erythrocytes per animal were scored for the presence of micronuclei. The ratio of polychromatic to normochromatic nuclei was determined by counting 1000 erythrocytes.

Note: OECD guidelines state that 2000 PCEs should be scored.

Results:

A single dose of 1000 mg/kg PPX to male and female mice did not significantly increase the number of micro nucleated polychromatic erythrocytes relative to control levels at 24, 48 or 72 hrs. The ratio of polychromatic to normochromatic erythrocytes also was not affected by PPX. The positive control cyclophosphamide produced the expected increase micronucleated polychromatic erythrocytes.

Table 1: Results of Micronucleus Test with SND 919 CL 2

Dose ^a	Sampling time	Sex	Number of mice	Micronucleated polychromatic erythrocytes (‰) Mean ± standard deviation
Vehicle control	24 h	male	5	1.8 ± 0.4
		female	5	1.2 ± 0.8
SND 919 CL 2 1000 mg/kg	24 h	male	5	2.6 ± 1.3
		female	5	2.2 ± 1.3
SND 919 CL 2 1000 mg/kg	48 h	male	5	1.6 ± 0.9
		female	5	2.2 ± 0.8
SND 919 CL 2 1000 mg/kg	72 h	male	5	2.2 ± 0.8
		female	5	1.2 ± 0.4
Cyclophosphamide 50 mg/kg	24 h	male	5	31.4 ± 8.1 ^b
		female	5	23.0 ± 5.4 ^b

^a Vehicle control, 10 ml dist. water per kg.

^b Significantly different from the vehicle control ($\alpha \leq 0.01$).

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C.5. Carcinogenicity

C.5.a. Two-Year Mouse Carcinogenicity Study

Conducted by : Boehringer Ingelheim KG
Depts. of Experimental Pathology and Toxicology,
and Pharmacokinetics and Metabolism
Research and Development Coordination
Muttentz, Switzerland

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Document #(s): BI Document U93-0589
Upjohn TR 7219-94-070

Sponsor Volumes: 1.45-1.48

This study complied with GLP

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Summary:

Pramipexole was administered in the diet at doses of 0.3, 2.0, and 10.0 mg/kg/day to Chbb:NMRI mice (50/sex/dose group, 100/sex/control) for two years. Relatively few non-neoplastic and no neoplastic lesions were clearly associated with PPX administration.

The rate of premature decedents was higher in PPX-treated animals than in controls; the effect was significant in males. The highest mortality rate was 46% in MDF and HDF. The primary cause of premature deaths were unscheduled sacrifices due to eczema, a condition observed in both control and treated animals. Body weight gain was significantly reduced by % in both sexes at the intermediate and high doses at study termination. A relative increase in the incidence of alopecia was also noted in PPX-treated animals. Spontaneous activity was increased in MD and HD females, and HD males.

No statistically significant increases or trends for increases in the incidence of neoplastic lesions in drug-treated animals were apparent according to the sponsor's analysis. A pooled analysis of all mesenchymal/epithelial uterine neoplasms was not presented, but the incidences suggest a possible dose-related positive trend (controls: 10%; LD: 10%; MD: 14%; HD: 16%). Statistically significant decreases in the incidence of adrenal cortical adenomas in HD males, and malignant lymphomas in MD and HD females were noted. For all other neoplastic findings, which included systemic neoplasms of the hemolymphoreticular system, and primary neoplasms in the lung, liver, and adrenals in males, and the reproductive tracts of both sexes, the incidences were low, and equivalent in PPX-treated and control animals.

The only histopathological findings that occurred at a higher incidence rate in PPX-treated animals were fibro-osseous proliferative lesions in the femurs of females (all dosage groups). This lesion occurred at a relatively high rate in control females (28%), but approximately doubled in incidence in treated animals (%; similar at the three dosage levels). The more severe lesions were found more frequently in treated animals. This type of lesion is known to occur spontaneously in female mice of other strains including B6C3F1 (Albassam, *et al.*, Vet. Pathol., 28:381, 1991), and has also been observed in mice after

administration of the prostaglandin E analogue misoprostol (Dodd and Port, Vet. Pathol., 24:545, 1987) and estrogens (Gaunt and Pierce, Vet. Pathol., 22:403, 1985). The increased incidence in drug-treated animals may be related to stimulation of estrogen release (Sass and Montali, Lab. Anim. Sci., 30:907, 1980), although no experimental evidence of such a hormonal effect of PPX was presented. Pathological changes that might be expected to accompany a bone abnormality (i.e., blood cell count changes) were not clearly associated with this lesion. Possibly compensatory stimulation of splenic erythropoiesis occurred in both treated and control female mice, and increased hematopoietic activity was noted in the femoral bone marrow of MDF and HDF.

Based on plasma level measurements in satellite groups during weeks 2, 40 and 80 at 4-5 hrs after light onset, exposure to PPX in the high dose group (ng/ml) was fold higher than the C_{max} in humans following the expected maintenance dose of 1.5 mg, t.i.d.

Thus, administration of PPX in the diet for two years was not significantly carcinogenic in mice. However, conclusive interpretation of these results is hindered by the marked impairment of body weight development at the mid- and high-dose levels. The low exposures at the lowest dose levels cannot be considered adequate for assessing the tumorigenic effects of this compound. The importance of the fibro-osseous proliferative lesion is questionable since similar lesions are known to occur spontaneously in certain strains of mice, and no similar lesion was observed in long-term rat and monkey PPX studies. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a trend for decreased food intake was apparent at this dose.

Methods:

Dosages: 0.3, 2.0, 10.0 mg/kg/day PPX dihydrochloride (Batch II)

The low dose is three times the ED₅₀ for anti-Parkinsonian effects in monkeys, and 5-15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation. The reduction in body weight gain by this dose was used as an indicator of drug toxicity.

Route of Administration: Drug-in-diet

Species/Strain/Number: Mouse (Chbb:NMRI)

250 males, 250 females for toxicology
20 males, 20 females for microbiology
159 males, 159 females for toxicokinetics

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Toxicology Groups:

Group size and dosage:

Group	Dose mg/kg	Number of animals		Identity number
		males	females	
0 (control A)	0	50	50	0001-0050 0501-0550
1	0.3	50	50	1001-1050 1501-1550
2	2.0	50	50	2001-2050 2501-2550
3	10.0	50	50	3001-3050 3501-3550
4 (control B)	0	50	50	4001-4050 4501-4550

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Toxicokinetic Analyses:

Group no.	Animals/sex per sampling	Animals/ plasma pool	Pooled samples/ group & date
5	20 / m	5	4
	20 / f	5	4
6	16 / m	4	4
	16 / f	4	4
7	12 / m	3	4
	12 / f	3	4

Blood was sampled during weeks 2, 40 and 80 at 10.00 to 11.00 AM (4-5 hrs after light onset.

Mean initial weights/age:

males: 29.3g / 37 days
females: 24.5g / 37 days

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Parameters monitored/Intervals:

Clinical - daily
Body weight - weekly (wks 1-26), monthly (wks 27-104)
Food consumption - weekly
Water consumption - weekly (weeks 14, 26, 39, 52, 65, 78, 91, 104)
Effective dose - calculated weekly (wks 1-26); monthly thereafter
Hematology - done only prior to sacrifice
Plasma Conc - in satellite groups as described above
Histopathology - on the following tissues:

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Adrenal glands	Rectum
Aorta	Salivary glands
Brain	Seminal vesicle
Caecum	Skeletal muscle
Cervical lymph node	Skin
Colon	Spinal cord
Duodenum	Spleen
Femur/stifle joint (incl. bone marrow)	Sternum ¹⁾
Heart	Stomach
Ileum	Testes with epididymides ²⁾
Jejunum	Thymus
Kidneys	Thyroid gland
Larynx ¹⁾	Tongue
Liver/gallbladder	Trachea
Lungs	Urinary bladder
Mammary gland area	Uterus with cervix
Mesenteric lymph node	Vagina
Oesophagus	
Ovaries	Both pinnae with ear tattoo ¹⁾
Pancreas	
Parathyroid glands	All gross lesions incl. tumours/suspected tumours and regional lymph nodes
Periph. (sciatic) nerve	
Pituitary gland	
Prostate gland	

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Both eyes with optic nerve and Harderian glands were fixed in Heidenhein's Susa solution.

- 1)= conserved but not prepared histologically.
2)= fixed in Bouin's solution.

Stains:	Hematoxylin/Eosin -	all organs/tissues, tumors/lesions
	Masson's Trichrome -	heart, kidney, liver, gall bladder lung, aorta, tumors/lesions

Statistics

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Routine group comparisons were made by the Bartlett test, one-way ANOVA and Newman-Keuls test. The Exact Log-rank test was used for group comparisons of categorical tumor-bearing animal data, and for between-group comparisons of the number of premature decedents.

Plasma concentration data were evaluated after logarithmic transformation by regression analysis and ANOVA to determine the effects dose, time point and sex.

Statistical evaluation of neoplastic lesions was according to Peto et al. (1980) using the trend test with respect to dose. Probability levels for significant findings were 0.05 for rare neoplasms and 0.01 for common neoplasms.

Results:

Mortality: 87 males and 101 females died or were sacrificed moribund prior to the end of the study.

Group Sex	Contr. A		Contr. B		1		2		3	
	m	f	m	f	m	f	m	f	m	f
Died	7	4	3	5	8	10	9	8	15	5
Sacr.	6	9	7	15	13	13	13	14	6	18
Total	13	13	10	20	21	23	22	22	21	23
‡	26	26	20	40	42	46	44	44	42	46

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The increased mortality in treated males was statistically significant ($p = 0.0298$ by a one-tailed positive trend test; $p \approx 0.0112$ by heterogeneity test). The major factor contributing to the higher mortality rate was sacrifice due to debilitating eczema.

Skin lesions, in particular eczematous changes and frank dermal ulceration, were a significant reason for sacrificing animals during study. As is evident from the following table, the incidence of these lesions in premature decedents was somewhat higher in the treated groups:

Controls		Group 1		Group 2		Group 3	
m	f	m	f	m	f	m	f
Absolute values:							
5	3	6	0	8	2	5	5
As a percentage of total animals in group:							
5	3	12	0	16	4	10	10

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Causes of death are listed in Table C.5.a.1

Table C.5.a. Causes of Death or Sacrifice:

Controls (A&B)			
<u>Males</u>	<u>23 deaths</u>	<u>Females</u>	<u>33 deaths</u>
neoplasia	- 10	neoplasia	- 22
dermatitis/eczema	- 4	eczema	- 1
edema	- 3	hemometra	- 1
botryomycosis	- 2	wound	- 1
undetermined	- 4	atrial thrombosis	- 1
		posterior paralysis	- 1
		amyloidosis	- 1
		undetermined	- 5
Low-Dose			
<u>Males</u>	<u>21 deaths</u>	<u>Females</u>	<u>23 deaths</u>
neoplasia	- 9	neoplasia	- 13
eczema	- 3	amyloidosis	- 3
edema	- 1	hemometra	- 1
botryomycosis	- 1	glomerulosclerosis	- 1
ulceration	- 1	skull fracture	- 1
glomerulosclerosis	- 1	undetermined	- 4
undetermined	- 5		
Mid-Dose			
<u>Males</u>	<u>22 deaths</u>	<u>Females</u>	<u>22 deaths</u>
neoplasia	- 4	neoplasia	- 9
dermatitis/eczema	- 8	amyloidosis	- 1
edema	- 3	eczema	- 2
purulent prostatitis	- 1	hemorrhage	- 2
brain hemorrhage	- 1	hemorrhagic cyst	- 1
undetermined	- 5	pyometra	- 1
		peritonitis	- 1
		abscess	- 1
		circulatory failure	- 1
		undetermined	- 3
High-Dose			
<u>Males</u>	<u>21 deaths</u>	<u>Females</u>	<u>23 deaths</u>
neoplasia	- 4	neoplasia	- 12
eczema	- 3	dermatitis/eczema	- 2
edema	- 3	wound	- 1
abd. wall perforation	- 1	botryomycosis	- 1
pyelonephritis	- 1	skin erosion	- 1
skin erosion	- 1	circulatory failure	- 1
mucosal hemorrhage	- 1	caudal paralysis	- 1
undetermined	- 7	pyometra	- 1
		undetermined	- 3

Clinical Signs:

Observation	Contr. A+B	Group		
		1	2	3
Incr. spont. activity	0	0	0	96
Alopecia	12	14	18	42

Males

Observation	Contr. A+B	Group		
		1	2	3
Incr. spont. activity	0	0	98	98
Alopecia	19	20	52	52
Skin lesion	6	6	18	20

Females

Body Weight Gain (Fig. C.5.a.1):

- M & HDM - sig. decrease - all time points
- LDF - sig. increase - wks 1-3, 5-6, 9, 15, 17, 19-70, 78, 86-98
- M & HDF - sig. decrease - from wk 3 to end of study

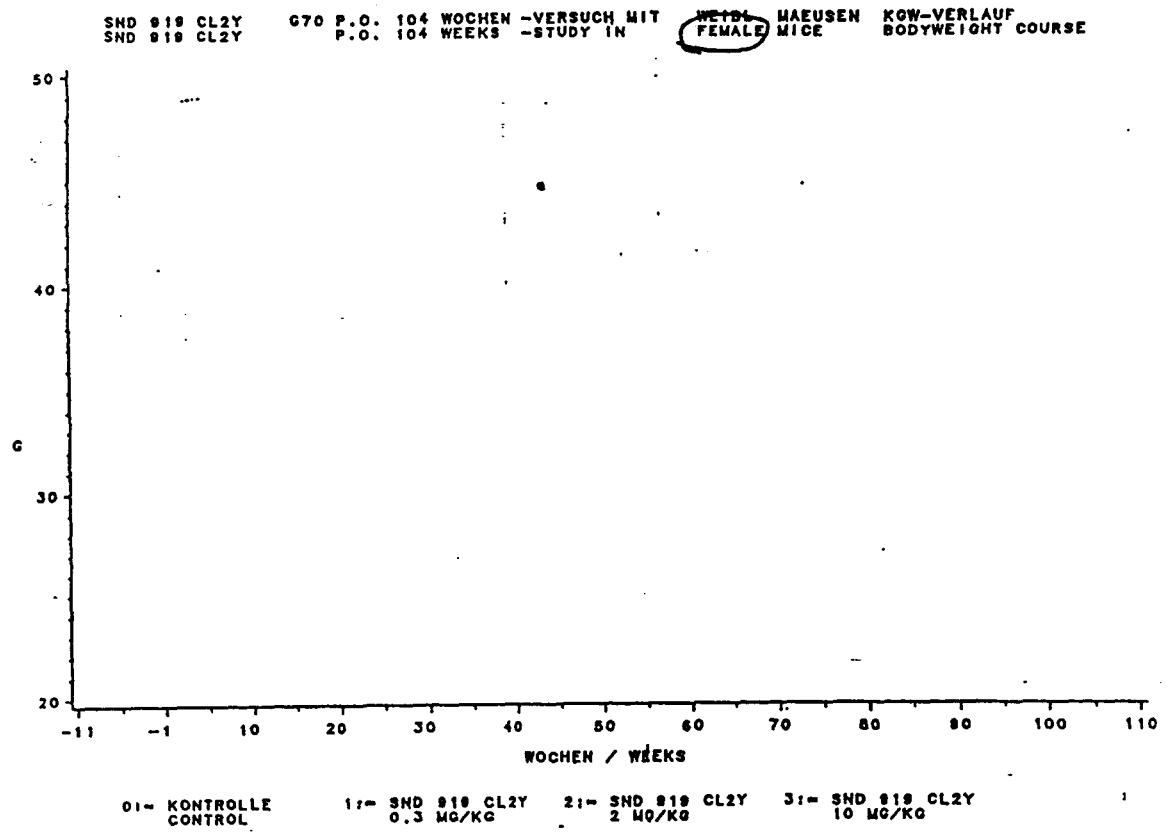
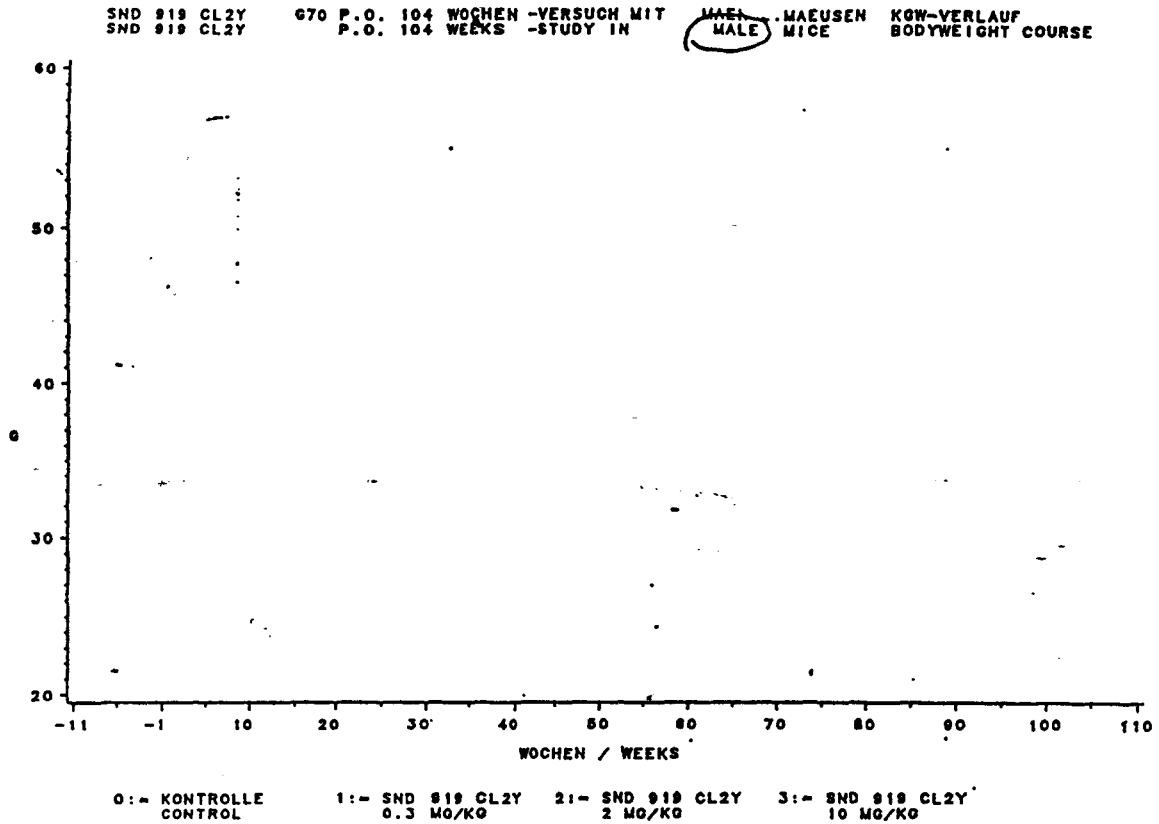
Food Intake:

- LDM - tendency for decrease; effect was significant at several time points
- M & HDM - tendency for increase; effect was significant at several time points
- LDF - tendency for decrease at wks 25-78
- M & HDF - tendency for increase; effect was significant at several time points

Water Intake:

- LDM - no effect
- M & HDM - tendency for increase; effect was significant at several time points
- LDF - no effect
- M & HDF - tendency for increase; effect was significant at several time points

Fig. C.5.a.1.



Alopecia:

	<u>Male</u>	<u>Female</u>
CON	12%	19%
LD	14%	20%
MD	18%	52%
HD	42%	52%

Effective dose: Weekly recordings indicated that effective drug intake was usually within 20% of intended intake. Most variations were in the direction of "greater than intended" intakes.

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	1	Group 2	3
Intended dose (mg/kg)	0.3	2.0	10.0
Males			
Effective dose (mg/kg)			
Mean	0.31	2.11	10.19
Range			
Percentage of intended dose			
Mean	102	105	102
Range			
Females			
Effective dose (mg/kg)			
Mean	0.31	2.11	10.07
Range			
Percentage of intended dose			
Mean	103	105	101
Range			

Hematology:

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A number of animals had abnormal WBC counts at sacrifice. This included several controls as well as PPX-treated animals, and there was no clear dose-relationship. (The sponsor has not indicated their criteria for the noted hematological findings in individual animals).

WBC
v

Individual variations in animals with abnormal blood counts at termination (Tab. C.5.a.2):

Tab. I. Control animals sacrificed at the end of the study

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
0018	+++	+++			+
0020	+	+++			
0040	+				+
0045	+	++			
0501	+	+++			
0536	+	++			
4008	+	++			
4025	+	++			
4041	+				
4044	+	++			
4045	++	++			
4049	+	++			
4519	++	++			
4548	+	++			

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Tab. II Treated animals sacrificed at the end of the study

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
1014	+	+			
1043	+	+++			+
2006	+		++		
2027	+++	+++			
2031	+	++			
3037	+	+			
3517	leucopenia				
3519	+++	+++			
3535	+	+			

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In addition, the following hematological changes were noted in animals with "normal" WBC counts:

anemia, slight	-	2 OM, 3 OF 3 LDF 2 MDM, 1 MDF 3 HDF
" , moderate	-	1 OM 1 LDF
" , marked	-	1 OF
erythrocytosis	-	1 OM, 1 OF 1 LDF 1 HDM

WBC
↓

Individual variations in animals with abnormal blood counts sacrificed moribund (Tab. C.5.a.3)

Tab. III Control animals sacrificed moribund

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
0029	+		↔		
0510	↔				•
0527	•				↔
0540	↔		↔		
4026	•				
4036	•				•
4527	•				•

sarcoma, body ca
lymphoma, thymic
" non-thymic
leiomyxoma
botryomycosis
" paralytic

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Tab. IV. Treated animals sacrificed moribund

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
1037	•		•		*
1039	•		↔		
1040	•		•		
1041	•				
1046	•		•		
1506	•		↔ 1)		•
1517	+++	+++			•
1537	•				•
2011	•		•		+++
2022	+++	+++			
2039	•				
2047	•		1)	•	
2505	•		↔ 1)		•
2507	•	↔			↔
2512	•	•			
3048	•		1)		•
3502	+++		1)		
3518	↔		↔		+++
3522	•				↔
3532	•				↔
3538	↔	+++			

Sacrifice
Cause of ~~Death~~
histio. sarc
?
histio. sarc
eczema
histio. sarc
thymic lymphoma
non-thy "
squamous CA (skin)
sarcoma
thymic lymphoma
eczema
" peritonitis
histio. sarc
?
eczema
botryomycosis
stromal cell CA (uto)
sarcoma
eczema
thymic lymphoma

1) shift to the left

* polycythemia

The following hematological changes were noted in animals with "normal" WBC counts:

anemia, slight	-	1 OM, 3 OF 1 LDM, 5 LDF 3 MDM, 5 MDF 3 HDM, 6 HDF
" , moderate	-	6 OF 1 LDF 2 MDF 3 HDF
" , marked	-	1 HDF (this animal was also stated to have polycythemia???)

Group variations:

Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident.

At termination:

increased Hct	-	HDM
decreased lymphocytes(%)	-	MDM, HDM
increased lymphocytes(%)	-	LDF

Moribund sacrifices:

decreased RBC, Hb	-	trend (N.S.) in males
decreased Hct	-	HDM
increased leucocytes	-	MDM (2° to 1 abnormally high value)
increased lymphocytes(%)	-	MDM

(The page containing mean values of RBC parameters for females sacrificed moribund was omitted.)

Plasma Concentrations:

The concentration of PPX was above the LOQ (0.1 ng/ml) in all samples at 4-5 hrs after light onset. Increases in plasma concentrations were approximately dose-proportional except for females during week 2 and both sexes during week 40 where the increases were greater than dose proportional (Fig. C.5.a.2; Tab. C.5.a.4). ANOVA indicated that significantly higher concentrations were present in females, although specific occurrences of this finding were not indicated (Tab. C.5.a.5). There was no evidence of drug accumulation.

Tab.
C.5.a.4.

Sex	Dose [mg/kg]	Week		
		2	40	80
male	0.3	1.28	1.19*	1.21
male	2.0	12.48	3.96 ✓<	7.48
male	10	41.27	69.69 ✓>	36.02
female	0.3	0.99	0.92*	1.77
female	2	10.55	9.09	9.54
female	10	79.81 ✓>	80.80 ✓>	53.14

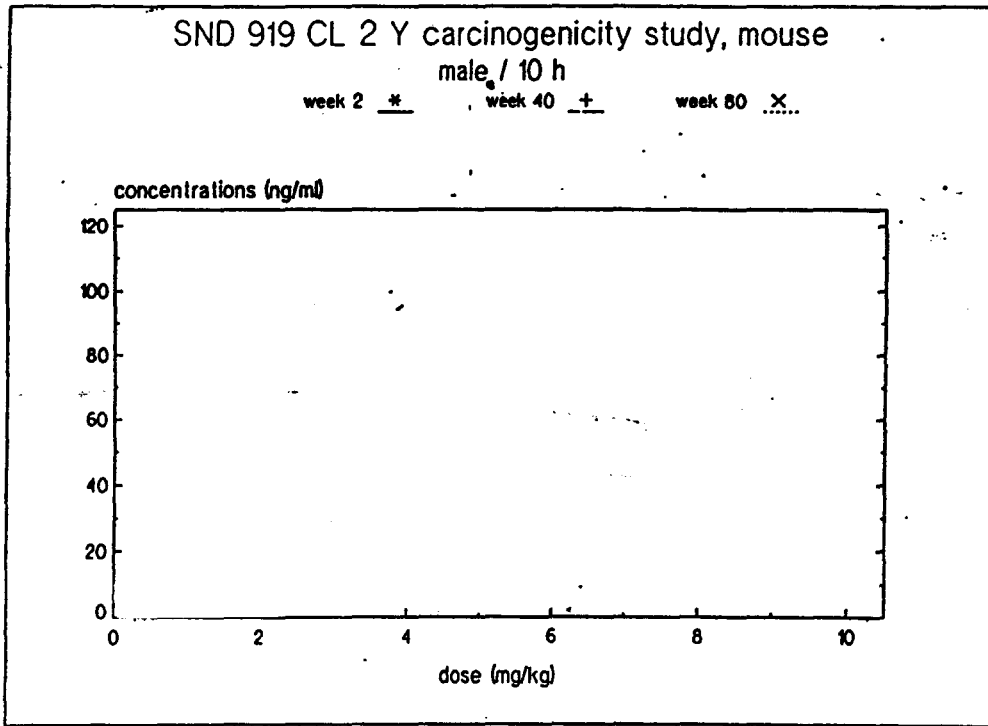
SND 919 C12 Y / carcinogenicity study / mouse
analysis of variance of the log-transformed plasma concentrations

Tab.
C.5.a.5

variability	df	mean squares	p value
between mean values of			
- weeks	2	0.07801	0.068
- sexes within weeks	3	0.09219	0.026
common regression	1	32.80579	< 0.001
between slopes of			
- weeks	2	0.13793	0.010
- sexes within weeks	3	0.05935	0.104
about regression lines	6	0.09966	0.004
between pooled samples.	52	0.02753	
total	69		

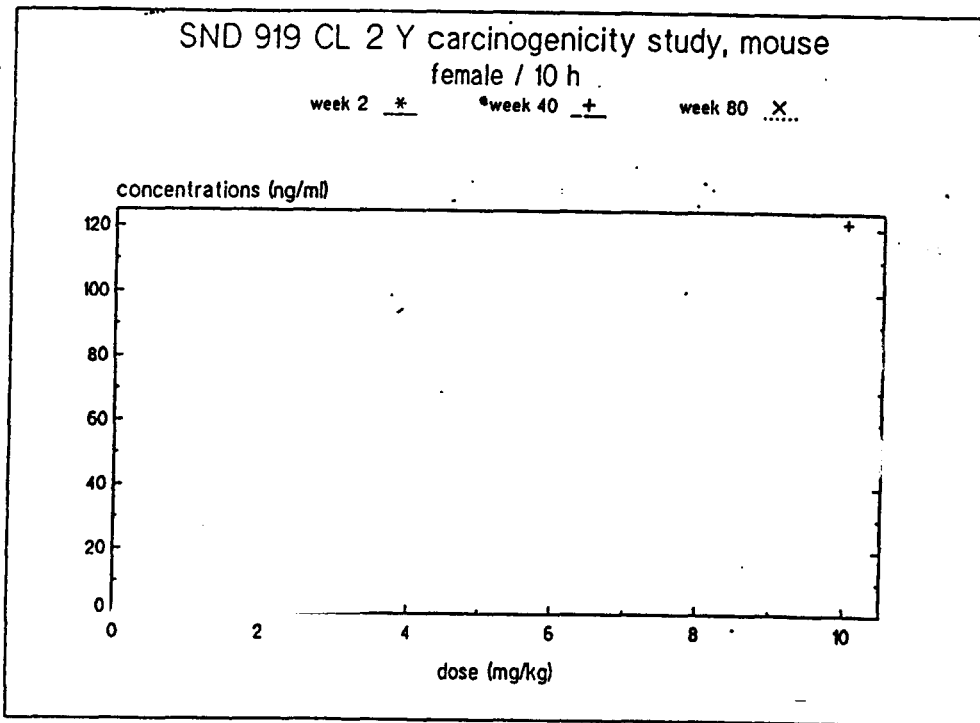
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Fig. C.5.a.2



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Report/Study No.: G70

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Pathology:

Non-Neoplastic Lesions

Statistically significant drug effects were:

Lesion	Group Incidence Rate (%)				
	0	4	1	2	3
Fibro-osseous proliferative lesion (femur) - increase (F)	36	20	62*	60*	56*
Fat marrow (femur epiphysis) - decrease (F)	48	56	42	20*	21*
seminiferous tubule atrophy - decrease	36	36	18	18*	14*

The most notable finding was the fibro-osseous proliferative lesion in the femurs of female mice, which was not described in detail by the sponsor, nor was any potential significance suggested. The lesion occurred spontaneously in control animals, but its incidence was significantly increased by PPX treatment; the incidence rates were similar in all dosage groups. A possibly related finding was decreased femoral fat content in MDF and HDF, suggestive of increased hematopoietic activity.

Albassam et al. (Vet. Pathol., 28:381, 1991) have reported upon the spontaneous occurrence of an apparently similar osseous lesion in the femurs and sternums of female B6C3F1 mice (but not male B6C3F1 or female CF1 mice). The lesion was characterized by the lining of epiphyseal plates by large osteoblasts and had large vascularized centers. Similar drug-induced lesions have been produced by estrogens (Silberberg and Silberberg, Gerontology, 16:201, 1970; Gaunt and Pierce, Vet. Pathol., 22:403, 1985), and the sponsor speculates that a dopaminergic-induced imbalance in estrogen:progesterone levels may account for this lesion. No experimental support for this mechanism (i.e., estrogen level measurements) was provided. The prostaglandin E analogue misoprostol also produces an osseous lesion in female mice (Dodd and Port, Vet. Pathol. 24:545, 1987), and the finding appears in the labeling of that product.

Neoplastic lesions

According to the sponsor's analysis, the only statistically significant differences in the incidence of neoplasia between treated and control animals were decreased occurrences of the following tumors:

Neoplasm	Group/Incidence rate (%)				
	0	4	1	2	3
malignant lymphomas - decrease (F)	46	42	32	22*	16*
adrenal cortical adenomas - decrease (M)	32	16	16	12	6*

There was also a non-significant trend for decreased occurrence of hepatocellular adenomas in treated males.

Inspection of the Tumor Distribution Summary (Tab. C.5.a.6) and statistical analysis tables (Tab. C.5.a.7) reveals some notable findings or tendencies. The incidence of uterine stromal polyps tended to increase at the higher doses (controls: 2%; LD: 2%; MD: 6%; HD: 6%; $p = 0.0778$ by the Trend Test), as did the incidence of all mesenchymal/epithelial uterine neoplasms (control: 10%; LD: 10%; MD: 14%; HD: 18%; not statistically analyzed). The Test of Heterogeneity indicated a statistically significant increase in the incidence of histiocytic sarcomas in PPX-treated male mice ($p = 0.0018$), but the tumors were found only in 4 LD animals and are thus not clearly drug-related.

There were no significant differences between PPX-treated and control animals with respect to the number of primary neoplasms, the number of mice with primary neoplasms, mice with more than one neoplasm, mice with metastases, the number of benign and malignant neoplasms per group and sex (Tab. C.5.a.8).

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TR No.: 7219-94-070

Tab. C.5.a.6

BOEHRINGER INGELHEIM KG Name of finished product	TABULATED STUDY REPORT	U93-0589
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210	
	2/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)		Frequency according to dose and sex (n)											
		(0)		(4)		(1)		(2)		(3)			
		Contr. A		Contr. B		m		f		m		f	
Bimetrical evaluation yes <x> no <>		m	f	m	f	m	f	m	f	m	f	m	f
Number of animals evaluated													
Organ	Identification of the tumour												
BRAIN	OLIGODENDROGLIOMA	1	-	-	-	-	-	-	-	-	-	-	-
	NEOPLASM (NOS)	-	-	-	-	-	-	-	-	-	-	-	1
LUNGS	ADENOMA	22	9	11	8	12	13	8	6	13	6		
	CARCINOMA	1	2	-	-	-	2	-	1	-	-	-	-
LIVER	ADENOMA/HEPATOC.	5	-	7	1	2	-	-	-	2	-	-	-
	HEMANGIOSARCOMA	3	1	4	-	2	1	1	-	1	-	-	-
	CARCINOMA/HEPATOC.	-	-	-	-	1	-	1	-	-	-	-	-
TONGUE	CARCINOMA/SQUAMOUS	1	-	-	-	-	-	-	-	-	-	-	-
DUODENUM	SARCOMA/OSSIFYING	-	-	-	-	-	-	1	-	-	-	-	-
TESTES	LEYDIG CELL TUMOR	4	-	3	-	2	-	-	-	5	-	-	-
PROSTATE	ADENOMA	1	-	-	-	-	-	-	-	-	-	-	-
SEMINAL													
VESICLES	LEIOMYOMA	1	-	-	-	-	-	-	-	-	-	-	-
OVARIES	LUTEOMA	-	-	-	-	-	-	-	-	-	-	-	1
	ADENOMA/TUBULAR	-	1	-	2	-	1	-	2	-	-	-	-
	TUMOR/GRANULOSA CELL	-	1	-	4	-	2	-	5	-	3	-	-
	LIPOMA	-	1	-	-	-	-	-	-	-	-	-	-

* P < 0.05 ** P < 0.01

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TR No.: 7219-94-070 . Tab. C.5.a.6. (cont)

BOEHRINGER INGELHEIM KG Name of finished product		TABULATED STUDY REPORT				U93-0589												
Name of active ingredient Pramipexole (SND 919 CL 2 Y)		ref. to III.E.210																
		3/6				Page Number												
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data																		
Ref. to document.: Volume: Page: to Addendum No.: Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991																		
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)					Frequency according to dose and sex (n)													
					(0) Contr. A		(4) Contr. B		(1)		(2)		(3)					
Biometrical evaluation yes <x> no <y>					m	f	m	f	m	f	m	f	m	f				
Number of animals evaluated																		
Organ	Identification of the tumour																	
UTERUS	POLYP/STROMAL				-	2	-	-	-	1	-	3	-	3				
	LEIOMYOMA				-	4	-	1	-	2	-	2	-	2				
	FIBROMA				-	-	-	-	-	-	-	-	-	1				
	GRANULAR CELL TUMOR (m)				-	-	-	-	-	-	-	-	-	1				
	LEIOMYOSARCOMA m				-	-	-	-	-	1	-	-	-	1				
	ADENOCARCINOMA m				-	-	-	-	-	1	-	-	-	-				
	SARCOMA/STROMAL CELL m				-	2	-	1	-	-	-	2	-	1				
VAGINA	FIBROMA				-	1	-	-	-	-	-	-	-	-				
URINARY																		
BLADDER	CARCINOMA/TRANSIT. CELL				-	-	-	-	-	-	-	-	-	1				
PITUITARY																		
GLAND	ADENOMA/P. DISTALIS				-	-	-	1	1	2	-	3	-	-				
THYROID	ADENOMA/FOLLICULAR				-	-	-	1	-	1	-	-	-	-				
	CARCINOMA/FOLLICULAR				-	-	-	-	-	-	1	-	-	-				
PARA-																		
THYROID																		
GLANDS	ADENOMA				-	2	-	-	-	-	-	-	-	-				

* P < 0.05 ** P < 0.01

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TR No.: 7219-94-070

Tab. C.5.a.6 (cont.)

BOEHRINGER INGELHEIM KG Name of finished product		TABULATED STUDY REPORT		U93-0589									
Name of active ingredient Pramipexole (SND 919 CL 2 Y)		ref. to III.E.210		4/6 Page Number									
CNOGENIC/CARCINOGENIC POTENTIAL Tumour data													
Ref. to document.: Volume: Page: to Addendum No.:		Report date: 28.06.93 Number: G70		Study period (years): 1989 - 1991									
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)				Frequency according to dose and sex (n)									
				(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Biometrical evaluation yes <x> no <>				m	f	m	f	m	f	m	f		
Number of animals evaluated													
Organ	Identification of the tumour												
ADRENAL													
CORTEX	ADENOMA/A-CELL			-	-	-	-	1	-	-	-	1	
	ADENOMA/B-CELL			6	-	3	-	3	-	6	-	3	1
	ADENOMA/B-CELL/EXTD.** (males)			8	-	5	-	3	-	2	-	-	
	ADENOMA/Z. FASCICUL.			3	-	-	1	1	-	-	-	-	
ADRENAL													
MEDULLA	MEDULL. TUMOR/BENIGN			1	-	-	-	-	-	-	-	-	
	MEDULL. TUMOR/MALIGN.			-	-	-	1	-	-	-	-	-	
MESENT.													
Lymph Node	HEMANGIOMA			-	-	-	1	-	-	-	-	-	
SYSTEMIC													
NEOPLASMS	THYMIC LYMPHOMA* (females)			3	18	4	16	4	13	4	8	4	7
	NONSPECIF. LYMPHOMA			1	-	1	1	1	-	-	-	-	-
	NON-THYMIC LYMPHOMA			3	5	4	3	6	3	3	3	4	1
	MAST CELL TUMOR			1	-	-	-	-	-	2	-	-	1
	BONE MARROW LYMPHOMA			-	-	-	1	-	-	-	-	-	-
	HISTIOCYTIC SARCOMA			-	1	-	4	4	2	-	2	-	1
	MYELOID LEUKEMIA			-	1	-	-	-	-	-	-	-	-

* P < 0.05, ** P < 0.01 (=negative trend) -

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TR No.: 7219-94-070

Tab. C.S.a.6. (cont.)

BOEHRINGER INGELHEIM KG Name of finished product	TABULATED STUDY REPORT	U93-0589
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210 <u>5/6</u> Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Biometrical evaluation yes <x> no <>		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
HARDERIAN											
GLANDS	ADENOMA	2	1	2	2	2	3	-	-	-	-
	ADENOCARCINOMA	-	-	-	-	-	1	-	-	-	-
SPLEEN	HEMANGIOSARCOMA	-	-	-	-	-	-	1	-	-	-
SKIN	LIPOMA	-	-	1	-	-	-	-	-	-	-
	HEMANGIOMA	-	-	-	-	-	1	-	-	-	-
	HEMANGIOSARCOMA	1	-	-	-	-	1	-	-	-	-
	CARCINOMA/BASAL CELL	-	-	-	-	-	1	-	-	-	-
	CARCINOMA/SQUAMOUS	-	-	-	-	-	1	-	-	-	-
	SARCOMA/OSSIFYING	-	1	-	-	-	-	-	-	-	-
	LEIOMYOSARCOMA	-	1	-	-	-	1	1	-	-	1
	SCHWANNOMA	-	-	-	1	-	-	-	-	-	-
	SARCOMA/UNDIFFERENT.	-	-	-	-	-	-	-	1	-	-
BODY											
CAVITIES	LIPOMA	-	-	-	-	-	-	1	-	-	-
	SARCOMA/OSSIFYING	1	-	-	-	-	-	-	-	1	-
	SARCOMA/UNDIFFERENT.	-	-	-	1	-	-	-	-	-	1

* P < 0.05 ** P < 0.01

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Tab. C.5.a.7.

PATHOLOGY REPORT PAGE : 781
 STATISTICAL EVALUATION BOE PROJECT: G 70

TEST ARTICLE : SMD 919 CL 2 Y PATHOL. NO.: 91009 HEW
 TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING DATE : 11-MAY-93
 SPONSOR : BOEHRINGER INGELHEIM KG PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
 COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0, G1, G2, G3, G4 SEX: MALE
 STATUS AT NECROPSY: KO INCL. +
 TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BRAIN	OLIGODENDROGLIOMA	2.204-	0.2776
LUNGS	ADENOMA	5.941+	0.4052#
LUNGS	CARCINOMA	2.197-	0.2776
TONGUE	CARCINOMA/SQUAMOUS	2.128-	0.2810
LIVER	ADENOMA/HEPATOC.	13.911-	0.1611#
LIVER	HEMANGIOSARCOMA	11.670-	0.1660#
LIVER	CARCINOMA/HEPATOC.	2.172-	0.3409
TESTES	LEYDIG CELL TUMOR	18.343+	0.0901#
PROSTATE	ADENOMA	2.203-	0.2776
SEMINAL VESICLES	LEIOMYOMA	2.176-	0.2776
PITUITARY GLAND	ADENOMA/P. DISTALIS	2.553-	0.2611
THYROID (BOTH LOBES)	CARCINOMA/FOLLICULAR	0.190-	0.4797
ADRENAL CORTEX	ADENOMA/B-CELL	2.901-	0.4286#
ADRENAL CORTEX	ADENOMA/Z. FASCICUL.	8.888-	0.1151#
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	35.788-	0.0094#
ADRENAL CORTEX	ADENOMA/A-CELL	1.876-	0.3050
ADRENAL MEDULLA	MEDULL. TUMOR/BENIGN	2.190-	0.2776
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	6.288-	0.1635
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	1.540+	0.4626#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	7.369+	0.3228#
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	7.470-	0.2539
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	2.517-	0.3483
SPLEEN	HEMANGIOSARCOMA	0.176-	0.4813
HARDERIAN GLANDS	ADENOMA	12.472-	0.0808
SKIN	HEMANGIOSARCOMA	2.405-	0.2611
SKIN	LIPOMA	2.149-	0.2776
BODY CAVITIES	SARCOMA/OSSIFYING	5.671+	0.1379

-?? highest
 con. #10

-highest in con.

Explanation of Symbols

- p = one-tailed p-value
- = negative trend
- + = positive trend
- # = number of animals with tumors > 5% in at least one sex/dose group

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Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

PAGE : 106/ 781
BOE PROJECT: G 70

TEST ARTICLE : SMD 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HEW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: KO INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: MALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BODY CAVITIES	LIPOMA	0.000+	0.5000#

POOLED ORGANS/FINDINGS

SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA		
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.736+	0.4876#

POOLED ORGANS/FINDINGS

ADRENAL CORTEX	ADENOMA/B-CELL		
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.		
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.		
ADRENAL CORTEX	ADENOMA/A-CELL	45.815-	0.0158#

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: KO INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BRAIN	NEOPLASM (NOS)	7.706+	0.0192
LUNGS	ADENOMA	19.597-	0.1788#

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Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

PAGE : 107/ 781
BOE PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HHW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0, G1, G2, G3, G4

SEX: FEMALE

STATUS AT NECROPSY: KO INCL. +

TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
LUNGS	CARCINOMA	9.616-	0.1170
LIVER	ADENOMA/HEPATOC.	2.242-	0.2743
LIVER	HEMANGIOSARCOMA	4.326-	0.1977
URINARY BLADDER	CARCINOMA/TRANSIT.C.	7.731+	0.0192
OVARIES	ADENOMA/TUBULAR	8.839-	0.1587
OVARIES	TUMOR/GRANULOSA CELL	4.570+	0.3707#
OVARIES	LIPOMA	2.190-	0.2743
OVARIES	LUTEOMA	7.810+	0.0170
UTERUS	SARCOMA/STROMAL CELL	0.012+	0.4996
UTERUS	LEIOMYOMA	1.019-	0.4653#
UTERUS	ADENOCARCINOMA	1.942-	0.3015
UTERUS	LEIOMYOSARCOMA	5.775+	0.1357
UTERUS	FIBROMA	7.758+	0.0188
UTERUS	GRANULAR CELL TUMOR	7.758+	0.0188
UTERUS	POLYP/STROMAL	15.578+	0.0778#
VAGINA	FIBROMA	2.282-	0.2709
PITUITARY GLAND	ADENOMA/P. DISTALIS	7.384-	0.2090#
THYROID (BOTH LOBES)	ADENOMA/FOLLICULAR	4.642-	0.1977
PARATHYROID GLANDS	ADENOMA	4.745-	0.1894
ADRENAL CORTEX	ADENOMA/B-CELL	7.758+	0.0188
ADRENAL CORTEX	ADENOMA/Z. FASCICUL.	2.242-	0.2743
ADRENAL CORTEX	ADENOMA/A-CELL	7.627+	0.0222
ADRENAL MEDULLA	MEDULL. TUMOR/MALIGN.	2.242-	0.2743
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	2.306-	0.2676
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	17.653-	0.1075#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	52.989-	0.0250#
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	2.242-	0.2743

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M+E
C = 9/200
LD = 3/100
MD = 6/100
HD = 4/100

Tab. C.S.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

PAGE : 108/ 781
BOE PROJECT: G 70

TEST ARTICLE : SNO 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HHW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PEYO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: KO INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN
SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	8.252-	0.2420#
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	7.758+	0.0188
SYSTEMIC NEOPLASMS	MYELOID LEUKEMIA	2.360-	0.2676
MESENT. LYMPH NODE	HEMANGIOMA	2.464-	0.2483
HARDERIAN GLANDS	ADENOCARCINOMA	1.976-	0.2981
HARDERIAN GLANDS	ADENOMA	12.725-	0.0778#
SKIN	HEMANGIOSARCOMA	2.038-	0.2946
SKIN	SARCOMA/OSSIFYING	2.362-	0.2644
SKIN	LEIOMYOSARCOMA	3.160+	0.3372
SKIN	CARCINOMA/BASAL CELL	2.075-	0.2912
SKIN	HEMANGIOMA	1.942-	0.3015
SKIN	CARCINOMA/SQUAMOUS	2.014-	0.2946
SKIN	SCHWANNOMA	2.333-	0.2676
SKIN	SARCOMA/UNDIFFERENT.	0.274-	0.4705
BODY CAVITIES	SARCOMA/UNDIFFERENT.	5.318+	0.1587

POOLED ORGANS/FINDINGS

SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA		
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA		
		75.982-	0.0059#

POOLED ORGANS/FINDINGS

		TREND	P-VALUE
ADRENAL CORTEX	ADENOMA/B-CELL		
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.		
ADRENAL CORTEX	ADENOMA/A-CELL		
		13.142+	0.0212

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Tab. C.S.a.7. (cont.)

PATHOLOGY REPORT

PAGE : 110/ 781
BOE PROJECT: G 70

TEST ARTICLE : SMD 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HHW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

SEX: MALES

ORGAN/TISSUE	TYPE OF NEOPLASM	P-VALUE
LUNGS	ADENOMA	0.4296
LIVER	ADENOMA/HEPATOC.	0.0663
LIVER	HEMANGIOSARCOMA	0.6462
TESTES	LEYDIG CELL TUMOR	0.1536
ADRENAL CORTEX	ADENOMA/B-CELL	0.5593
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	0.0720
ADRENAL CORTEX	ADENOMA/Z. FASCICUL.	0.5123
ADRENAL CORTEX	ADENOMAS/TOTAL	0.1450
HARDERIAN GLANDS	ADENOMA	0.3355
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.8941
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	-
SYSTEMIC NEOPLASMS	NONTHYMIC LYMPHOMA	0.5578
SYSTEMIC NEOPLASMS	MALIGN. LYMPHOMA/TOTAL	0.5740
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.0018

SEX: FEMALES

LUNGS	ADENOMA	0.1048
OVARIES	TUMOR/GRANULOSA CELL	0.5743
UTERUS	POLYP/STROMAL	0.3589
UTERUS	LEIOMYOMA	0.9954
PITUITARY GLAND	ADENOMA/P. DISTALIS	0.1239
HARDERIAN GLANDS	ADENOMA	0.1154
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.0715
SYSTEMIC NEOPLASMS	NONSPEC. LYMPHOMA	-
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	0.6700
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	-
SYSTEMIC NEOPLASMS	MALIGN. LYMPHOMA/TOTAL	0.0204
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.9139

NOTE: STATISTICAL CALCULATION WAS PERFORMED ONLY IF THE NUMBER OF NEOPLASMS EXCEEDED 5% PER DOSE GROUP AND SEX.

END OF REPORT SECTION

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Tab. C.5.a.8.

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 24/ 781
BOE PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HW
DATA : 11-MAY-93
PATHDATA SYSTEM Vb3.6

EVALUATION OF NEOPLASTIC LESIONS
STATUS AT NECROPSY: NO, INCL. +

NUMBER OF ANIMALS WITH NEOPLASMS:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO.EXAM:	50	50	50	50	50	50	50	50	50	50
NO.AFF.:	40	35	30	33	32	37	23	27	24	30
% :	80.0	70.0	60.0	66.0	64.0	74.0	46.0	54.0	48.0	60.0

DOSE GR:	TOTAL	
SEX :	M	F
NO.EXAM:	250	250
NO.AFF.:	149	162
% :	59.6	64.8

NUMBER OF ANIMALS WITH MORE THAN ONE PRIMARY NEOPLASM:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO.EXAM:	50	50	50	50	50	50	50	50	50	50
NO.AFF.:	24	12	14	15	11	15	7	10	9	5
% :	48.0	24.0	28.0	30.0	22.0	30.0	14.0	20.0	18.0	10.0

DOSE GR:	TOTAL	
SEX :	M	F
NO.EXAM:	250	250
NO.AFF.:	65	57
% :	26.0	22.8

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Tab. C.5.a. 8. (cont.)

NUMBER OF ANIMALS WITH METASTASES:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO. EXAM:	50	50	50	50	50	50	50	50	50	50
NO. AFF.:	0	0	0	1	0	1	0	0	0	1
% :	0.0	0.0	0.0	2.0	0.0	2.0	0.0	0.0	0.0	2.0

DOSE GR:	TOTAL	
SEX :	M	F
NO. EXAM:	250	250
NO. AFF.:	0	3
% :	0.0	1.2

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NUMBER OF PRIMARY NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
PRIM. T.:	76	55	46	52	46	56	32	39	35	35

DOSE GR:	TOTAL	
SEX :	M	F
PRIM. T.:	235	237

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NO. OF BENIGN, UNCLASSIFIED, MALIGN. NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
BENIGN :	61	23	33	23	28	28	18	21	25	19
UNCLASS.:	0	0	0	0	0	0	0	0	0	0
MALIGN.:	15	32	13	29	18	28	14	18	10	16

DOSE GR:	TOTAL	
SEX :	M	F
BENIGN :	165	114
UNCLASS.:	0	0
MALIGN.:	70	123

C.5.b. Two-Year Rat Carcinogenicity Study

Conducted by : Boehringer Ingelheim KG
Depts. of Experimental Pathology and Toxicology and
Pharmacokinetics and Metabolism
Research and Development Coordination
MuttENZ, Switzerland

Document #(s): BI Document U94-0250
Upjohn TR 7219-94-068

Sponsor Volumes: 1.49-1.54

This study complied with GLP

Summary:

Pramipexole was administered in the diet at doses of 0.3, 2.0, and 8.0 mg/kg/day to Wistar rats (50/sex/dose group, 100/sex/control) for two years. Toxicokinetic analyses were conducted in satellite groups at weeks 2, 50, and 100.

Mortality occurred in all treatment groups at various times during the study; there were no clear drug-related effects. The highest percentage of mortality was 40% in LDF. Body weight gain was significantly reduced at most time points in all three treatment groups. In MDF and HDF, body weight gain was reduced by 22 and 28%, respectively, at the end of the study. Other clinical observations included increased spontaneous activity in HDF, decreased food intake in males and LDF, and increased food intake in MDF and HDF.

The only neoplastic lesion that occurred at a higher incidence rate in PPX-treated rats were Leydig cell adenomas in MD (2.0 mg/kg/day) and HD (8.0 mg/kg/day) males. Leydig cell hyperplasia also occurred in MD and HD rats. Drug-related decreases in the incidence mammary gland neoplasia (MDF, HDF), benign adrenal medullary neoplasms (LDF, MDF, HDF), and pituitary adenomas (MD, HD of both sexes) were observed. Adrenal medullary hyperplasia was also reduced in MDF and HDF. Non-neoplastic changes in females were enlarged corpora lutea (HD rats), uterine lesions and hemorrhage (MD and HD), alterations in mammary gland patterns from female-like to male/female-like (MD and HD), and diffuse hepatocellular fatty changes (MD and HD). Retinal degeneration occurred in MD and HD groups of both sexes.

Toxicokinetic analyses indicated that in the low dose group, plasma exposure levels 2 hrs after light onset were lower the steady-state C_{max} in humans receiving the projected maintenance dose of 1.5 mg PPX, t.i.d., 2-5 fold higher than the human C_{max,ss} after the intermediate dose, and 10-30 fold higher after the highest dose.

The proposed mechanism for the neoplastic and non-neoplastic lesions in reproductive and endocrine tissues is PPX-induced inhibition of prolactin secretion as demonstrated at week 60 and 69 (ca. 10-fold decrease in females, 100-fold decrease in males). In males, reductions in serum prolactin purportedly lead to a down-regulation of LH receptors. This triggers a compensatory increase in LH production and release leading to Leydig cell

hyperplasia and adenomas. The sponsor cites a study by Rao et al. (1984) which demonstrates that the dopamine agonist bromocriptine elevates LH; however, no evidence for a similar action of PPX on serum LH or LH receptor number was provided. Nonetheless, the finding is suggested to be of questionable relevance to humans given the high background incidence of this tumor in rats (as demonstrated in this experiment), and since several widely-used compounds also produce Leydig cell tumors in rats but are not known to do so in humans (cimetidine, hydralazine, vidarabine, israpidine). Additional evidence that Leydig cell adenomas may be species-specific is that a similar tumor was not observed in the mouse. The reduction in serum prolactin is also suggested to underlie the decreased incidence of pituitary adenomas, since prolactin normally stimulates anterior pituitary cell proliferation. The decreased incidence of benign adrenal medullary neoplasia is suggested to result from a dopamine receptor-mediated inhibition of chromaffin cell catecholamine release which decreases the proliferative potency of the chromaffin cells.

The corpora lutea enlargement, uterine changes, and changes in the glandular pattern of the mammary glands in PPX-treated female rats were also observed in the one year rat study. The sponsor has presented an argument to discount the potential human relevance of this finding based on the divergent effects of prolactin in rats and humans. In the rat, prolactin is luteolytic, and in its absence non-functional corpora lutea persist (and enlarge). In addition, prolactin stimulates progesterone secretion in the rat, and a reduction in the prolactin-progesterone stimulus results in unopposed actions of estrogen. Aging rats are susceptible to a chronic estrogenic state which leads to the uterine changes. However, this does not occur in aging women due to ovarian involution. Once again these proposed pathways in rats should be considered speculative in the case of PPX since studies of PPX-induced hormonal changes were not presented to support these arguments. The role of PPX inhibition of prolactin secretion in the mammary gland tissue pattern change was described in the one-year rat study.

Retinal degeneration in both male and female rats from the mid- and high-dose groups was the most notable non-neoplastic finding of this study. Follow-up studies to address this issue have been conducted by the sponsor, submitted to the IND, and reviewed. These studies will be independently reviewed by an FDA consultant (Dr. Tim O'Neill). The only noteworthy aspect of the current NDA submission that needs to be addressed as a part of this review is related to dosage level/exposure. The sponsor minimizes the relevance of the retinal degeneration findings in the discussion since the doses at which the effects were observed were "between 20 and 80 times the intended therapeutic dose in man." Based on an expected C_{max} in humans of ng/ml, the exposure level in MD rats (ng/ml) is only times higher than this level.

Hepatocellular fatty changes (steatosis) were observed in PPX-treated females. These were characterized as either diffuse or restricted to zones 1 and 2. Increased incidences of diffuse changes were dose-dependent and statistically significant in the MD and HD groups. Fatty changes restricted to zones 1 and 2 occurred at a lower rate (Con=7%; LD=24%, MD=22%, LD=18%). The potential mechanism or significance of these findings were not discussed. However, in the 52-week rat study, PPX caused a dramatic dose-dependent reduction in serum cholesterol and triglycerides suggesting a possible interference with hepatic transport or mobilization by PPX. Since both the biochemical and histological changes were observed only in females, a hormonal-based mechanism may be responsible. A direct relationship between the biochemical and histological changes could not be established in

either study. In the 52-week study, steatosis (peripheral fatty changes) occurred in all treatment groups, but the biochemical changes were more clearly dose-dependent. Clinical chemistry was not analyzed in the two-year study. Finally, there was no clear relationship between steatosis and more severe liver histopathologies; the highest incidence of necrosis (multicellular) was in MD females.

In summary, the only potential tumorigenic effect of PPX identified in this study was the induction of Leydig cell adenomas in males, possibly through an indirect hormonal mechanism that is not clinically relevant. The marked impairment of body weight development in MDF and LDF interferes with the interpretation of this study, and no conclusions regarding the carcinogenicity of PPX in female rats can be drawn. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a decrease in body weight gain was apparent at this dose.

Methods:

Dosages: 0.3, 2.0, 8.0 mg/kg/day PPX (Lot: Batch II)

Low dose is 3-4 fold higher than the ED₅₀ for anti-Parkinsonian effects in monkeys. It is 5-15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation.

Route of Administration: Drug-in-diet

Species/Strain/Number: Rat/Wistar (Chbb:THOM)

250 males, 250 females for toxicology

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Group size and dosage:

Group	Dose mg/kg	Number of animals		Identity number
		males	females	
0 (control A)	0	50	50	0001-0050 0501-0550
1	0.3	50	50	1001-1050 1501-1550
2	2.0	50	50	2001-2050 2501-2550
3	8.0	50	50	3001-3050 3501-3550
4 (control B)	0	50	50	4001-4050 4501-4550

Three satellite groups (5, 6 and 7) were used for toxicokinetic analyses. Blood was sampled from 5 rats/sex in each group on days 2 and 7 of weeks 2, 50 and 100.

Mean initial weights/age:

males: 144.8g / 39 days
females: 131.6g / 39 days

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Parameters monitored/Intervals:

Clinical	- -	daily
Body weight	-	weekly (wks 1-26), monthly (wks 27-104)
Food consumption	-	weekly
Water consumption	-	weekly (weeks 13, 26, 39, 52, 65, 78, 91, 104)
Effective dose	-	calculated weekly (wks 1-26); monthly thereafter
Hematology	-	done only prior to sacrifice
Prolactin measurements	-	by RIA in wks 60 and 69
Plasma Conc	-	in satellite groups as described above
Histopathology	-	on the following tissues:

The following organs were placed in 7.5% buffered formaldehyde solution for histological preparation:

Adrenal glands	Prostate gland
Aorta	Rectum
Brain	Salivary glands
Caecum	Seminal vesicle
Cervical lymph node	Skeletal muscle
Colon	Skin
Duodenum	Spinal cord
Eyes/Hardnerian glands ³⁾	Spleen
Femur/stifle joint (incl. bone marrow)	Sternum ¹⁾
Heart	Stomach
Ileum	Testes with epididymides ²⁾
Jejunum	Thymus gland
Kidneys	Thyroid gland
Larynx ¹⁾	Tongue
Liver	Trachea
Lungs	Urinary bladder
Mammary gland	Uterus with cervix
Mesenteric lymph node	Vagina
Oesophagus	Both pinnae with ear tattoo ¹⁾
Ovaries	All gross lesions incl. tumours/suspected tumours and regional lymph nodes
Pancreas	
Parathyroid glands	
Periph. (sciatic) nerve	
Pituitary gland	

1) = conserved but not prepared histologically.

2) = fixed in Bouin's solution.

3) = fixed in Heidenhein's Susa solution.

Tissues were fixed in 7.5% formalin (except eyes and Harderian glands were fixed in Susa's solution, and the testes with epididymides in Bouin's solution), embedded in Paraplast, and stained with H/E. Aorta, heart, kidneys, liver, lungs, and gross lesion were also stained with Masson-Goldner's trichrome technique. Sectioning was as follows:

Adrenal glands (6), aorta (1), bone and bone marrow [femur] (1), brain [cerebrum, cerebellum] (2), cervix (1), epididymides (2), esophagus (1), eyes (2), Harderian glands (2), heart (1), kidneys (2), large intestine [cecum, colon, rectum] (3), liver (1), lungs (1), lymph nodes [cervical, mesenteric] (2), mammary gland area (1), optic nerves (2), ovaries (2), pancreas (1), parathyroids (6), pituitary gland (3), prostate (1), salivary glands [sublingual, submandibular] (2), sciatic nerve (2), seminal vesicle (1), skeletal muscle (1), skin (1), small intestine [duodenum, jejunum, ileum] (3), spinal cord [cervical, thoracic, lumbar] (3), spleen (1), stomach (1), testes (2), thymus (1), thyroid gland (2), tongue (1), trachea (1), urinary bladder (1), uterus (3), vagina (1), and all gross lesions.

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Statistics

Analyses of routine samples were by Bartlett's test, or one-way ANOVA and Newman-Keuls test.

Tumor-bearing animals were categorized according to Peto *et al.* (1980) (1: incidental; 2: probably incidental; 3: probably fatal; 4: fatal), and analyzed using the positive and negative trend tests with respect to dose, and test for heterogeneity. Only p-values <0.05 for rare neoplasms, and <0.01 for common neoplasms were considered statistically significant.

The Exact Log Rank test was also used for group comparisons only when the number of tumor-bearing animals in a group was greater than 2, and for between-group comparisons of the number of premature decedents.

Results:

Mortality: 40 males and 69 females died over the course of the study. Causes of death are in Table C.5.b.1.

Group Sex	Contr. A		Contr. B		1		2		3	
	m	f	m	f	m	f	m	f	m	f
Died	4	4	0	2	3	6	1	9	3	7
Sacr.	4	9	9	8	4	14	5	6	7	4
Total	8	13	9	10	7	20	6	15	10	11
‡	16	26	18	20	14	40	12	30	20	22

No clear time- or dose-relationship was evident to implicate PPX as a causative factor.

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Table. C.5.b.1. Causes of Death or Sacrifice:

Controls (A&B)

<u>Males</u>	<u>17 deaths</u>	<u>Females</u>	<u>23 deaths</u>
neoplasia	- 11	neoplasia	- 16
pneumonia	- 2	cong. heart failure	- 1
dermatitis	- 1	pyometra/pyometritis	- 3
renal failure	- 1	pneumonia	- 1
cong. heart failure	- 1	multicell. necrosis	- 1
undetermined	- 1	pyelonephritis	- 1

Low-Dose

<u>Males</u>	<u>7 deaths</u>	<u>Females</u>	<u>20 deaths</u>
neoplasia	- 3	neoplasia	- 11
myodegeneration	- 1	pyometra/pyometritis	- 5
pyelitis/cystitis	- 1	ovarian abscesses	- 2
pneumonia	- 1	cong. heart failure	- 1
undetermined	- 1	liver abscesses	- 1

Mid-Dose

<u>Males</u>	<u>6 deaths</u>	<u>Females</u>	<u>15 deaths</u>
neoplasia	- 2	neoplasia	- 6
myocarditis	- 1	pyometra/pyometritis	- 5
undetermined	- 3	pyelonephritis	- 2
		pneumonia	- 1
		multicellular necrosis-	1

High-Dose

<u>Males</u>	<u>10 deaths</u>	<u>Females</u>	<u>11 deaths</u>
neoplasia	- 8	neoplasia	- 2
pneumonia	- 2	pyometra/pyometritis	- 9

Clinical: increased activity - HDF

Body Weight Gain (Fig. c.5.b.1):

- LDM - sig. decrease - weeks 1-12, 15, 19, 21-23, 25-82
- M & HDM - sig. decrease - all time points except HDM at wks 90-106

- LDF - sig. decrease - all time points except wks 14, 15, 90
- M & HDF - sig. decrease - all time points

Food Intake (Fig. C.5.b.2):

- Males - tendency for decrease; no sig. effect at end of study

- LDF - tendency for decrease; no sig. effect at end of study
- M & HDF - tendency for increase

Water Intake: No remarkable trends

Effective dose: The large ranges in means, particularly in females, are primarily the result of larger than intended intakes in the latter portion of the study (i.e., after week 74).

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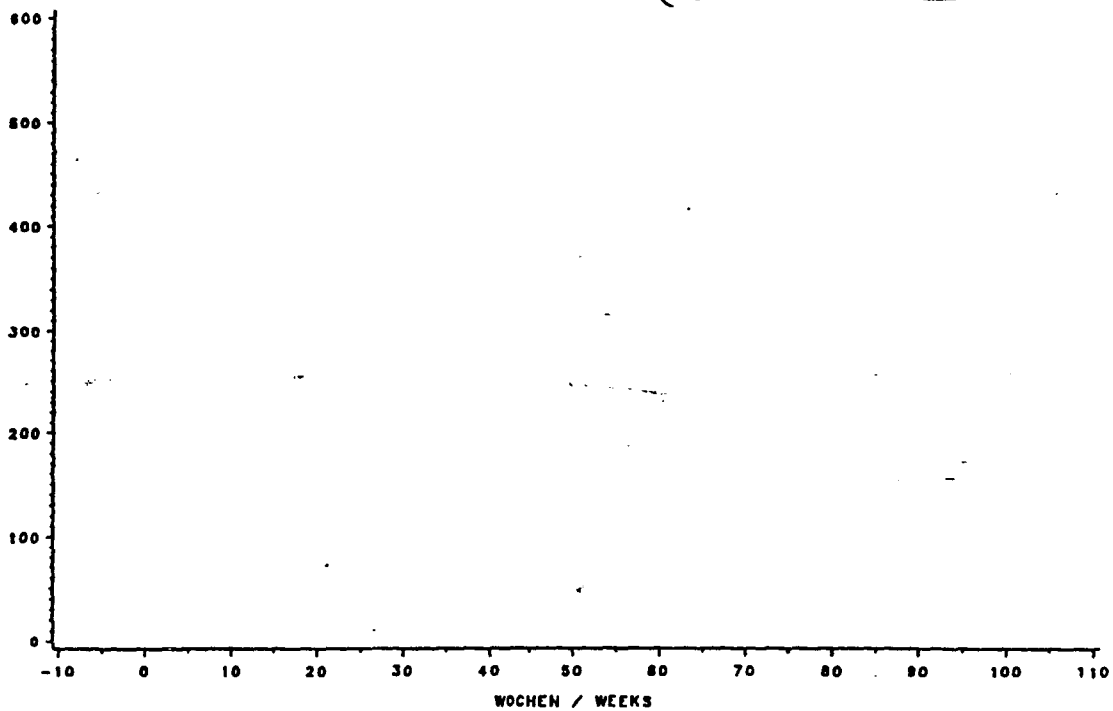
SKD 919 CL2Y : 104 - WEEK - STUDY IX RATS

EFFECTIVE DOSE

SEX		INTENDED DOSE					
		0.30 MG/KG		2.0 MG/KG		8.0 MG/KG	
		MEAN	%	MEAN	%	MEAN	%
FEMALE	MIN	0.24	79.7	1.76	88.1	6.83	85.4
	MAX	0.38	127.6	2.62	131.1	10.27	128.3
MALE	MIN	0.26	87.9	1.66	83.2	6.45	80.6
	MAX	0.34	114.3	2.38	118.8	9.70	121.2

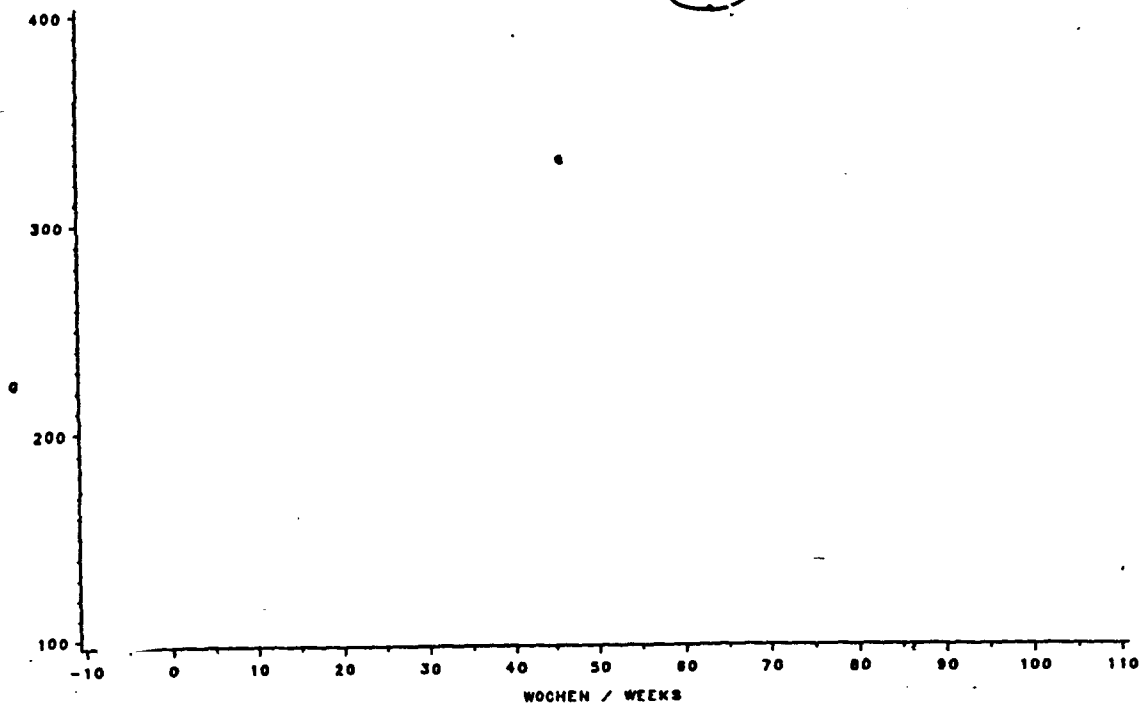
Fig. C.5.b.1.

SND 919 CL2Y 075 P.O. 108 WOCHEN -VERSUCH MIT MAENNL. RATTEN KGW-VERLAUF
 SND 919 CL2Y P.O. 108 WEEKS -STUDY IN MALE RATS BODYWEIGHT COURSE



0:- KONTROLLE CONTROL 1:- SND 919 CL2Y 0.3 MG/KG 2:- SND 919 CL2Y 2 MG/KG 3:- SND 919 CL2Y 8 MG/KG

SND 919 CL2Y 078 P.O. 108 WOCHEN -VERSUCH MIT WEIBL. RATTEN KGW-VERLAUF
 SND 919 CL2Y P.O. 108 WEEKS -STUDY IN FEMALE RATS BODYWEIGHT COURSE



0:- KONTROLLE CONTROL 1:- SND 919 CL2Y 0.3 MG/KG 2:- SND 919 CL2Y 2 MG/KG 3:- SND 919 CL2Y 8 MG/KG

Fig. C.5.b.2.

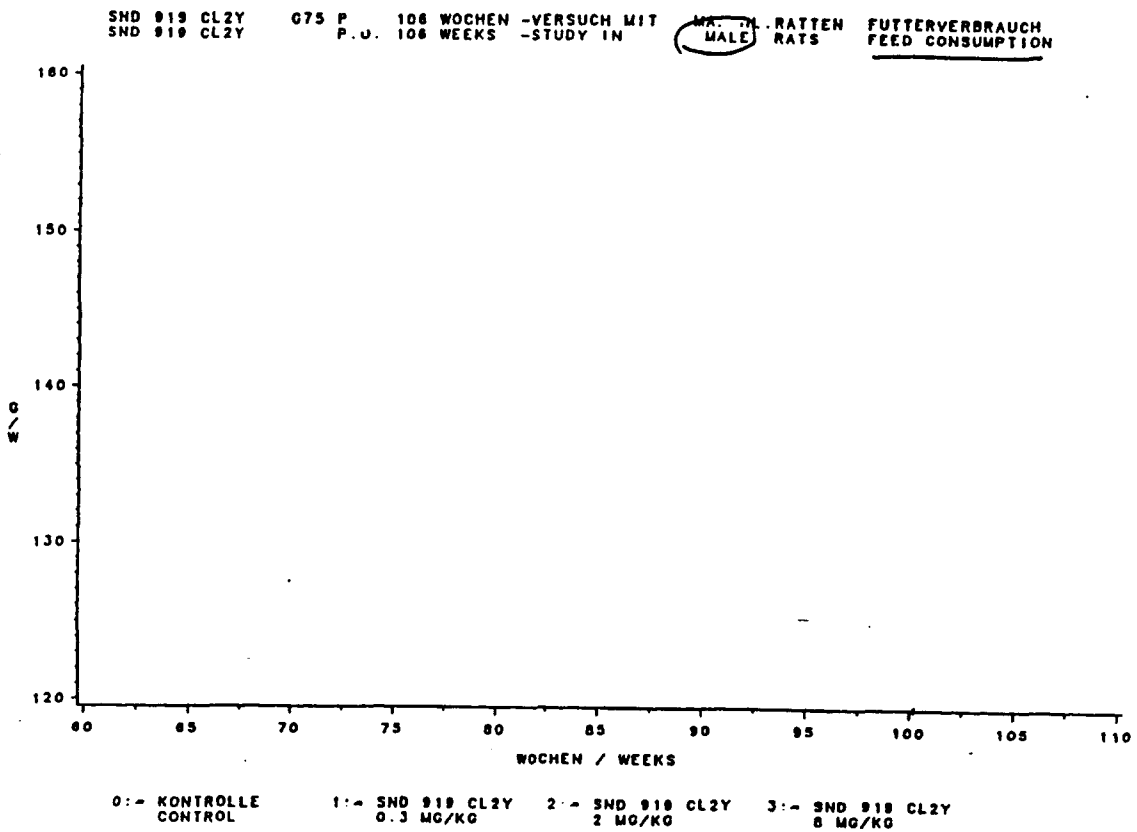
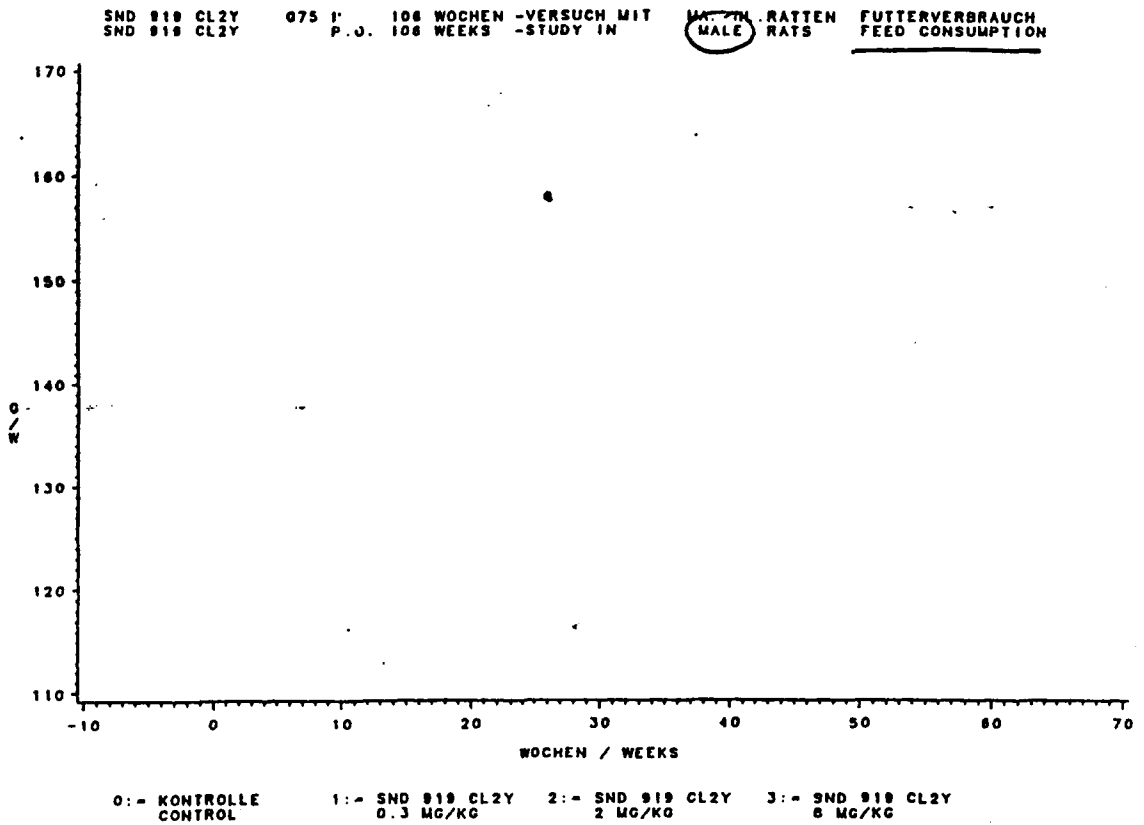
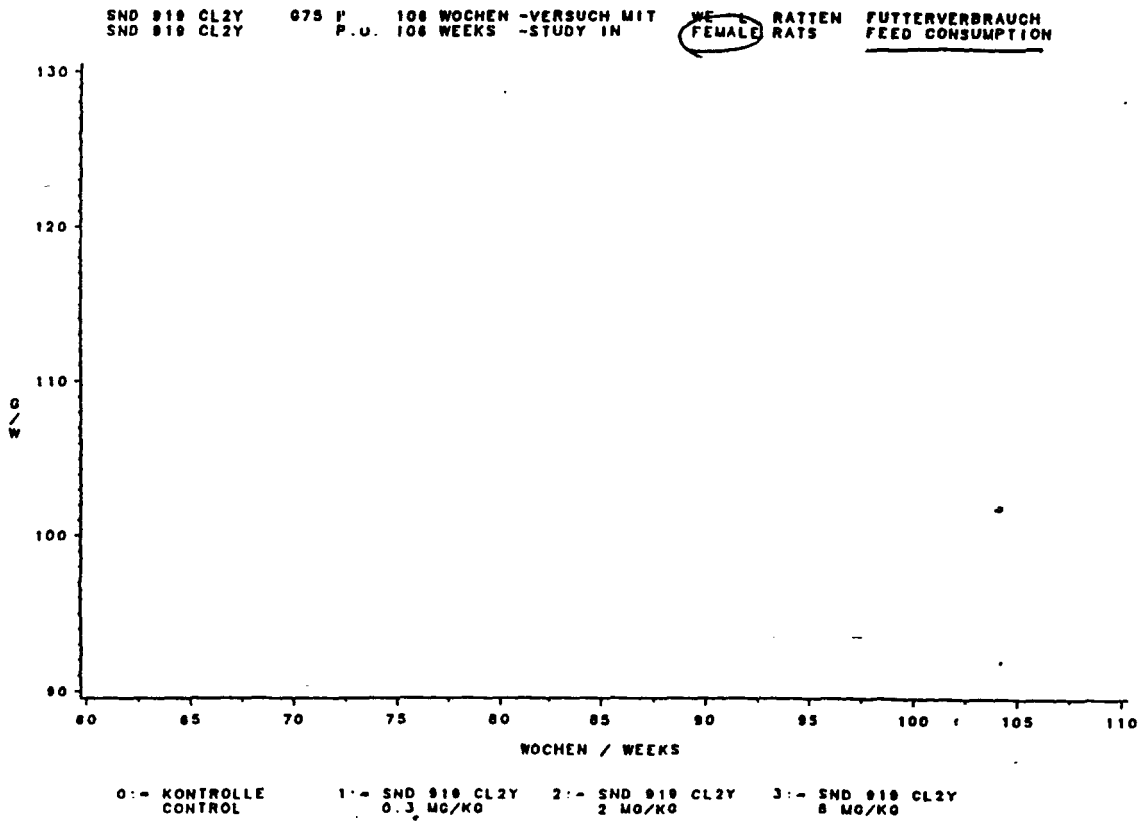
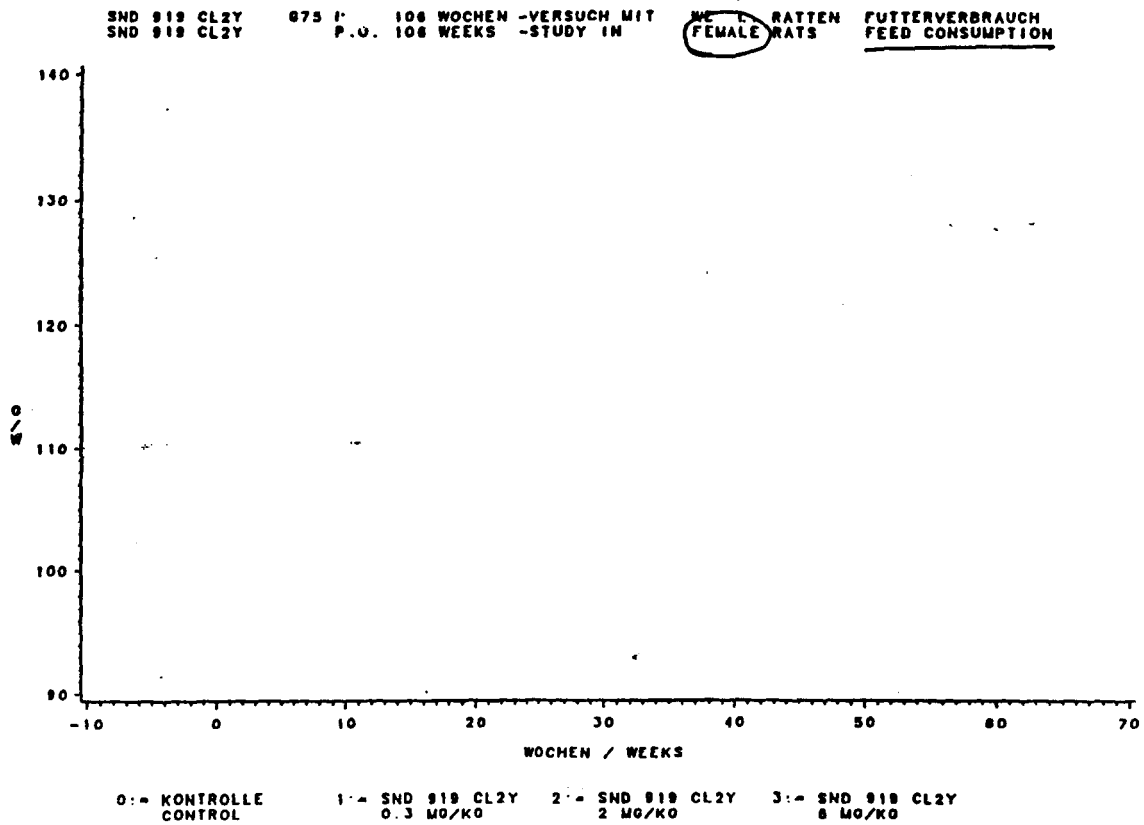


Fig. C.5.b.2. (cont.)



Hematology:

Group variations (at termination):

Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident.

increased RBC	-	MDF, HDF
increased Hct	-	MDF, HDF
increased MCH	-	HDM
decreased MCH	-	HDF
increased MCHC	-	HDM
decreased MCHC	-	L, M & HDF
decreased eosinophils	-	L, M & HDF
decreased monocytes	-	M & HDF

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Individual variations (at termination):

increased WBCs	-	1 Con M, 1 Con F 1 LDM, 1 LDF 1 MDM 1 HDM
anemia, slight	-	5 Con M, 7 Con F 2 LDF 2 MDM 2 HDF
" , marked	-	1 MDF
polycythemia	-	1 Con M 1 MDM 1 HDM

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Individual variations (in moribund sacrifices) (Tab. C.5.b.2):

Control
Animals

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
0514	.		.		.
0515	.		.		+++
0549	.		..		
4009	.		..		+++
4034	+++	+++			.
4047	.		monocytosis		
4535	.				.

LD

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
1503	.		.		
1519	..				+++
1525	.		.		.
1534	.		.		.
1536	+++	..			.
1537	..		..		..
1543	.		.		

MD

2005	..		..		.
2020	.		..		
2034	.		.		
2502	.		.		..
2507	.		.		..

HD

3009	.		eosinophilia		
3023	.		..		
3024	.				.
3040	.				.
3505	..		..		.
3521	.				.
3536	.		.		.

In a further 11 animals without changes in the total white blood cell count, a slight (nos. 0520, 1036, and 3050), moderate (nos. 1011, 1510, 1548, 2048, 2530, and 3523), or marked (nos. 0013 and 4517) anaemia was established.

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Prolactin Measurements (Tab. C.5.b.3):

An inverse dose-relationship was observed at both time points in both sexes except for MDM at week 60, which had higher levels than control males.

Tab. C.5.b.3.

Influence of SND 919 CL 2 Y on Prolactin Levels (ng/ml)
(week 60)

Dose (mg/kg)		Male	Female
0 (control)	mean	108.03	166.44
	s.d.	48.64	117.19
	n	4	4
0.3	mean	30.68	141.33
	s.d.	12.36	158.43
	n	7 **	6
2.0	mean	134.60	34.35
	s.d.	54.37	27.04
	n	10	9 *
8.0	mean	< 0.39	15.87
	s.d.	-	9.53
	n	9 **	9 **

Influence of SND 919 CL 2 Y on Prolactin Levels (ng/ml)
(week 69)

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Dose (mg/kg)		Male	Female
Control	mean	66.98	251.64
	s.d.	28.38	103.41
	n	4	4
0.3	mean	37.56	136.86
	s.d.	28.77	76.26
	n	7 *	8
2.0	mean	<18.59	86.38
	s.d.	-	46.07
	n	9 *	9 *
8.0	mean	< 0.66	27.76
	s.d.	-	24.75
	n	7 **	10 **

Plasma Concentrations (Tab. C.5.b.4): .

Increases in plasma concentrations were approximately dose-proportional. Levels at the 8.00 time-point (time of day) were higher than the 14.00 hr time-point. Measurements taken on different days within the same week did not appear to differ. There was a tendency for drug accumulation in males, but not females; this was particularly evident at week 100. There was no clear sex difference with the exception of the HD groups at week 100, where levels in males appeared to be higher.

(Note: There appears to be a discrepancy between the graphical and tabular data presentation. This likely occurred because 8 hr was used as a time point reference under two different scenarios - according to time of day (8.00 hr), and according to the number of hours after light onset (14.00 hr) (i.e., blood was collected at 8.00 hr (AM) - two hrs after light onset, and 8 hr after light onset - 14.00 hr). Analysis of the individual data indicates that the tabular presentation on pages 5/24/241-2 is the accurate presentation).

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study*

Sex	Dose (mg/kg)	Two Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	2.39	1.96	1.86	1.66	4.52	3.64
	2.0	14.86	16.08	19.30	19.54	22.66	18.80
	8.0	77.53	103.11	80.25	75.43	65.81	70.79
Male	0.3	1.71	1.60	2.12	2.13	3.18	2.85
	2.0	15.03	13.13	20.18	18.51	27.14	22.97
	8.0	77.20	79.44	93.21	70.11	140.66	133.95

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study*

Sex	Dose (mg/kg)	Eight Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	0.88	0.60	1.43	0.64	4.97	2.63
	2.0	3.73	7.09	6.73	5.93	26.10	19.50
	8.0	14.34	32.67	21.72	25.00	66.10	24.58
Male	0.3	0.34	0.75	0.96	1.03	1.51	1.38
	2.0	5.42	3.20	9.59	7.02	16.28	8.47
	8.0	24.59	25.23	57.09	47.30	65.52	47.17

Pathology:

Non-neoplastic lesions

Aside from the retinal degeneration findings which are discussed in other portions of this review, the most significant findings were primarily in reproductive tissues, putatively due to the prolactin-inhibiting effects of PPX. Macroscopic lesions in treated females included enlarged or discolored ovaries, and uterine dilatation with hemorrhagic or watery contents. Microscopic alterations in these tissues were enlarged corpora lutea, and chronic suppurative lesions in the uterus. These lesions are suggested to result from an estrogen:progesterone imbalance in the absence of prolactin, which normally stimulates progesterone secretion. In addition, the glandular pattern of mammary gland tissue changes from a female-type tubuloalveolar pattern to a more male-like lobuloalveolar pattern in the absence of prolactin. The Leydig cell hyperplasia is also suggested to be linked to prolactin inhibition. In the absence of prolactin, LH receptors will down-regulate leading to compensatory increases in serum LH, and supposedly hypertrophy of Leydig cells (this is a speculative mechanism; a question that arises is how the Leydig cells respond to LH if the receptors are reduced in density). The reduced incidence of adrenal medullary hyperplasia is suggested to result from PPX-inhibition of catecholamine release from adrenal chromaffin cells.

Changes in the incidences of microscopic lesions were summarized as follows:

Group/Incidence Rate (%)

	Lesion	0	4	1	2	3
I N C R E A S E	retinal degeneration (M)	0	0	0	51*	90*
	" (F)	2	0	0	21*	77*
	Leydig cell hyperplasia	70	78	80	92*	92*
	corpora lutea - enlarged	16	10	8	10	74*
	uterus, pyometra	4	10	14	24*	28*
	" , dilatation	18	47	34	58*	90*
	" , hemorrhage	2	10	18	24*	24*
	mammary gland - lobuloalveolar pattern (F)	0	0	0	0	34*
	mammary gland - mixed lobuloalveolar/tubuloalveolar pattern (F)	0	0	2	26	46
	hepatocellular fatty change (F)	6	4	4	34*	52*
	vagina, blood	0	4	4	2	10

D E C R	adrenal medullary hyperplasia (F)	47	57	55	30*	29*
	mammary gland - cystic change (F)	42	18	38	6*	0*
	pulmonary alveolar macrophages (F)	44	40	44	40	22*

Neoplastic Lesions:

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According to the sponsor's analysis, the only tumor that occurred with a higher frequency in PPX-treated animals than in controls was the Leydig cell adenoma. However, this tumor occurred with a high background incidence. The mechanism for increased incidence in PPX-treated animals is similar to that described for the Leydig cell hyperplasia.

Neoplasm	Group/Incidence rate (%)				
	0	4	1	2	3
Leydig cell adenoma - increase	26	18	34	44*	44*
mammary gland (all types) - decrease	14	8	12	0*	0*
pituitary adenoma - decrease (M)	8	20.4	12	0*	2*
" - " (F)	40	64	60	20.4 *	4.1*
benign adrenal medullary neoplasm - decrease (F)	38.8	65.3	32.7 *	8.7*	6.1*
thyroid C-cell carcinoma - decrease (F)	2	8	6	2	0
total # neoplasms - decrease (F)				*	*

The incidence of squamous papillomas in the cervix approached statistical significance by the Heterogeneity test ($p = 0.0548$), but the highest incidence of these tumors occurred at the lowest dose.

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Summary of Distribution of Neoplasms (Tab. C.5.b.6):

Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT ref. to III.E.210 ————3/9———— Page Number										
Name of finished product												
Name of active ingredient Pramipexole (SND 919 CL 2 Y)												
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data												
Ref. to document.: Volume:		Page:		to		Addendum No.:						
Report date: 05.05.94		Number: 675		Study period (years): 1989 - 1991								
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)			Frequency according to dose and sex (n)									
			(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Biometrical evaluation yes < x > no < y >			m	f	m	f	m	f	m	f	m	f
Number of animals evaluated			50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour											
BRAIN	GRANULAR CELL TUMOUR		1	1	-	-	-	2	1	-	-	-
	OLIGODENDROGLIOMA		-	1	-	-	1	-	-	-	-	-
LUNGS	BRON./ALV. CARCINOMA		-	1	-	1	1	-	-	-	-	-
TONGUE	HEMANGIOMA		-	-	-	-	1	-	-	-	-	-
	GRANULAR CELL TUMOUR		-	-	-	1	-	-	-	-	-	-
	SARCOMA, NOS		-	-	-	-	-	-	-	-	1	-
JEJUNUM	LEIOMYOMA		-	-	-	-	-	-	-	1	-	-
	ADENOCARCINOMA		-	-	-	-	-	1	-	-	-	-
	LEIOMYOSARCOMA		-	-	-	1	-	-	-	-	-	-
ILEUM	LEIOMYOSARCOMA		-	-	-	-	-	1	-	-	-	-
STOMACH	ADENOCARCINOMA		1	-	-	-	-	-	-	-	-	-
CAECUM	ADENOCARCINOMA		-	-	-	-	-	-	1	-	-	-
LIVER	HEPATOC. ADENOMA		3	-	4	1	3	1	4	1	1	-
	CHOLANGIOMA		-	-	-	2	-	1	-	1	-	1
	HEPATOC. CARCINOMA		3	-	2	-	5	-	1	-	2	-
	CHOLANGIOCARCINOMA		-	-	1	-	-	-	-	-	-	-
PANCREAS	ISLET-CELL ADENOMA		3	-	-	-	-	-	1	-	-	-
	ACINAR CARCINOMA		-	-	-	-	-	1	-	-	-	-

* P < 0.05 ** P < 0.01

Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT		ref. to III.E.210		4/9 Page Number								
Name of finished product														
Name of active ingredient Pramipexole (SND 919 CL 2 Y)														
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data														
Ref. to document.: Volume: Page: to Addendum No.:		Report date: 05.05.94 Number: 675		Study period (years): 1989 - 1991										
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)					Frequency according to dose and sex (n)									
					(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Biometrical evaluation yes <x> no <y>					m	f	m	f	m	f	m	f	m	f
Number of animals evaluated					50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour													
KIDNEYS	TUBULAR ADENOMA				-	1	-	-	-	-	-	-	1	-
	NEPHROBLASTOMA				1	-	-	-	-	-	-	-	-	-
	LIPOSARCOMA				-	1	1	-	-	-	-	-	-	-
URINARY BLADDER														
	TRANSIT. PAPILLOMA				-	2	-	1	-	-	-	1	1	1
	SQUAMOUS PAPILLOMA				-	-	-	-	-	-	-	-	-	1
	TRANSIT. CARCINOMA				-	-	-	-	-	-	1	-	1	-
SQUAMOUS CARCINOMA				1	-	-	-	-	-	-	-	-	-	-
TESTES	LEYDIG CELL ADENOMA**				13	-	9	-	17	-	22	-	22	-
OVARIES	GRANULOSA CELL TUMOR (B)				-	5	-	1	-	1	-	1	-	1
	THECA CELL TUMOR				-	-	-	1	-	2	-	1	-	-
	LUTEOMA				-	-	-	4	-	-	-	1	-	-
	CARCINOMA, NOS				-	-	-	-	-	-	-	1	-	-
UTERUS	ADENOMA				-	-	-	1	-	-	-	-	-	-
	LEIOMYOMA				-	-	-	-	-	-	-	-	-	1
	HEMANGIOMA				-	-	-	-	-	-	-	2	-	1
	GRANULAR CELL TUMOR				-	-	-	1	-	1	-	-	-	-
	ADENOCARCINOMA				-	2	-	2	-	2	-	2	-	1
	HEMANGIOSARCOMA				-	-	-	1	-	-	-	3	-	1

* P < 0.05 ** P < 0.01 (positive trend)

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Name of company BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT
Name of finished product	
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	
	ref. to III.E.210
	5/9
	Page Number

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: 675 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Bimetrical evaluation yes < x > no < >		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
UTERUS	LEIOMYOSARCOMA	-	-	-	-	-	1	-	-	-	1
CERVIX	SQUAMOUS PAPILLOMA	-	1	-	1	-	5	-	3	-	1
	SERIAL SARCOMA	-	3	-	1	-	3	-	4	-	1
	SQUAMOUS CARCINOMA	-	-	-	1	-	-	-	-	-	-
PERIUTERINE											
GLAND	ADENOMA m: **, f: ***	4	20	10	32	6	30	-	10	1	2
THYROID											
GLAND	FOLLICULAR ADENOMA	-	-	1	-	-	-	-	-	-	1
	C CELL ADENOMA	3	5	2	7	2	4	5	1	3	9
	GANGLIONEUROMA	1	-	-	-	-	-	-	-	-	-
	FOLLICULAR CARCINOMA	-	-	-	1	-	1	1	-	-	-
	C CELL CARCINOMA f: *	2	1	2	4	3	3	3	1	1	-
PARA-THYROID											
GLANDS	ADENOMA	-	1	2	2	2	3	1	-	1	-
ADRENAL											
CORTEX	ADENOMA	1	4	1	-	1	-	-	2	-	1
	CARCINOMA	1	-	-	-	-	-	-	1	-	1

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

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Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG Name of finished product Name of active ingredient Framipexole (SND 919 CL 2 Y)		TABULATED STUDY REPORT ref. to III.E.210 — 6/9 — Page Number									
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data											
Ref. to document.: Volume: Page: to Addendum No.:		Report date: 05.05.94 Number: 675 Study period (years): 1989 = 1991									
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Bimetric evaluation yes < x > no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr. B		-(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
ADRENAL											
MEDULLA	MEDULLARY TUMOUR (B) f: ***	10	19	13	32	7	16	9	4	6	3
	MEDULLARY TUMOUR (M)	2	-	2	1	1	-	-	-	1	-
THYMUS	THYMOMA	-	-	-	-	-	1	-	-	-	-
MESENT.											
LYMPH NODE	HEMANGIOMA	-	-	5	1	2	-	3	1	4	-
HEMOLYMPH.											
SYSTEM	HISTIOCYTIC SARCOMA	-	1	1	1	-	1	-	1	-	-
	MALIGNANT LYMPHOMA	3	1	8	4	6	3	1	1	4	3
SPLEEN	HEMANGIOSARCOMA	1	1	-	1	-	1	1	-	2	-
SUBLINGUAL											
GLAND	ACINAR CARCINOMA	-	-	-	-	-	1	-	-	-	-
MAMMARY											
GLAND AREA	FIBROADENOMA	-	5	-	2	-	2	-	-	-	-
	ADENOMA	-	1	-	-	-	-	-	-	-	-
	PAPILL. CYSTADENOMA	-	-	-	-	-	1	-	-	-	-
	CARCINOMA	-	1	-	2	-	3	-	-	-	-
BONE	GRANULAR CELL TUMOUR	-	1	-	-	-	-	-	-	-	-
	SCHWANNOMA (M)	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

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Tab. C.5.b.6. (cont.)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG Name of finished product	TABULATED STUDY REPORT ref. to III.E.210 —7/9— Page Number
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
 Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no <y>		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
BONE											
MARROW	HEMANGIOSARCOMA	-	-	1	-	-	-	-	-	-	-
SUBMANDIB.											
GLAND	SARCOMA, NOS	-	-	2	-	-	-	-	-	-	-
SKIN	KERATOACANTHOMA	2	-	2	-	1	-	-	-	-	-
	TRICHOFOLLICULOMA	-	-	1	-	-	-	-	-	-	-
	SEBACEOUS ADENOMA	-	-	1	-	-	-	-	-	-	-
	TRICHOLEMMA	-	-	-	-	-	-	1	-	-	-
	LIPOMA	-	-	1	-	-	-	-	-	-	-
	FIBROMA	1	-	1	-	1	-	-	-	-	-
	SQUAMOUS CARCINOMA	-	-	-	-	-	1	-	-	2	-
	BASAL CELL CARCINOMA	-	-	1	-	2	-	-	-	-	2
	SEB/SQUAM. CARCINOMA	1	-	-	-	-	1	-	-	-	-
	SCHWANNOMA (M)	-	-	-	-	-	-	-	-	2	-
	HEMANGIOSARCOMA	-	-	1	-	-	-	-	1	-	1
	MAST CELL TUMOUR	-	-	-	-	-	-	-	-	-	1
SARCOMA, NOS	-	-	1	-	-	-	-	-	-	1	
FIBROSARCOMA	-	-	-	-	-	-	1	-	-	-	

* p < 0.05 ** P < 0.01

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TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT	
~~Name of finished product~~	ref. to III.E.210	
~~Name of active ingredient~~ Pramipexole (SND 919 CL 2 Y)	— 8/9 — Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
 Report date: 05.05.94 Number: 675 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no <>	Frequency according to dose and sex (n)									
	(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
	m	f	m	f	m	f	m	f	m	f
Number of animals evaluated	50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour									
ADIPOSE										
TISSUE	LIPOMA									
	1	-	2	1	-	-	1	-	-	-
EARS	HEMANGIOMA									
	-	-	-	-	1	-	-	-	-	-
TAIL	SCHWANNOMA									
	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01

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TREND TEST STATISTICS ON NEOPLASTIC LESIONS
P VALUES FOR POSITIVE AND NEGATIVE TRENDS

DOSE GROUPS : 0, 1, 2, 3, 4 SEX: MALE
STATUS AT NECROPSY: NO INCL. +

ORGAN/TISSUE	TYPE OF NEOPLASM	POSITIVE TREND	NEGATIVE TREND
LIVER	HEPATOC. ADENOMA	-	0.1236
LIVER	HEPATOC. CARCINOMA	-	0.2608
PANCREAS	ISLET-CELL ADENOMA	-	0.1567
TESTES	LEYDIG CELL ADENOMA	0.0057	-
PITUITARY	ADENOMA	-	0.0066
THYROID GLAND	C CELL ADENOMA	0.3635	-
THYROID GLAND	C CELL CARCINOMA	-	0.2286
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	-	0.1110
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	-	0.2998
MESENT. LYMPH NODE	HEMANGIOMA	0.1590	-
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	-	0.2715

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TREND TEST STATISTICS ON NEOPLASTIC LESIONS
P VALUES FOR POSITIVE AND NEGATIVE TRENDS

DOSE GROUPS : 0, 1, 2, 3, 4 SEX: FEMALE
STATUS AT NECROPSY: NO INCL. +

ORGAN/TISSUE	TYPE OF NEOPLASM	POSITIVE TREND	NEGATIVE TREND
OVARIES	GRANULOSA CELL TUMOR	-	0.1607
OVARIES	LUTEOMA	-	0.1026
CERVIX	SQUAMOUS PAPILLOMA	-	0.2051
CERVIX	STROMAL SARCOMA	-	0.2054
PITUITARY	ADENOMA	-	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0858	-
THYROID GLAND	C CELL CARCINOMA	-	0.0382
PARATHYROID GLANDS	ADENOMA	-	0.0558
ADRENAL CORTEX	ADENOMA	-	0.3407
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	-	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.4648	-
MAMMARY GLAND AREA	FIBROADENOMA	-	0.0234
MAMMARY GLAND AREA	CARCINOMA	-	0.0566
MAMMARY GLAND AREA	(COMBINED NEOPLASMS)	-	0.0032
UTERUS	HEMANGIOSARCOMA	0.3030	-

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: MALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
LIVER	HEPATOC. ADENOMA	0.5938
LIVER..	HEPATOC. CARCINOMA	0.3381
PANCREAS	ISLET-CELL ADENOMA	0.4029
TESTES	LEYDIG CELL ADENOMA	0.0100
PITUITARY	ADENOMA	0.0071
THYROID GLAND	C CELL ADENOMA	0.5848
THYROID GLAND	C CELL CARCINOMA	0.7685
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	0.3218
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	0.4930
MESENT. LYMPH NODE	HEMANGIOMA	0.7732
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.2421

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: FEMALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
OVARIES	GRANULOSA CELL TUMOR	0.5104
OVARIES	LUTEOMA	0.3011
UTERUS	HEMANGIOSARCOMA	0.1430
CERVIX	SQUAMOUS PAPILLOMA	0.0548
CERVIX	STROMAL SARCOMA	0.4969
PITUITARY	ADENOMA	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0723
THYROID GLAND	C CELL CARCINOMA	0.2787
PARATHYROID GLANDS	ADENOMA	0.0755
ADRENAL CORTEX	ADENOMA	0.4655
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.7136
MAMMARY GLAND AREA	FIBROADENOMA	0.0632
MAMMARY GLAND AREA	CARCINOMA	0.0887

C.6. Local Tolerance and Allergenic Studies

Sponsor Volumes: 1.49-1.54

Summary:

PPX was relatively free of locally irritating or allergenic effects. In rabbits, PPX caused mild ocular effects only after repeated treatment for 4 weeks, and mild irritation of abraded skin after repeated applications. PPX was considered a mild sensitizing agent in guinea pigs. PPX did not induce hemolysis in human blood.

Study Results:

- C.6.a. Rabbit Eye Irritation (single dose)- 0.1g PPX (formulation not specified) into one eye did not produce local ocular irritation.
- C.6.b. Rabbit Eye Irritation (multiple doses) - 0.05, 0.1, 0.25, and 0.5% PPX in 0.1 ml (8 times daily for 3 days) did not produce local ocular irritation (high dose of 0.5% = 0.5 mg/dose).
- C.6.c. Rabbit Eye Irritation (4-week study) - 0.00625, 0.05, and 0.5% in 50 µl applied 6 times daily to the conjunctival sac caused a mild to moderate increase in conjunctival secretion and mild reddening. The effect was not concentration-related.
- C.6.d. Dermal Irritation in Rabbits (single dose) - Topical application of 0.5g/0.5 ml PPX to shaved skin area did not produce irritation, erythema or edema.
- C.6.e. Dermal Irritation in Rabbits (multiple doses) - 0.1g/0.1 ml PPX was applied topically to a shaved intact or a shaved abraded skin area once daily for 5 days. No irritation occurred on the intact area. Mild irritation with erythema and eschar occurred on the abraded area.
- C.6.f. Dermal Irritation in Rabbits (4-week patch application) - Application of a patch containing 10.75 mg PPX free base for 4 weeks to shaved areas caused slight irritation. Irritation was also observed in placebo-treated animals, and thus may have resulted from mechanical trauma due to repeated patch removal and replacement.
- C.6.g. Paravenous Injectable Tolerability in Rats - 0.2 ml of an 0.1% PPX solution was injected medially and laterally to the jugular vein. Slight hemorrhages and edema in the area were observed between 1-24 hr after treatment.
- C.6.h. Acute Intravenous Tolerance in Rabbits - 0.2 ml of an 0.1% PPX solution was injected into the rabbit ear vein. Slight erythemas were observed in 3 of 4 animals, and bluish-red discoloration in 2 of 4 animals within the first few days of administration. Saline injection also caused 2 cases of erythemas.

- C.6.i. Acute Intra-arterial Local Tolerance in Rabbits - 0.5 ml of an 0.1% PPX solution was injected into the rabbit ear central artery. Slight erythemas were observed in 4 of 4 animals, and bluish-red discoloration in 3 of 4 animals. Similar effects were observed in saline-treated controls (2 of 4 cases of erythemas, 3 of 4 cases of discolorations).
- C.6.j. Skin Sensitization in Guinea Pigs - Animals were sensitized by six intradermal injections of 1% PPX free base (0.1 ml) into the dorsal skin. On days 8-10, 12.5 mg PPX was applied to the same area. On day 22, the animals were challenged by application of 12.5 mg PPX to an area of the left flank. A contact dermatitis response was noted in 5 of 20 animals. On day 36, animals were rechallenged with 6.25 mg PPX. Four of 20 animals had an allergic contact dermatitis, but only one of these animals had the reaction previously. Thus, PPX was considered a mild sensitizing reagent.
- C.6.k. Skin Sensitization in Guinea Pigs to Patch Exposure - Animals were sensitized to the PPX patch exposure (contains mg PPX free base) by either nine applications over 3 weeks or 15 applications over 5 weeks (6 hrs per application). Animals were challenged on day 29 and rechallenged on day 43. No allergic contact dermatitis and no primary skin irritations occurred.
- C.6.l. Test for Hemolytic Effect - An 0.1% solution of PPX (HCl) did not induce hemolysis in preparations of citrated human blood.

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D. PHARMACOKINETIC/ADME STUDIES

Conducted by : Boehringer Ingelheim KG
Depts. of Exp. Pathol. & Toxicol., Pharmacokinetics and Metabolism,
and Biochemistry
D-6507 Ingelheim am Rhein
West Germany

1. Rats

- a. Biochemical investigations with [¹⁴C]-SND 919 CL2Y in rats (absorption, distribution, excretion, metabolism).
- b. Whole body autoradiographic studies with SND 919 CL2Y in rats.
- c. Studies on the placental transfer and on the crossing of the blood-brain barrier of [¹⁴C]-SND 919 CL2Y in the rat.
- d. Pramipexole: Steady-state concentrations in brain, liquor, and plasma of male rats after oral administration of 0.5 mg/kg (once per day) over 8 days.
- e. Excretion of [¹⁴C]-SND 919 CL2Y into rat milk after a single oral dose of 0.5 mg/kg.

2. Rabbit

- a. Pharmacokinetics and metabolism [of pramipexole] in the rabbit after intravenous and oral administration of a single dose of 1 mg/kg.

3. Monkeys

- a. Plasma concentrations and renal excretion in Rhesus monkeys after administration of three single intragastric doses (0.1, 0.5 and 1.0 mg/kg) and one intravenous dose (0.5 mg/kg).

4. Humans

- a. Pharmacokinetics and metabolism of [¹⁴C]-pramipexole after single intravenous and oral doses in healthy volunteers.
- b. A single dose tolerance and pharmacokinetic study of intravenous pramipexole in healthy male volunteers.

5. Multiple Species

- a. Balanced excretion studies and metabolic profile following oral administration of [¹⁴C]-SND 919 CL2Y to the mouse, rat, rabbit, dog, monkey and pig.
- b. Studies on the metabolism of pramipexole including experiments to detect a potential metabolic inversion at the optical active center of the molecule.

D.1. Rat Pharmacokinetics

D.1.a. Biochemical investigations with [¹⁴C]-SND 919 CL2Y in rats (absorption, distribution, excretion, metabolism).

Document #(s): BI Document U88-0097
Upjohn TR 7256-94-035

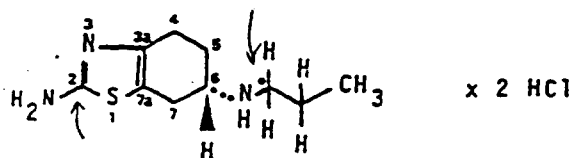
Sponsor Volume: 1.56

Summary:

Radiolabeled PPX was administered to Wistar rats at doses of 0.25 mg/kg i.v. or ... mg/kg, p.o. Plasma levels and excretion balances were determined. PPX was absorbed rapidly and nearly completely following oral administration. Elimination of radiolabel is relatively slow, and not complete by ... hr. The parent compound is eliminated primarily by renal excretion, whereas the fecally excreted portion is primarily polar metabolites of biliary origin. Plasma protein binding was relatively low in rat and other species (dog, pig, monkey, man).

Methods:

Substance administered: [¹⁴C]-pramipexole labeled at the 2-position of the thiazole ring, or C1 of the propyl group



* = ¹⁴C labelling
(Active substance carrying the ¹⁴C label in the
.2 position of the thiazole ring was used in some
preliminary experiments.)

Dosing Regimen:

Study	Dose (mg/kg)	Route of Administration	No. of Animals N	Batch No.*
Exhalation of ¹⁴ CO ₂	0.24	IV	2	1
"	0.6	IV	3	2
"	0.5	IV	2	3
Blood levels	0.4	Oral	10	1
Plasma levels	2.5	IV	5	-
Excretion	0.25	IV	11	1
Excrétion	0.01	Oral	4	1
"	0.1	Oral	4	
"	1.4	Oral	4	
"	10.8	Oral	4	
"	79.1	Oral	4	
Excretion (bile)	0.28	IV	4	3

Parameters measured: exhalation, excretion balance (urine, feces), blood levels, plasma protein binding (different species), biliary excretion, metabolite profiles (urine, feces)

Results:

Exhalation study: With the propyl-C radiolabelled material, 4.6% of an i.v. dose was exhaled as CO₂ during 0-24 hrs postdose. With the thiazole ring-labeled material, less than 1% was eliminated by this route. Thus, the ring-labeled material was used for subsequent studies.

Excretion balance: Average elimination (% dose) during 0-96 hr collection:

		<u>Urine</u>	<u>Feces</u>
intravenous	0.25 mg/kg	52.9	36.5
oral	0.01 "	51.9	28.7
	0.1 "	64.8	38.3
	1.4 "	48.2	41.2
	10.8 "	52.1	29.3
	79.1 "	43.6	25.8

No effect of dose or sex

Biliary Excretion: % of iv dose in 0-24 hr (ca. equivalent to fecal excretion).

PK parameters:

Blood [¹⁴C]-Activity after Oral dosing (0.4 mg/kg)

		AUC (ng.ml/hr)	MRT (hr)	Cl (ml/min)
Single dose	Male	469	9.8	3.9
	Female	581	19.0	3.4
After 3 doses	Male	537	16.0	3.4
	Female	577	14.6	3.5

Parent Compound after IV dosing (2.5 mg/kg)

	AUC (ng.ml/hr)	MRT (hr)	Cl (ml/min)	t _{1/2} (α) (min)	t _{1/2} (β) (hr)	Vd (l)
2m/3f	840	1.5	13	4.0	1.2	1.2

Plasma Protein Binding: Relatively low (%) in all species tested (rat, dog, pig, monkey, man)

Metabolite Profiles:

- Urine: 0-24 hr collection.
Chromatographic profiles are similar irrespective of route, dose and sex.
Parent accounts for % of radioactivity; metabolites are %.
- Bile: 0-6 or 0-12 hr collection.
Parent accounts for $\leq 5\%$ of radioactivity.
9-11 metabolites are present; % are polar.
- Feces: 0-24 hr collection.
Parent accounts for $\leq 5\%$ of radioactivity.
% polar metabolites.

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D.1.b. Whole body autoradiographic studies with SND 919 CL2Y in rats.

Document #(s): BI Document U86-0727
Upjohn TR 7256-95-018

Sponsor Volume: 1.59

Summary:

After i.v. administration of 1.3 mg/kg [¹⁴C]-pramipexole, radioactivity was rapidly distributed. Aside from the gut, the highest tissue concentrations were found in the lacrimal, salivary, and adrenal glands, kidney, pancreas, bone, liver and lung. The significant levels of radioactivity in the small intestine after i.v. administration is indicative of biliary excretion of PPX or its metabolites. Brain levels of radioactivity peaked at 2 hrs, and were detectable up to 6 hrs. At 24 hrs, radioactivity was still detected in liver, kidney, and adrenals.

Two hrs after p.o. administration of 1.3 mg/kg, a similar pattern of distribution was observed, although levels of radioactivity were lower. At 24 hrs, radioactivity was still present in the lacrimal, salivary, adrenal glands, kidney, and liver.

Methods:

Substance administered: [¹⁴C]-pramipexole labeled at the of the propyl group; Batch I, 7400 MBq/g (200 μCi/mg)

Dosages/Routes: 1.3 mg/kg (ca. 1.57 MBq/animal) administered i.v. (tail vein) or p.o.

Animals: Male Chbb:THOM Wistar rats, 150-170 g.

Sacrifice times: i.v.: 10 min, 2, 4, 6, 24 hr
p.o.: 30 min, 2, 4, 6, 24 hr

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Tissue Preparation: Animals were sacrificed, frozen and sectioned for autoradiography by standard techniques. Autoradiogram exposure time was 7 days. Tissue uptake of radioactivity was determined with a microscope photometer; field sections were 100 μm in diameter. Intensities of light penetration, which decrease with uptake of radioactivity, was scored on a scale of 0-7.

Results:

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The following table summarizes the experimental results.

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Tab. 1: Photometric analysis of the whole body autoradiograms after
 i.v. and p.o. administration of SMD 919 CL 2 Y
 0 = maximum transmission = no radioactivity
 7 = minimum transmission = maximum radioactivity

Organ	i.v.					p.o.				
	30'	2 h	4 h	6 h	24 h	30'	2 h	4 h	6 h	24 h
Pancreas	6	4	2	0	0	2	2	0	0	0
Blood	2	1	1	0	0	1	0-1	0	0	0
Brown nuchal fat	4	2	1	0	0	1	2	0	0	0
Contents of large intestine	0	1	7	upto 7	upto 7	0	2	7	upto 7	upto 7
Mucosa of large intestine	4	2	-	0	0	1	0	0	0	0
Contents of small intestine	upto 7	7	upto 7	upto 6	0	upto 7	7	upto 7	upto 7	upto 6
Mucosa of small intestine	5-5	3	3	0	0	0	0	0	0	0
Fat	1	0	0	0	0	0	0	0	0	0
Brain	3	4	3	1-2	0	0-1	2	1	0-1	0
Urine	7	6	2	1	0	4	4	2	0	0
Skin	3	2	2	1	0	1	2	1	0	0
Heart	4	2	1	0	0	1	1	0	0	0
Testes	2	3	2	2	0	0	2	0	0	0
Bone	5	4	-	0	0	1	-	0	0	0
Liver	5	4-5	5	3	2	3	4	3	3	2
Lung	5	2	1	0	0	1	2	0	0	0
Gastric contents	upto 7	7	7	upto 6	0	7	7	7	7	upto 6
Gastric mucosa	4-7	2	2	2	0	-	0	1	2	0
Spleen	5	4	2	1	0	1	3	0	0	0
Muscle	4-5	2	1	0	0	1	2	0	0	0
Adrenal medulla	7	4	3	1	1	2	3	1	1	0-1
Kidney	6	4	3	1-2	1	2	3	2	1	1
Rib	5	3	1	0	0	1	3	0	0	0
Spinal marrow	3	3	1	0	0	0-1	2	1	0	0
Thyroid	2	1	1	0	0	0-1	2	1	0	0
Salivary glands	6-7	5-6	3-4	2	0	3	4-5	3	2	1
Thymus	4	3	2	0	0	1	3	0	0	0
Lacrimal gland	5	4	3	2	0	2	5	2	1	1
Vertebra	5	4	1	0	0	1	3	0	0	0
Dental germ	-	3	1	0	0	1	2	0	0	0
Intervertebral disks	3	1	0	0	0	0	1	0	0	0

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D.1.c. Studies on the placental transfer and on the crossing of the blood-brain barrier of [¹⁴C]-SND 919 CL2Y in the rat.

Document #(s): BI Document U94-0359
Upjohn TR 7256-94-103

Sponsor Volume: 1.59

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Summary:

[¹⁴C]-PPX (1.0 mg/kg) was administered to pregnant Wistar rats by the i.v. or oral routes, and its capacity to penetrate the blood:brain barrier or blood:placental barrier was determined. By either route, PPX and/or its metabolites rapidly crossed both the blood:placental and blood:brain barriers. Concentrations of label tended to be higher in the placenta than in maternal blood or in the fetus. Highest fetal tissue concentrations of radiolabel were detected in the liver. In both dams and fetuses, brain levels are higher than plasma levels for up to 6 hrs postdose.

Methods:

Substance administered: [¹⁴C]-pramipexole labeled at the 2-position of the thiazole ring; Batch 7, 7800 MBq/g (210 μCi/mg). Cold substance was Batch II.

Dosages/Routes: 1.0 mg/kg (ca. 1.57 MBq/animal) administered i.v. (tail vein) or p.o.

Animals: 44 pregnant Chbb:THOM Wistar rats

Design: Radioactivity distribution was assessed by tissue analysis with liquid scintillation spectroscopy, and by whole body autoradiography (WBAR). In the tissue analysis studies, animals (n=2 per condition) were administered drug by i.v. or p.o. routes on day 14 or 19 of gestation and sacrificed at for time points (i.v.: 1, 3, 6 or 24 hr; p.o.: 30 min, 3, 6 or 24 hr). For the WBAR study, rats (n=1) were sacrificed at 10 min, 6 or 24 hrs after i.v., and 1, 6 or 24 hrs after p.o. treatments on day 14 or 19 of gestation.

Analysis: WBAR studies were conducted according to standard procedures. Tissue analyses were conducted on the following tissues:

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14th day of pregnancy:	blood	-	dam
	plasma	-	dam
	heart	-	dam
	liver	-	dam
	muscle	-	dam
	brain	-	dam
	uterus		
	placenta		(3-4 placentas were pooled as one sample and measured)
	amniotic fluid		
	fetus		(4 fetuses were measured individually per animal)

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19th day of pregnancy:	blood	-	dam
	plasma	-	dam
	heart	-	dam
	liver	-	dam
	muscle	-	dam
	brain	-	dam
	uterus		
	placenta		(4 placentas were measured individually per animal)
	amniotic fluid		
	fetus		(4 fetuses were measured individually per animal)

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blood	-	fetus
liver	-	fetus (livers of 3-4 fetuses)
fetal tissue		(muscle and bones of the hind limbs)
fetal brain		

Results:

WBAR Studies:

After intravenous treatment, radioactivity distributed rapidly, and crossed the placental barrier within 10 min. Label was detected in the fetus up to 6 hr postdose. Levels appeared to be higher in the placenta than in the fetus. Low levels were detectable within the placenta and fetus at 24 hrs.

A similar pattern of distribution was observed at 6 and 24 hrs after oral administration.

Isolated Tissue Analyses:

Intravenous studies: Levels of radioactivity appeared to be higher in the placenta than in the fetus on both day 14 and day 19. Maternal blood and liver concentrations were higher than in corresponding fetal tissues. Within the fetus, highest concentrations of radiolabel were detected in liver. Low levels of radioactivity were present in amniotic fluid. Up to six hrs postdose, brain concentrations of radiolabel were higher than blood concentrations in both the dams and fetuses. The calculated half-life of tissue elimination in fetuses is slightly longer than in the dams.

Spectroscopic radioactivity determinations in isolated tissues are summarized in the Tables D.1.c.1-4.

Table ●: Comparison of the concentration values (ng equivalent/g blood or D.1.c.1 ng equivalents/g organ) in the blood of the dams, in the placentas and in the total fetus after i.v. administration of [¹⁴C]-SND 919 CL 2 Y (days 14 and 19 of pregnancy, mean values each of 2 animals)

measuring time	day 14			day 19		
	blood dam	placenta	fetus	blood dam	placenta	fetus
10 min	326.16	623.36	406.82	430.20	707.70	287.70
3 h	114.88	255.81	102.99	147.43	433.09	179.64
6 h	74.29	106.37	80.92	81.27	138.92	69.43
24 h	37.71	35.52	23.71	40.28	52.97	29.16

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Table ●: Comparison of the concentration values (ng equivalents/g blood) in D.1.c.2 the maternal blood and in the fetal blood after i.v. administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

measuring time	day 19		
	blood dam	blood fetus	ratio blood dam : blood fetus
10 min	430.20	184.76	2.3 : 1
3 h	147.43	103.84	1.4 : 1
6 h	81.27	49.87	1.6 : 1
24 h	40.28	34.37	1.2 : 1

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D.I.C.3 Table 12: Comparison of the concentration values (ng equivalents/g organ) in the livers of the dams and the livers of the fetuses and quotient of the concentrations in the livers and concentration in the blood after i.v. administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

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measuring time	liver dam	liver fetus	<u>liver dam</u> blood dam	<u>liver fetus</u> blood fetus
10 min	3477.98	448.29	8.1	2.4
3 h	1481.78	278.85	10.1	2.7
6 h	787.19	105.39	9.7	2.1
24 h	380.99	82.33	9.4	2.4

D.I.C.4 Table 13: Ratios of the radioactivity concentrations in the brains and the blood of dams and fetuses after i.v. administration of [¹⁴C]-SND 919 CL 2 Y

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	time			
day 14 of pregnancy	0.166 h	3 h	6 h	24 h
<u>brain dam</u> blood dam	1.5	4.5	2.7	0.8
day 19 of pregnancy				
<u>brain dam</u> blood dam	1.5	2.9	3.1	1.1
<u>brain fetus</u> blood fetus	1.6	1.9	1.9	1.0

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Oral studies: As with the i.v. route, maternal blood and liver concentrations are higher than in corresponding fetal tissues, and the fetal liver contains higher concentrations than other fetal tissues. Also, higher brain levels relative to blood levels of radioactivity were detected in both dams and fetuses.

Data from the oral administration studies are summarized in Tables D.1.c.5-8:

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D.1.c.5. Table 10: Comparison of the concentration values (ng equivalent/g blood or ng equivalents/g organ) in the blood of the dams, in the placentas and in the total fetus after oral administration of [¹⁴C]-SND 919 CL 2 Y (days 14 and 19 of pregnancy, mean values each of 2 animals)

measuring time	day 14			day 19		
	blood dam	placenta	fetus	blood dam	placenta	fetus
1 h	139.58	229.15	145.79	131.39	255.65	114.61
3 h	91.82	192.68	102.81	166.69	354.22	201.78
6 h	98.46	147.70	65.94	148.69	274.94	146.78
24 h	37.91	54.71	33.17	39.61	64.29	38.43

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D.1.c.6. Table 11: Comparison of the concentration values (ng equivalents/g blood) in the blood of the dams and in the blood of the fetuses after oral administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

measuring time	day 19		
	blood dam	blood fetus	ratio blood dam : blood fetus
1 h	131.39	69.33	1.8 : 1
3 h	166.69	114.65	1.4 : 1
6 h	148.69	111.65	1.3 : 1
24 h	39.61	44.49	1 : 1

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Table 7: Comparison of the concentration values (ng equivalents/g organ) in the livers of the dams and in the fetal livers, and the quotients of the concentrations in the livers and the concentrations in the blood after oral administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

D.l.c.7.

measuring time	liver dam	liver fetus	<u>liver dam</u> blood dam	<u>liver fetus</u> blood fetus
1 h	1773.72	183.52	13.5	2.6
3 h	1648.20	280.52	9.5	2.4
6 h	1305.84	197.75	8.8	1.7
24 h	369.57	74.05	9.3	1.6

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Table 8: Ratios of the radioactivity concentrations in the brains and the blood of dams and fetuses after oral administration of [¹⁴C]-SND 919 CL 2 Y

D.l.c.8

	time			
	1 h	3 h	6 h	24 h
day 14 of pregnancy				
<u>brain dam</u> blood dam	1.8	3.3	2.4	1.7
day 19 of pregnancy				
<u>brain dam</u> blood dam	1.8	3.5	2.9	1.5
<u>brain fetus</u> blood fetus	2	1.6	1.1	0.9

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D.1.d. Pramipexole: Steady-state concentrations in brain, liquor, and plasma of male rats after oral administration of 0.5 mg/kg (once per day) over 8 days.

Document #(s): BI Document U94-0378
Upjohn TR 7256-95-031

Sponsor Volume: 1.60

Summary:

This study was conducted to determine the steady-state pharmacokinetics of PPX in rats following once daily oral administration of 0.5 mg/kg/day for 8 days. Highest levels of PPX were observed in brain tissue, and occur at later time points than in the plasma or CSF. The half-life of PPX in the three compartments was similar.

Methods:

Dosing Regimen: Oral administration of 0.5 mg/kg PPX (Batch II) once daily for 8 days.

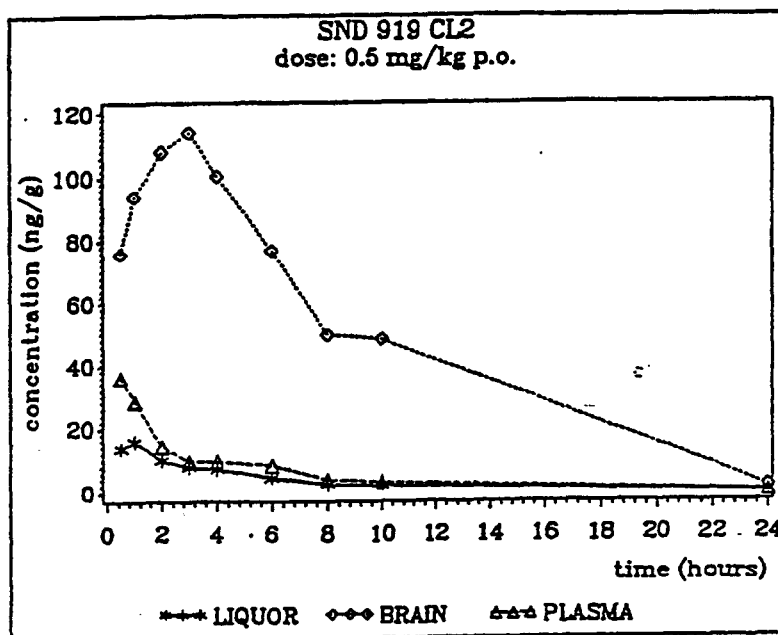
Animals: 35 male Chbb:THOM rats (32 drug, 3 controls), 7g.

Sample collection: Rats (n=3-4/time point) were anesthetized for collection of brain "liquor", then sacrificed for collection of brain and plasma samples.

Pramipexole measurements: by after suitable sample preparation.

Results:

The time-course profiles and kinetic parameters for pramipexole in various matrices were as follows:



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Tab. D.l.d.1

Kinetic steady state parameters of pramipexole in rats after a multiple oral administration of 0.5 mg/kg (calculated from geometric means of concentrations in Table 5)

parameter	dimension	brain	liquor	plasma
AUC (0- ∞)	ng/ml · h	1131.00	79.24	129.57
AUC ratio (plasma=1)		8.7	0.6	1
half-life	hours	3.29	3.33	3.18
log-lin. regression. *)	hours	6-24	4-10	4-24
MRT _{ss}	hours	6.49	4.87	4.68
peak concentration	ng/ml	113.82	15.89	36.20
time to reach peak	hours	3	1	0.5

*) within the time period given the concentration data were used for the estimation of the terminal half-life ($t_{1/2}$)

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D.1.e. Excretion of [¹⁴C]-SND 919 CL2 into rat milk after a single oral dose of 0.5 mg/kg.

Document #(s): BI Document U88-0097
Upjohn TR 7256-94-035

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Sponsor Volume: 1.56

Summary:

This study determined the excretion of [¹⁴C]-PPX and/or its metabolites into rat milk following oral administration of 0.5 mg/kg. Greater levels of radioactivity were detected in milk than in plasma, and the rates of elimination from the two compartments were relatively similar. Most of the radioactivity appeared to be metabolites of pramipexole.

Methods:

Test article: 0.5 mg/kg, p.o. ($\mu\text{Ci}/\text{rat}$) [¹⁴C]-pramipexole labeled at the 2-position of the thiazole ring (Batch 14; 7800 KBq/mg = 210.8 $\mu\text{Ci}/\text{mg}$)

Animals: Six nursing female rats (Chbb:THOM, weight g) with pups (days old).

Procedure: Pups were weaned 4 hrs before first milking. Samples were collected at 1, 4 and 8 hrs after drug administration (n=2/time point). Lactation was stimulated in the mothers by oxytocin, and milk collected using a vacuum pup (under anesthesia). After milking, blood was collected by exsanguination and a portion was processed to plasma. Radioactivity in the milk, blood, and plasma samples was determined by A fraction of each sample was also chromatographed for determination of metabolites.

Results:

Levels of radioactivity in the milk were times higher than in plasma. The milk:plasma concentration ratio did not change over time suggesting relatively equivalent rates of elimination from the two compartments (Fig. D.1.e.1).

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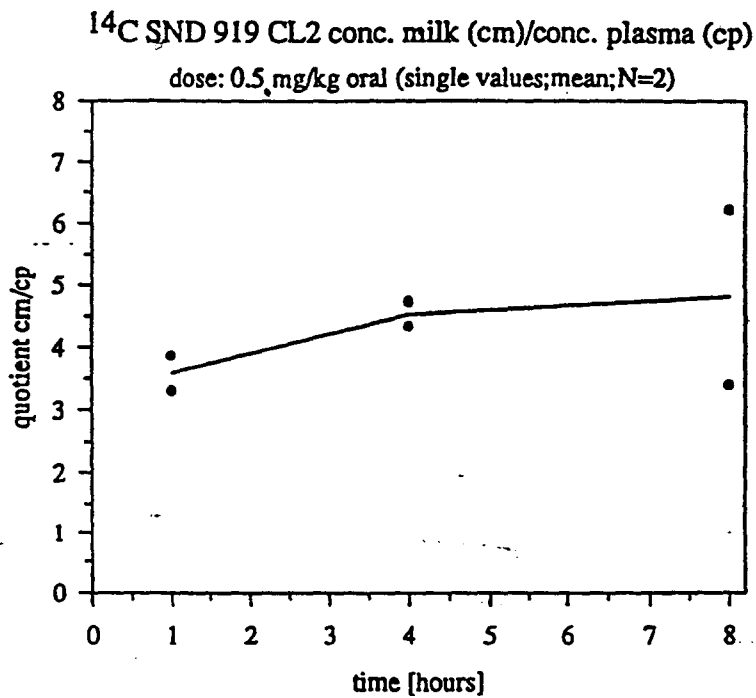


Figure 9. Distribution of radioactivity between milk and plasma in albino rats after oral D.l.e.l. administration of 0.5 mg/kg [^{14}C]SND 919 CL₂ (• individual values).

indicated that the primary radioactive peak in the plasma extracts is pramipexole. In contrast, very little pramipexole was present in rat milk extracts. The .n milk extracts was an apparently lipophilic metabolite. Several smaller polar metabolites were also evident

D.2 Rabbit Pharmacokinetics

D.2.a. Pramipexole: Pharmacokinetics and metabolism in the rabbit after intravenous and oral administration of a single dose of 1 mg/kg.

Document #(s): BI Document U94-0340
Upjohn TR 7256-94-102

Sponsor Volume: 1.56

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Summary:

Plasma concentration and balanced excretion determinations of parent compound and radiolabel were made in rabbits following the intravenous or oral administration of 1 mg/kg [¹⁴C]-PPX. Absorption after oral administration was rather slow (T_{max} = ca. 6 hrs), but relatively high (F = 68.7). The radiolabel was slowly excreted in urine and feces as indicated by long mean residence times. The degree of metabolism of PPX is more extensive in rabbits than in other species on both a qualitative and quantitative basis.

Methods:

Drug Lot: Batch II (non-radioactive material) used to prepare Batch 7 of [¹⁴C]-PPX labeled in the 2-position of the thiazole ring (7.8 MBq/mg).

Dosages: 1 mg/kg/day (prepared in distilled water)

Route of Administration: oral (gavage) or intravenous

Species/Number: 4 female Himalayan rabbits

Mean initial weights/age: ca. 2.8 kg

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Parameters measured:

Plasma concs -	pramipexole and [¹⁴ C]-activity
Excretion -	urine (pramipexole and [¹⁴ C]-activity) and feces ([¹⁴ C]-activity) from hrs
Metabolic profile -	and hr urine analyzed by with radiochemical detection

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Results:

Plasma concentrations:

PK parameters for 1 mg/kg pramipexole (i.v. or p.o.) in rabbits

	AUC (ng.ml/hr)	Cmax (ng/ml)	MRT (hr)	Cl (ml/min)	Vd (l)	t _{1/2} (hr)	Tmax (hr)	F (%)
i.v.	1243	486.2	8.6	32.2	16.6	12.1		
p.o.	990	64.1	12.0	-		11.0	6	68.7

* Peak concentration of [¹⁴C]-activity after oral dose was 282.8 ng/ml, 4.4-fold higher than parent compound, indicating a high degree of biotransformation.

Excretion Balance (0-192 hrs):

	% Dose (Radioactivity)		
	urine	feces	total
i.v.	74.3	14.7	89.0
p.o.	74.4	14.6	89.0

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Metabolic Profiles:

In addition to the parent compound, 7-9 metabolites are present in urine after 24-48 hrs. None were identified in this study, but one appears to be rabbit specific.

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D.3 Monkey Pharmacokinetics

D.3.a. SND 919 CL 2 Y: Plasma concentrations and Renal Excretion in Rhesus Monkeys after administration of three single intragastric doses (0.1, 0.5 and 1.0 mg/kg) and one intravenous dose (0.5 mg/kg).

Document #(s): BI Document U92-0337
Upjohn TR 7256-94-042

Sponsor Volume: 1.59

Summary:

Plasma and urine concentrations of PPX in rhesus monkeys were determined after oral (0.1, 0.5 and 1.0 mg/kg) and intravenous (0.5 mg/kg) administrations. PPX was readily absorbed from the gut, had a high bioavailability (%), and demonstrated linear kinetics. Tmax was approximately 2 hrs, and the half-life of elimination from plasma was 3 hr. The plasma concentration:time profile suggested enterohepatic circulation of PPX. The renal clearance of PPX was 4.3 ml/min.kg, and the degree of biotransformation is moderate (p.o.: 35-42%, iv: 48%; based on amount detected as unchanged in urine).

Methods:

Dosages: intragastric: (i.g.) 0.1, 0.5, 1.0 mg/kg PPX (Batch II, in water)
intravenous: 0.5 mg/kg (in saline)

Subjects: 4 rhesus monkeys (2M, 2F)
Average weights: M = 6.8 kg, F = 6.4 kg

Parameters measured:

Plasma concs -
Urine concs -

exhalation, excretion balance (urine, feces), blood levels, plasma protein binding (different species), biliary excretion, metabolite profiles (urine, feces).

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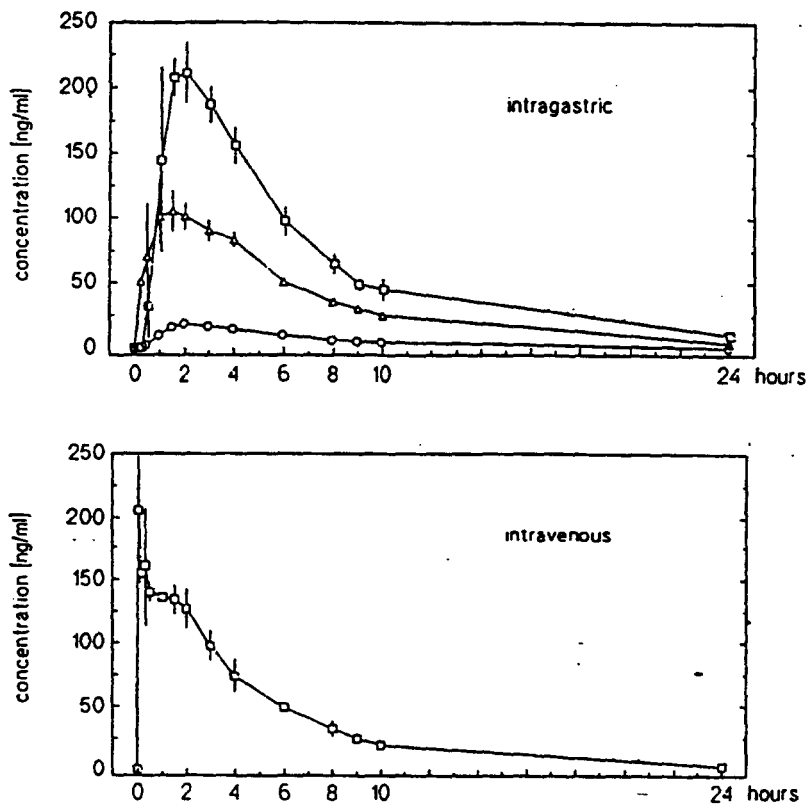
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Results:

Single Dose Pharmacokinetic Parameters in Rhesus Monkeys:

	AUC (ng.ml/hr)	Cmax (ng/ml)	Tmax (hr)	MRT (hr)	Cl (ml/min)	Vd(l)	t _{1/2} λ (hr)	F (%)
					(ml/min/kg)	(l/kg)		
0.1 i.g.	141.9	19.0	1.9	6.2			3.7	79.2
0.5 i.g.	832.9	106.3	1.6	6.0			3.6	93.0
1.0 i.g.	1519.9	218.6	2.0	6.2			3.3	84.6
1.0 i.v.	886.6			4.8	61.5	17.6	3.0	
					9.4	2.7		

Increases in AUC were approximately dose proportional. The t_{1/2} calculation was based on data from 10 hrs postdose, i.g., or 10 hrs postdose, i.v. Elimination kinetics were not uniformly monotonic. A small secondary maxima was evident in the plasma concentration:time profile following i.v. administration suggesting enterohepatic recirculation (Fig. D.3.a).



D.3.a.
 Fig. 3: Mean plasma concentrations of pramipexole [ng/ml] ± SD in the rhesus monkey after single dose
 intra-gastric: 0.1 (○—○), 0.5 (△—△), 1.0 (□—□) mg/kg
 intravenous: 0.5 mg/kg

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Renal Excretion:

Cumulative Renal Excretion as Percent Dose

Renal Clearance

	0-24 hr	0-96 hr
0.1 mg/kg, i.g.	30.8	34.9
0.5 " , i.g.	37.6	42.0
1.0 " , i.g.	37.1	41.7
0.5 " , i.v.	44.1	47.8

ml/min
24.6
25.2
27.0
24.5

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D.4 Human Pharmacokinetics (provided for comparisons to animal pharmacokinetics)

D.4.a. Pharmacokinetics and metabolism of [¹⁴C]-pramipexole after single intravenous and oral doses in healthy volunteers.

Document #(s): BI Document U92-0018
Upjohn TR 7215-94-014

Sponsor Volume: 1.57

Summary:

The single dose pharmacokinetics of orally (0.304 mg) and intravenously (0.099 mg) administered [¹⁴C]-PPX were determined by monitoring levels of radiolabel and parent compound over 24 hrs in healthy volunteers. Following oral administration, PPX was quantitatively absorbed from the GI tract (F = ca. 90%), and peak plasma concentrations were achieved in approximately 1 hr. Elimination from the plasma was rather slow $t_{1/2\gamma} = 12.8$ hrs). Renal excretion is the primary route of elimination (ca. 90%; $Cl_{ren} = 409$ ml/min), and the major fraction is unchanged parent compound. Plasma protein binding was low (14.1%). The only clinical change were slight decreases in systolic pressure and pulse rate.

Methods:

Drug Lot: Batch VI (non-radioactive)
Radioactive Batch 6 (labeled in the 2-position of thiazole ring)

Subjects: Oral/IV cross-over design with 6 subjects. Washout period of 5 weeks between administrations.

Doses: 0.099 mg [¹⁴C]-pramipexole, i.v. (0.812 MBq), or
0.304 mg [¹⁴C]-pramipexole, p.o. (2.15 MBq)

Parameters measured:

Plasma concs	-	pramipexole and [¹⁴ C]-activity over 24 hrs
Ce/Cp	-	erythrocyte/plasma distribution
Excretion balance	-	or hrs
Plasma protein binding	-	
Metabolic profile	-	and hr urine analyzed by with radiochemical detection

Results:

Human PK parameters for PPX (0.099 mg, i.v., or 0.304 mg, p.o.):

(PK data for the parent compound, pramipexole, were analyzed using both a 3-compartment open model and a moment analysis, but [14C]-activity data were analyzed only by moment analysis. PK parameters for the parent compound were similar by both methods. In order to compare the PK parameters for parent compound and [14C]-activity, the values obtained by moment analysis are presented, except where indicated*).

	AUC (ng.ml/hr)	Cmax (ng/ml)	MRT (hr)	Cl (ml/min)	Vd (l)	t _{1/2λ} (hr)	Tmax (hr)	F (%)
PPX (iv)	3.64		16.1	506.2	451	12.6		
[¹⁴ C] (iv)	4.75		18.8	355.6	395	14.4		
PPX (p.o.)	10.43	0.85*	17.0			12.1	1.0	93.3
[¹⁴ C] (p.o.)	15.84	0.91*	24.8			17.6	1.0	108.6

PPX was still present in plasma at 24 hrs.

F calculations based on AUCs corrected for dose:

$$(AUC_{po})(0.99/3.04)/AUC_{iv}$$

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Absorption/Bioavailability:

Absorption of [14C]-activity and bioavailability of PPX were determined by two methods:

- normalization of AUCs (as described under PK parameters Table), and
- renal excretion

$$\frac{\text{renal excretion } (^{14}\text{C, oral})}{\text{renal excretion } (^{14}\text{C, iv})} \times 100$$

By either method, the absorption of radioactivity and bioavailability of PPX were essentially quantitative:

	AUC method	renal excretion method
[¹⁴ C] absorption	108.6	98.3
PPX bioavailability	93.3	95.6

Erythrocyte/Plasma Distribution:

Most values were in the range of 1.3-2.6, indicating slight enrichment of [¹⁴C] activity in erythrocytes.

Excretion:

		% Dose		
		urine	feces	total
[¹⁴ C] (0-96 hr)	i.v.	89.1	2.0	91.1
	p.o.	87.6	1.6	89.2
Pramipexole (0-24 hr)	i.v.	61.8	nd	
	p.o.	56.3	nd	
Pramipexole (0-inf)	i.v.	81.5	nd	
	p.o.	77.9	nd	

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Small amounts of radioactivity were excreted later than 120 hrs.
Mean renal clearance of PPX was 409 ml/min (exceeds GFR).

Plasma Protein Binding: (Assessed at two concentrations of PPX)

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[PPX]	% Bound (Range)
2.5 ng/ml	
5.0 "	

Metabolism pattern:

In NOT PPX (of urines collected after dosing, very little of the radioactivity was % of dose; .% of dose).

Vital Signs:

Small decreases in systolic blood pressure and heart rate were evident between 1-8 hrs after dosing by either route. No clear changes in ECG, diastolic blood pressure, or laboratory values were observed.

D.4.b. A single dose tolerance and pharmacokinetic study of intravenous pramipexole in healthy male volunteers.

Document #(s): BI Document U92-0018
Upjohn TR 7217-94-014

Sponsor Volume: 1.58

Summary:

This study was primarily a dose tolerance study with limited pharmacokinetic evaluations. PPX (μg) was administered by intravenous infusion and plasma levels were determined over 24 hrs; levels were below the LOD by 24 hrs. Increases in AUC were slightly greater than dose proportional. Cardiovascular changes were increases in pulse rate after doses of 200 and 300 μg , and decreases in diastolic blood pressure after 300 μg . Orthostasis occurred in 1/5 patients after 200 μg , and 2/4 patients after 300 μg . No other drug-related effects on ECG or laboratory parameters were observed.

Methods:

Drug Lot: Batch 802203

Subjects: Healthy, adult male volunteers; three groups of eight subjects.

Group A: 10 and 50 μg

Group B: 25 and 100 μg

Group C: 50, 200 and 300 μg (50 μg administered as a pretest)

Five subjects per dose received active drug, three received placebo.

Drug administered as an i.v. infusion over 20 min.

Washout period was 6 days.

Parameters measured:

Plasma concs -

Laboratory - hematology, clinical chemistry, urinalysis

Vitals - blood pressure, ECG, etc.

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Results:

Pharmacokinetics:

The pharmacokinetic data were not subjected to rigorous analysis.

Dose (μg)	AUC (ng.ml/hr)	$C_{20\text{min}}$ (ng/ml)	$t_{1/2}$ (hr)
50	1.01	0.40	
100	2.06	0.64	4.8
200	4.94	1.89	7.9
300	7.35	2.26	6.6

Increases in AUC were generally dose proportional, although slightly nonlinear (slope > 1). Plasma PPX levels were below LOD at 24 hrs. The $t_{1/2}$ calculation was based on plasma levels determinations between hrs

Clinical Determinations:

Increases in pulse rate lasting up to 4 hrs occurred following doses of 200 and 300 μg . A decrease in diastolic blood pressure was noted 40 min after 300 μg infusion. Orthostasis occurred in 1/5 patients after 200 μg , and 2/4 patients after 300 μg . The cardiovascular changes suggest a vasodilating effect of pramipexole. No significant drug-related effects on ECG or laboratory determinations were observed.

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D.5 Multiple Species Pharmacokinetic Studies

D.5.a. Balanced excretion studies and metabolic profile following oral administration of [14C]-SND 919 CL2Y to the mouse, rat, rabbit, dog, monkey and pig.

Document #(s): BI Document U88-0215
Upjohn TR 7256-94-036

Sponsor Volume: 1.59

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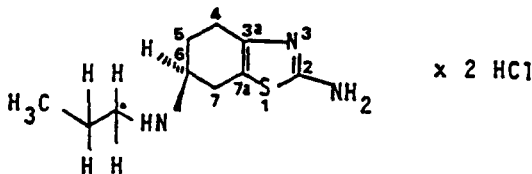
Summary:

The excretion and metabolism of [14C]-PPX were evaluated in several species following oral administration. In general between % of administered label was recovered in urine and % in feces. The urinary metabolic profile in mouse, rat, dog, monkey and pig were relatively similar on both a quantitative and qualitative basis. The rabbit had the highest proportion of radioactive metabolites, and a species-specific polar metabolite.

Methods:

Substance administered: [14C]-PPX labeled at C1 of the propyl group (Batch 2) or the 2-position of the thiazole ring (Batch 3). Batch 2 was used in all studies except in the rabbit study.

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$C_{10}H_{17}N_3S + 2 HCl$
* = labelling with ^{14}C

Molecular weight: 284.25 (base)
357.17 (dihydrochloride)

Parameters measured:

- Excretion balance (urine, feces) - collect samples at 24 hr intervals for 96 hrs (rat), 168 hrs (mouse, dog, monkey, pig), or 192 hrs (rabbit). Analyze for radioactivity by liquid scintillation spectroscopy.
- Metabolic profile - analyzed 0-24 hr urine samples by HPLC with radiometric analysis

Animals:

Species	n (sex)	weight (ca.)	dose (mg/kg, ca.)	dose (MBq, ca.)
mouse	10M, 15F	22 g	0.5	0.09
rat	2M, 2F/dose	208-232 g	0.01, 0.1, 1.4, 10.8 79.1	
rabbit	2M, 2F	2.5 kg	0.5	3.44
dog	4F	kg		
monkey	2M, 2F	kg	0.5	12.95
minipig	2M, 2F		0.5	9.59

*variation in dog dose due to emesis

Results:

Excretion balance:

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Tab. ●: Mean balances of excretion in % of dose after oral administration
D.S.a. | of ^{14}C -SND 919 CL 2 Y in 6 animal species

species	N	mg/kg	collection period [h]	urine	feces	sum
mouse	25	0,6		68,42	27,79	96,21
rat	4	0,01		51,87	28,71	80,58
"	4	0,1	"	64,78	38,26	103,04
"	4	1,4	"	48,16	41,15	89,31
"	4	10,8	"	52,14	28,29	80,43
"	4	79,1	"	43,61	25,81	69,42
rabbit	4	0,6		79,25	12,88	92,13
dog*)	4					
monkey	4	0,5		69,07	8,43	77,5
minipig	4	0,5		58,88	12,72	71,5

*)strong emesis in 3 out of 4 animals

The sponsor suggests that adsorption of [¹⁴C]-material to surfaces may contribute to low recovery. The fact that the rabbit studies were conducted with material labeled at a different (more metabolically stable) position, and 3 of 4 dogs experienced emesis, hinders species comparisons. In general, % of material was eliminated in the urine, and % was excreted in the feces.

Metabolic Profile:

Generally similar chromatographic profiles are obtained with hr urine specimens from the rat, mouse, dog, minipig, and monkey in that a primary peak, identified as the parent compound, and several are present. However, the major peak in the rat sample elutes approximately 3 min after the major peaks in samples from other species. The sponsor did not indicate how the major peak was identified as pramipexole, or the reason for this discrepancy in elution times for the major peaks.

The chromatograms of the rabbit 0-24 hr urine samples were markedly different from other species examined (e.g. Fig. D.5.a.1; comparison with rat). The largest peak in most of the rabbit chromatograms is not PPX, but appeared much earlier in the elution profile (9-10 min). In addition, numerous smaller peaks were present in these chromatograms. The variation in the position of the radiolabel on the PPX moiety (i.e., ring-labeled material used in the rabbit studies versus side-chain-labeled material in other species) did not appear to contribute to the differences in metabolic profile.

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D.5.b. Studies on the metabolism of pramipexole including experiments to detect a potential metabolic inversion at the optical active center of the molecule.

Document #(s): BI Document U95-0494
Upjohn TR 7256-95-057

Sponsor Volume: 1.60

Summary:

These studies were conducted to chromatographically separate and purify pramipexole metabolites in rat and rabbit urine, and determine the propensity for chiral inversion of PPX in rat and human.

Methods:

Substance administered: [¹⁴C]-pramipexole (batch and position of label not identified)

Animals/Dosing: according to the scheme:

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running no.	species	subjects N	treatment			
			dose	regimen	route	MBq/subject
1	rat	3	12 mg/kg	single dose	oral	1.6737
2	rat	2	0.5 mg/kg	single dose	oral	0.743
-	-	2	-	-	-	0.743
3	rabbit	1	1 mg/kg	single dose	oral	3.66
4	rabbit	1	1 mg/kg	single dose	oral	13.16
5	man *)	1	1.5 mg	t.i.d.	steady state	oral
-	(male, subj. 2)		1.5 mg			
-	(female, subj. 9)	1	t.i.d.	steady state	oral	-

*) samples from study M/2730/0047, ref. [6]

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Note: the dose in rabbit study is in conflict with the dose stated in the text (0.5 mg/kg)

Experimental

Procedures: Samples were subjected to appropriate extraction techniques then analyzed by various methods for metabolite identification

Enantioselective chromatographic techniques were used to determine the occurrence of chiral inversion from the (6S)-(-) configuration to the (6R)-(+ configuration).

Results:

Metabolite Identification:

Rabbit urine: 6 chromatographic peaks were separated and tentatively identified.

- M1 - may be a labile conjugate
- M2 - N-dealkylated metabolite
- M3,M4 - hydroxylated metabolites (4 and 5 position of the thiazole ring)
- M5 - parent compound
- M6 - glucuronic acid conjugate

Rat urine: 2 chromatographic peaks were separated and tentatively identified.

- M2 - N-dealkylated metabolite
- M3,M4 - hydroxylated metabolites (4 and 5 position of the thiazole ring)

The "species-specific" polar metabolite suggested in the preceding study was identified as M1. The proportion of total metabolites, M1, and PPX in rat and rabbit urine were as follows:

The proportions of total metabolites, M1 and parent compound in the urines used for metabolite isolation were in % of ¹⁴C activity registered:

species	figure	Total metabolites	Metabolite M 1	Pramipexole
rabbit	1	70.5	12.4	29.5
rabbit	3	96.1	42.6	3.9
rat	4			

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The proposed metabolic pathways are shown in Fig. D.5.b.1.

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Chiral Inversion Studies:

In rat and human urine, very minor peaks that coeluted with the (6R)-(+)
enantiomer of pramipexole were detected ($\leq 3\%$ total peak area; Tab. D.5.b.1).

Table ● D.5.b.1

Evaluation of data from stereoselective chromatography of extracts of rat
urines

Estimation of apparent SND 919 R(+) concentration

measured/calculated:	dimension	rat no1	rat no.2	rat no. 3
concentration				
pramipexole	$\mu\text{g/ml}$	17.935	15.391	41.655
	%	100	100	100
R(+) region standard (background)	dpm/region	484	484	484
R(+) region in vivo urine	dpm/region	685	427	761
R(+) region (net)	dpm/region	201	0	277
S(-) region				
(no background correction possible)	dpm/region	53761	44070	65153
sum: R(+) + S(-)	dpm/2 regions	53962	44070	65430
apparent SND 919 R(+)/R(+) region *)	ng/region	4.8	0	6.6
apparent SND 919 R(+)/ml urine	ng/ml	66.8	0	176
apparent SND 919 R(+) as % of pramipexole concentration	%	0.4	0	0.4

*) specific activity: 42.371 dpm/ng ; f=0.0236 ng/dpm

Table ●

Stereoselective separation of extracts from human urine after oral steady
state administration of 1.5 mg t.i.d. pramipexole (SND 919 S(-) CL2)

subject/ gender	fraction [hours]	pramipexole [ng/ml]	region1 SND 919 R(+)	region2 SND 919 S(-)	ratio [%]
2 (male)	0-4	1860	3962	234497	1.7
	4-8	1270	3273	169776	1.9
	8-12	472	1598	67211	2.4
	intercept *)	8-12	472	491 *)	76575 *)
9 (female)	0-4	899	3619	122147	3.0
	4-8	551	2188	76818	2.9
	8-12	811	1080	119556	0.9
	intercept *)	8-12	811	390 *)	132950 *)

*)The areas given result from the the linear regression of peak area data of the spiking
experiments in Figure 20 (peak area ratio vs. ng/ml SND919 R(+) added).
They were calculated using the intercept of the regression line and a mean value (N=5
injections) of the SND 919 S(-) peak areas

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SUMMARY

Pharmacodynamics

Degeneration of dopaminergic neurons in the substantia nigra is widely accepted as the neuropathological basis of Parkinson's disease (PD). The clinical utility of the dopamine (DA) precursor L-DOPA and dopamine receptor agonists in PD therapy supports this mechanism. However, currently available PD therapies have clinical drawbacks (e.g., on-off fluctuations, delusional side effects) that limit their utility.

Pramipexole (PPX) is a selective dopamine receptor agonist being developed as a replacement therapy for PD. PPX is distinguished from its predecessors by its receptor binding profile. In contrast to other therapeutic DA agonists such as pergolide (Permax) and bromocriptine (Parlodel), PPX preferentially binds to D₃ rather than D₂ receptors when both subtypes are expressed in their agonist conformations. The therapeutic significance of D₃ receptor selectivity is not readily apparent since the role of this subtype in PD is not well-established. However, the sponsor suggests that because of the high D₃ receptor density in mesolimbic regions associated with reward and motivation, PPX may alleviate depression that is often co-morbid with PD. PPX is also distinguished from Permax and Parlodel since the latter compounds have relatively high affinities for 5-HT receptor subtypes, whereas the only non-dopaminergic receptor activity of PPX was detected at α_2 receptors ($K_i = 250$ nM).

In vivo dopaminergic agonist activity of PPX was demonstrated in behavioral, neurochemical and electrophysiological studies. In contrast to the usual locomotor stimulation observed with D₂ agonists and high doses of PPX, low doses of PPX decreased locomotor activity in mice. The dose-dependence may be the result of pre- versus post-synaptic receptor sensitivity. Neurochemical evidence of presynaptic D₂ autoreceptor activity of PPX was a decrease in DA synthesis in striatum and limbic system at doses less than 0.1 mg/kg, s.c., and a decrease in dopamine release in *in vivo* microdialysis studies. In electrophysiology studies, PPX decreased the firing rate of nigrostriatal (SNPC) and mesolimbic (VTA) neurons presumably due to activation of D₂ autoreceptors, but stimulated the firing of postsynaptic anterior caudate neurons, possibly via D₃ receptor activation.

Experimental evidence for the proposed utility of PPX in PD was obtained in the standard animal models. In 6-hydroxydopamine (6-OHDA)-lesioned rats, PPX was approximately equipotent to apomorphine ($ED_{50} = 0.026$ mg/kg, s.c.) at inducing contralateral turning, but had a longer duration of action. In the MPTP-induced Parkinson's disease model in primates, PPX (0.075 mg/kg, p.o.) reversed parkinsonian symptoms for 5-24 hr. By comparison, the combination of L-DOPA/carbidopa (15 mg/kg, p.o.) was effective for only 2 hrs. Bromocriptine (2 mg/kg) was relatively ineffective in these studies.

Potential neuroprotective effects of PPX were evaluated in three preclinical models of neurodegeneration. Multiple doses of PPX (1 mg/kg, p.o.) beginning shortly after insult prevented degeneration of putative dopaminergic neurons following transient forebrain

ischemia in gerbils or high doses of methamphetamine to mice. PPX also prevented the loss of TH-positive cells due to micromolar concentrations of L-DOPA in primary cultures of rostral mesencephalic tegmentum cells. While these studies are interesting from a mechanistic standpoint and may be considered preliminary evidence of neuroprotection, they are not sufficient to support the sponsor's proposed labeling claim that pramipexole "reduces dopamine-induced neuronal degeneration."

Safety Pharmacology

The safety pharmacology studies of PPX revealed relatively few safety concerns. The most significant issue arose from early clinical studies where hypotensive effects of PPX were identified. Because of concerns that combining PPX with other PD drugs may potentiate this effect, the cardiovascular effects of PPX in combination with Sinemet and Eldepryl were evaluated in rhesus monkeys. The modest bradycardia and blood pressures decreases produced by PPX (0.05 mg/kg, p.o.) were not potentiated by either Sinemet (100 mg/kg L-DOPA/10 mg/kg carbidopa, p.o.) or Eldepryl (0.2 mg/kg, p.o.). Other notable effects of PPX in safety studies were sedation in monkeys, sleep suppression in cats and rats, and emesis in dogs. PPX doses of _____ mg/kg lowered basal plasma prolactin levels in male rats. Similar effects of PPX were demonstrated as part of the chronic toxicology studies because of the speculated role of prolactin inhibition in some of the observed histopathological and reproductive changes.

Toxicology

Acute Studies

The acute toxicity of PPX was evaluated in mice, rats and dogs following oral and intravenous administration. Animals were observed for 14 days. In rodents, signs of toxicity were exophthalmus, piloerection, irregular breathing, and tremors/convulsions. The ratios of LD₅₀s by the p.o. and i.v. routes were approximately 10 in mice (p.o. = 1700, i.v. = 169) and greater than four in rats (p.o. > 800, i.v. = 210). The most prominent toxicity in dogs was emesis at doses of _____ mg/kg, i.v., and _____ mg/kg, p.o.

Chronic Studies

The toxicity and toxicokinetics of PPX administration for one year were evaluated in rats at doses of 0, 0.5, 3.0 and 15.0 mg/kg. The lowest test dose resulted in slight behavioral activation and decreased body weight gain in both sexes. Decreases in cholesterol and triglycerides occurred at all doses in females. Other sporadic clinical chemistry changes were modest elevations in transaminases, alkaline phosphatase and urea, and decreases in serum potassium at the mid and high doses; these were generally more frequent in females than in males. Hematological changes were slight thrombocytopenia (MD, HD) and slight-to-moderate increases in the granulocyte/lymphocyte ratio in females. Ovarian weights were increased at all dosage levels, and enlarged corpora lutea were observed at the mid and high

dose. Histopathological changes in the uteri (dilatation, serous contents, pyometra) and changes in the glandular epithelial pattern of mammary tissue were also evident in MDF and HDF. The female reproductive changes were attributed to inhibition of prolactin secretion. Eleven animals (4 controls, 7 PPX-treated) were identified with tumors, none of which could be clearly attributed to PPX treatment. The decreases in serum cholesterol, shift in granulocyte/lymphocyte ratios, and ovarian changes were consistent with observations in previous subchronic rat studies

Rat plasma concentrations at the "No Toxic Effect" dose level of 0.5 mg/kg are near the anticipated steady-state C_{max} in humans (ng/ml).

The toxicity and toxicokinetics of orally administered PPX (0, 0.1, 0.5 and 2.0 mg/kg/day) for one year were evaluated in rhesus monkeys. Prominent clinical signs of toxicity were behavioral changes (agitation, jumping, swinging, gripping) that diminished over the course of treatment. Body weight and food consumption were not affected by PPX. Dosing was limited to 2.0 mg/kg because of drug-induced injurious behavior in the animals during the early phase of the study. The most significant drug-related effect was bradycardia with increased R-R and Q-T intervals recorded at various times during the study; however, this effect was only observed in mid-dose males. No treatment-related hematological or urinary changes were evident, and only some modest changes in clinical chemistry occurred. Organ weights were not altered and no histopathological findings were attributed to PPX. One death, a low-dose female, occurred late in the study and did not appear to be drug-related. Plasma concentrations of PPX were approximately 2- (low test dose) to 80-fold (high test dose) higher than the anticipated human steady-state C_{max}. Thus, oral administration of mg/kg/day PPX for 52 weeks does not produce significant pathologic effects in monkeys. PPX was also devoid of toxicities in 4-week intravenous toxicity study at doses up to 0.6 mg/kg.

Reproductive Toxicology

In a rat Segment I study, PPX (mg/kg, p.o.) was given to males for 70 days prior to mating, and females for 14 days prior to mating through gestation (C-section on day 22) or weaning (spontaneous delivery group). The most notable reproductive toxicities in the HD dams were prolongation of estrus in HDF, and reductions in the number of implantations, pregnant females and successful deliveries. Body weight development was impaired in pups of MD and HD dams, possibly because of reduced suckling opportunities or inhibition of prolactin secretion by PPX. Teratogenic effects of pramipexole were not evident, although the data were limited by the low number of evaluable pups. A follow-up Segment I study was conducted which identified PPX-treated females rather than males as the source of infertility. These findings were expected since PPX, like other dopamine agonists, inhibits secretion of prolactin which is necessary for the maintenance of rat pregnancy.

In the rat Segment II study, PPX (mg/kg, p.o.) was administered from day 7 to 16 of gestation. Dams were either sacrificed on day 22 for delivery of pups by Caesarean section, or allowed to raise the pups to weaning (21 days). Significant embryoletality

occurred with the high dose as only 7 of 32 pregnant females had viable offspring. The other 25 pregnancies were classified as complete "early" resorptions. Abnormalities identified in fetuses of drug-treated dams included one case each of anal atresia (LD), sirenomelia and gastroschisis (LD), and a cleft vertebra (MD). Teratology information from the high-dose group was limited by the low number of evaluable pups. Body weight development was not impaired in this study, which suggests that PPX administration during lactation is responsible for this effect.

In contrast to the rat Segment II study, oral administration of PPX (0.1, 1.0, 10 mg/kg) to rabbits from day 6 to 18 of gestation did not produce any embryotoxic, fetotoxic or teratogenic effects.

In a Segment III study, oral administration of PPX (0, 0.1, 0.5 and 1.5 mg/kg/day) to female rats from day 16 of gestation to day 21 of the rearing phase (lactation) caused an impairment of pup development as indicated by a decreased body weight gain during the lactation/rearing phase. As in the Segment I study, reduced suckling opportunities or impaired milk production in the dams may underlie this effect. Fertility of the F₁ offspring was not impaired. No other remarkable drug-related changes in litter parameters or at necropsy of the pups were evident.

Taken together, these data suggest that PPX has toxicological consequences on reproductive and developmental parameters in rats but not rabbits. The prolongation of estrus, impairment of female fertility and early resorptions are likely related to the D₂ receptor-mediated suppression of prolactin, a hormone necessary for the maintenance of rat pregnancy, and may not necessarily be a great human concern. However, a significant consequence of this effect is a low number of evaluable pups from dams treated with the highest dose of PPX (2.5 mg/kg in Segment I study, 1.5 mg/kg in Segment II study), which drastically limits conclusions on the teratogenicity of PPX. Although the Segment III study produced a relatively large sample of pups with no drug-related effects on skeletal, visceral or external abnormalities, these animals were not exposed to drug until after the critical period of organogenesis. Since some relatively rare fetal abnormalities were present in PPX-treated pups in the Segment I and II studies (anal atresia, sirenomelia and gastroschisis, and cleft vertebra), teratogenic effects of PPX cannot be discounted in the absence of data from a larger pup population.

The impairment of body weight development in the Segment III study is clearly a PPX-related effect. The sponsor suggests as a basis for this finding that pups are inadequately nursed because of behavioral activation in the dams. Inadequate milk production due to insufficient prolactin levels in the dams is an alternative possibility. However, a direct effect of PPX on pup development cannot be discounted.

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Genotoxicity

PPX was tested for mutagenic effects in four standard *in vitro* assays (Ames test, SHE cell transformation assay, chromosomal aberrations in CHO cells, V79 gene mutation assay) and the *in vivo* mouse micronucleus test. The testing procedures were generally adequate; where deficiencies existed (i.e., SHE cell assay, micronucleus test), further testing will not be recommended.

No reproducible mutagenic responses to PPX were observed. The only positive signal in any assay was a small, non-reproducible clastogenic effect with S9 activation at the highest test dose (3300 µg/ml) in the CHO chromosomal aberration study.

Carcinogenicity

In the two-year mouse study, no neoplastic and few non-neoplastic lesions were associated with PPX administration (0.3, 2.0 and 10 mg/kg/day in diet). However, the validity of this study as an assessment of the tumorigenicity of PPX is questionable because of the marked impairment of body weight development () at the intermediate and high test dosages. Plasma exposures at the lowest test level (equal to or less than expected human exposures) were not considered adequate for valid risk assessment.

The rate of premature decedents was higher in PPX-treated animals, primarily because of unscheduled sacrifices due to eczema; a sufficient number of survivors remained at termination. Drug-related clinical observations were increased spontaneous activity at the mid and high dose levels. No statistically significant increases or trends for increases in the incidence of neoplastic lesions in drug-treated animals were apparent according to the sponsor's analysis. A pooled analysis of all mesenchymal/epithelial uterine neoplasms was not presented, although a possible dose-related positive trend was noted (controls: 10%; LD: 10%; MD: 14%; HD: 16%). Unusual histopathological findings in PPX-treated animals were fibro-osseous proliferative lesions in the femurs of females (all dosage groups). This lesion occurred at a relatively high rate in control females (28%), but approximately doubled in incidence in treated animals (); similar at the three dosage levels). This type of lesion is known to occur spontaneously in female mice. However, administration of the prostaglandin E analogue misoprostol has also been associated with this lesion in mice, and the issue is addressed in the labeling of that product. A hormonal basis for this effect is suggested, but no experimental evidence was presented. A similar lesion was not observed in long-term studies of PPX in rats or monkeys.

As in the mouse study, a marked impairment of body weight gain in MDF and HDF prevents conclusions regarding the tumorigenicity of PPX (0.3, 2.0 and 8.0 mg/kg/day) in female rats. Body weight gain reductions in males were less than 10%. Mortality occurred in all treatment groups at various times during the study, but no clear drug relationship was evident. An adequate number of survivors remained at termination. The only tumors found at a statistically significant greater incidence in PPX-treated animals were Leydig cell adenomas in MD (44%) and HD (44%) males. A relatively high incidence of these tumors also occurred in control animals (Group 0: 26%, Group 4: 18%). Leydig cell hyperplasia was also increased in MD and HD rats. Changes in females were enlarged corpora lutea (HD

rats), uterine lesions and hemorrhage (MD and HD), alterations in mammary gland patterns from female-like to male/female-like (MD and HD), and diffuse hepatocellular fatty changes (MD and HD). Retinal degeneration occurred in MD and HD males and females.

The proposed basis for the neoplastic and nonneoplastic lesions in reproductive and endocrine structures is PPX-induced inhibition of prolactin secretion, which was demonstrated at week 60 and 69 (ca. 10-fold decrease in females, 100-fold decrease in males). Reductions in serum prolactin in males purportedly trigger an elevation in LH production and release leading to the Leydig cell adenomas and hyperplasia. Direct evidence for a PPX effect on serum LH was not provided. Nonetheless, the finding is suggested to be of questionable relevance to humans given the high background incidence of this tumor in rats (as demonstrated in this experiment), and since several widely-used compounds also produce Leydig cell tumors in rats but are not known to do so in humans (cimetidine, hydralazine, vidarabine, israpidine). The female reproductive changes (corpora lutea enlargement, uterine lesions, and mammary gland pattern changes) were also observed in the one year rat study. The sponsor contends that the potential human relevance of these findings is questionable because of the divergent influences of prolactin on female hormone levels in rats and humans. However, the effect of PPX on estrogen and progesterone was not shown in any study. Thus, the proposed mechanisms for the pathological changes in rodents are plausible and supported in the literature by studies with other dopamine agonists, but direct support for these mechanisms specifically in the case of PPX is not present in this submission.

Retinal degeneration was the most notable non-neoplastic finding of this study. Follow-up studies to address this issue and were independently reviewed by an FDA consultant (Dr. Tim O'Neill). Briefly, the sponsor has provided evidence that treatment with PPX (25 mg/kg, p.o.) for 13 weeks in combination with constant light exposure produces retinal degeneration in non-pigmented albino rats, but not in pigmented Brown-Norway rats. Retinal degeneration was not observed after long-term treatment of minipigs and monkeys. Thus, pigmentation may protect against the retinotoxic effects of PPX. The proposed mechanism for this effect is inhibition of retinal disk-shedding, which occurs universally in vertebrates. This leaves open the possibility that a similar effect could occur in humans.

Pharmacokinetics/ADME

The absorption, distribution, metabolism, and excretion of pramipexole were evaluated in several species (mouse, rat, rabbit, monkey, human, dog, and minipig) following oral and intravenous administration of single or multiple doses. Only the single dose pharmacokinetic studies conducted in species used for animal toxicology (rat, monkey, rabbit) studies are reviewed here. Human studies are included for comparative purposes. Toxicokinetic studies were reviewed as part of the main study review.

The analytical methodologies included the use of radiolabeled [¹⁴C]-PPX, HPLC with electrochemical detection, radioimmunoassay, or GC with chemical ionization mass spectroscopy. The former two methods were used for the majority of analyses, and provided adequate sensitivity.

In most test species, PPX is absorbed rapidly and nearly completely following oral administration. Peak plasma concentrations are generally reached within 2 hrs of treatment, except for the rabbit ($t_{max} = 6$ hrs.). The calculated bioavailabilities in all species exceeded 69%, and in humans this value was greater than 90%. After intravenous administration, the systemic clearance of PPX was high, and terminal half-lives were relatively short (<4 hrs), except for rabbits and humans ($t_{1/2} =$ hr). The excretion and metabolism of [^{14}C]-PPX were evaluated in several species following oral administration. In general, between % of administered label was recovered in urine and % in feces. Renal excretion of PPX is the primary route of elimination in humans (ca. 90%; $Cl_{ren} = 409$ ml/min). Except for the rabbit, the major urinary fraction is unchanged parent compound. Significant biliary excretion of radioactivity was detected in cannulated rats. The plasma concentration:time profile of PPX in monkeys suggested enterohepatic circulation of the drug. The degree of biotransformation is low to moderate in most species, and the urinary metabolic profile in mouse, rat, dog, monkey and pig were relatively similar. Biotransformation in rabbits differed from the other species on both a qualitative and quantitative basis. The rabbit had the highest proportion of radioactive metabolites, and a species-specific polar metabolite. Plasma protein binding of PPX was relatively low in all species (dog, pig, monkey, man). PPX did not undergo chiral inversion *in vivo* in rats or humans.

The tissue distribution of PPX was evaluated in rat. A similar pattern was observed following i.v. or oral administration with highest concentrations detected in the lacrimal, salivary, and adrenal glands, kidney, pancreas, bone, liver and lung. At 24 hrs, radioactivity was still present in liver, kidney, and adrenals. Brain levels of radioactivity peaked at 2 hrs after i.v. PPX, and were detectable for up to 6 hrs. In a steady-state pharmacokinetic study of PPX, the highest levels of PPX were observed in brain tissue when compared to plasma and CSF. In a study of pregnant Wistar rats, [^{14}C]-PPX and/or its metabolites rapidly crossed the blood:placental and blood:brain barriers after i.v. or oral administration (1.0 mg/kg). PPX Concentrations of label tended to be higher in the placenta than in maternal blood or in the fetus. Highest fetal tissue concentrations of radiolabel were detected in the liver. In both dams and fetuses, brain levels were higher than plasma levels for up to 6 hrs postdose. In lactating rats, [^{14}C]-PPX and/or its metabolites were excreted into rat milk following oral administration of 0.5 mg/kg; higher levels of radioactivity were detected in milk than in plasma. Most of the radioactivity appeared to be metabolites of pramipexole.

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EVALUATION

The following issues were identified in nonclinical studies as pertinent to the human use and labeling of pramipexole:

1. Carcinogenicity/Mutagenicity:

The carcinogenicity study in mice cannot be considered adequate for risk assessment purposes because of the marked impairment of body weight development (37-45%) at the intermediate (2.0 mg/kg/day) and high (10.0 mg/kg/day) dose levels, and inadequate plasma levels at the lowest test dose (0.3 mg/kg/day). Because of the potent effects of PPX on body weight development, it is likely that similar difficulties with study interpretation would be encountered at doses levels between 0.3 and 2.0 mg/kg. Thus, additional studies will not be recommended. The Carcinogenicity Assessment Committee will be consulted for a resolution.

A similar problem was encountered in the carcinogenicity study of female rats where body weight gain was reduced by % at the intermediate and high dose levels. In males, which received adequate exposures based on toxicity and plasma level determinations, the only tumor that occurred at clearly higher incidence in PPX-treated animals were Leydig cell adenomas (CON: 22%, 0.3 mg/kg: 34%, 2 mg/kg: 44%, 10 mg/kg: 44%). PPX did not appear to reduce the latency of tumor appearance. Because of the high background incidence of this tumor type in rats, and the possibility that species-specific hormonal mechanisms may be involved in their appearance, the significance of these findings in humans is questionable. The sponsor has included a description of the findings in the proposed labeling, which is an acceptable means of addressing this issue.

PPX did not cause significant mutagenicity in an appropriate test battery at acceptable concentrations.

2. Reproductive Toxicology

The reproductive toxicology studies do not adequately support the sponsor's proposed labeling of PPX in Pregnancy Category B. Three major concerns arose from the studies that are incongruent with the proposed labeling statements:

- a. PPX is clearly embryotoxic in rats at doses of mg/kg/day
- b. Because of embryotoxicity, teratology information is severely limited by the low number of evaluable pups from HD dams
- c. A developmental parameter, body weight gain, was significantly impaired in pups from HD dams in both Segment I and III studies

The data that forms the basis for statements a & b can be summarized as follows:

Study	Delivery	# Dams w/ Viable Pups		# Viable Pups/Group	
		Other Groups	HD Group	Other Groups	HD Group
Seg I ^a	C-Section	35/36	1/12	146-174	10
	Spontaneous	34/34	5/12	158-160	75
Seg I ^b	C-Section	46/48	6/48	308-330	31-53
Seg II	C-Section	58/72	4/24	222-250	51
	Spontaneous	32/36	3/11	133-138	39

Other Groups = controls, LD and MD combined; ^a = initial study, ^b = follow-up study

The impairment of rat pregnancy (i.e., low number of implantations, high number of early resorptions) by mg/kg/day PPX was predictable based on the pharmacological effect of PPX as a dopamine agonist. The sponsor has demonstrated that PPX, like other dopamine agonists, inhibits prolactin secretion in rats. Prolactin is well-established as a factor necessary for the maintenance of rat pregnancy. In fact, dopaminergic inhibition of prolactin secretion is the basis for the proposed ICH guidelines stating that **the rat is an inappropriate model for reproductive toxicology studies of dopamine agonists**. Thus, the reproductive toxicology studies could theoretically be considered deficient since it is comprised of only of one Segment II study in a single "appropriate" species, the rabbit. The rabbit is also problematic since it is unique among all species with regard to pramipexole pharmacokinetics. Although the reproductive impairments in the rat were expected, the data cannot be completely disregarded because of design flaws on the part of the sponsor. The rat studies clearly demonstrated impaired fertility and harm to the fetuses, and thus the drug should be placed in Pregnancy category C according to CFR 21, Part 201.57.

The limitations on the teratogenicity study which arose as a consequence of embryoletality should also be mentioned in labeling, particularly in light of the occurrence of some rather rare malformations in fetuses of the Segment II study (LD: one case of atresia ani, one case of sirenomelia and gastroschisis; MD: one case of cleft vertebra), which may also merit a labeling statement.

(Note: The background incidence of cleft vertebra varies markedly depending the type of affected vertebra. Fetal incidences are 0.638% for cleft thoracic vertebra, and 0.033% for cleft lumbar vertebra - MARTA Glossary of Fetal Alterations).

Body weight development was significantly impaired in pups from MD and HD dams in the Segment III study, which is not consistent with the sponsor's labeling statement that pups from PPX-treated dams develop normally. Body weight development in pups from HD dams in the Segment I study also appeared reduced, but could not be statistically evaluated because of the low pup number. A slight (insignificant) delay in eye-opening was also observed in the Segment I study. The sponsor's assertion that this impairment of body weight development is due to a drug

effect in the dam, and not a direct effect on pup development is plausible, and may be correct, but no experimental support is provided. The sponsor suggests that the basis for this finding is that PPX stimulates the dams and thereby reduces suckling opportunities by the pups; inhibition of lactation is another possibility. Irrespective of the mechanism, the question of whether the drug is affecting the dams or the pups could be addressed in a cross-fostering study. This study will not be required for approval, but until evidence is presented that argues against a direct effect of PPX on pup development, the labeling should accurately reflect the submitted findings.

Although the sponsor does not suggest inhibition of lactation as a basis for impaired pup development, the label states that PPX decreased lactation in rats. No reports addressing this effect were found in the submission. The sponsor needs to identify the pertinent reports that support this statement so that they can be reviewed.

Pharmacokinetic-studies indicated that drug exposures in the rat and rabbit LD groups in the Segment II studies approximated the exposures of humans receiving the expected PPX maintenance dose of 1.5 mg, t.i.d.

3. Other Toxicology

a. Retinal degeneration

The sponsor has addressed the issue of retinal degeneration by submission of the original findings from the rat 2-year carcinogenicity study to an Expert Scientific Panel for review, and by conducting experiments suggested by the panel aimed at characterizing a potential mechanism of degeneration and the influence of pigmentation on the development of retinal lesions in two strains of rats. These studies were reviewed under IND 34,850, and were also reviewed by an FDA consult, Dr. Tim O'Neill (see Appendix for Dr. O'Neill's review).

The sponsor's conclusion from these studies was that PPX inhibits retinal disk-shedding, a mechanism of disk turnover. Inhibition of this mechanism leads to degeneration of the retinal epithelium and photoreceptor cells. Degeneration occurred only in albino rats, and not in pigmented Brown-Norway rats suggesting that pigmentation may protect against this toxicity. This finding tends to reduce this concern with respect to human exposure. However, as concluded by the Expert Panel, disk-shedding is a universal vertebrate phenomenon. Thus, humans may still be at risk for this toxicity, albeit less sensitive due to the presence of pigmentation.

With respect to the sponsor's contention that retinal degeneration is a species/strain-specific effect, Dr. O'Neill raised the question of how closely the other species (monkeys, swine) were evaluated for retinotoxicity. The sponsor did not conduct ultrastructural or quantitative (e.g., thickness of cell layers) analyses in these species, which would have provided a more sensitive measure of toxicity. The sponsor emphasizes the point that the original findings in the rat carcinogenicity study was made during week 76, a long latency period. The monkey study was 52 weeks, and the minipig study was only 13 weeks, which may have been too short to create the

lesion. More sensitive indices of toxicity may have identified early stages of degeneration. The monkey and minipig studies were conducted several years before the 2-year rat study, so there was no reasonable basis to monitor for this lesion. However, a retrospective analysis of the tissues from these studies could have provided firmer support for the statement that retinal degeneration does not occur in these species. Thus, the sponsor's label will require modification to more accurately describe the studies in other species and their limitations. In view of the limitations, the possibility that pramipexole may damage human retinas cannot be discounted, and patients should be periodically monitored.

The proposed labeling statement that there is a long latency period for the effect is misleading since the sponsor has demonstrated that the effect can be produced in rats in 13 weeks.

The sponsor claims in the submission that the retinal lesions in Wistar rats are not indicative of retinotoxicity. Dr. O'Neill disagreed with this conclusion, and recommended (oral communication) the inclusion of a labeling statement to this effect.

b. Fibro-osseous proliferative lesions in mice

An unusual histopathological finding from the 2-year mouse study was the development of a bone lesion in female mice described as a fibro-osseous proliferative lesion. The spontaneous occurrence of this lesion was relatively high (28%), but its incidence rate approximately doubled in drug-treated mice. A dose-related trend was not evident. Similar lesions in mice have been described in the literature as arising spontaneously in aging females of certain strains (Sass and Montali, Lab Animal Sci, 30:907, 1980), and have also been observed following treatment with estrogen (Silberberg and Silberberg, Gerontology, 16:201, 1970), or the prostaglandin E1 analogue misoprostol (Dodd and Port, Vet Pathol., 24:545, 1987). The speculated mechanism for this PPX effect is an estrogen:progesterone imbalance, which is consistent with the positive effect of estrogens on bone deposition (i.e., osteoporosis therapy). No hormonal data was presented to support this mechanism.

Based on the literature descriptions, the toxicological consequence of this lesion is an invasion of marrow space by new bone and fibrous structures due to enhanced osteoblastic activity. This may be expected to reduce hematopoiesis, but this effect did not occur in this study. The potential significance of this lesion in humans is difficult to assess because of the paucity of information in the literature. The occurrence of this lesion in female mice following misoprostol appears in the labeling. Thus, inclusion of these findings in the PPX product labeling should also be considered.

4. "Neuroprotection" claim

The sponsor cites studies in which PPX protects against neurodegeneration in response to ischemia, methamphetamine (*in vivo*), and L-DOPA (*in vitro*). Only the ischemia model is generally recognized as a clinically relevant model, and in the best

case scenario this study would be acceptable evidence of efficacy to support a clinical trial for stroke. However, this data is inadequate to support a labeling claim with such widespread implications.

5. Application Deficiency

The sponsor's INDICATIONS AND USAGE statement does not specify that PPX is for use as an adjunct to any other Parkinson's disease medications (e.g. L-DOPA). Therefore, toxicology studies on the possible long-term, reproductive, or carcinogenic/mutagenic effects of PPX in combination with any other PD medications were not requested by the agency. A short-term cardiovascular study of PPX in combination with Sinemet or Eldepryl in monkeys was requested prior to the initiation of Phase I studies in patients stabilized on these drugs; no significant interactive effects occurred. Since combination therapies are frequently used in PD, and PPX may become part of that approach, the fact that the toxicological consequences of such interactions have not been evaluated in animals should appear in the label.

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LABELING

CLINICAL PHARMACOLOGY

Para. 2, Sent. 2:

"Animal studies additionally suggest that pramipexole affect dopaminergic mesolimbic pathways thought to promote motivation."

This statement is very speculative should be deleted.

Para. 3 and 4:

These paragraphs address the potential neuroprotective effects of PPX in *in vivo* (transient forebrain ischemia, methamphetamine neurotoxicity) and *in vitro* (L-DOPA neurotoxicity) models of neurodegeneration. Only the ischemia model is generally accepted as clinically relevant, but it is not sufficient to support a labeling claim with such widespread implications.

PRECAUTIONS

Include a statement to this effect:

"The toxicological consequences (long-term, reproduction, carcinogenicity/mutagenicity) of using pramipexole in combination with other Parkinson's disease medications have not been evaluated in animals."

Carcinogenesis, Mutagenesis, Impairment of Fertility

Para. 1:

Control group B is indicated as having 60 animals. The number should be 50.

Para. 2:

The findings and significance of Leydig cell adenomas and hyperplasia in rats should be simplified since there is no experimental support for an effect of PPX on LH secretion or LH receptor number:

"These findings are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice treated with PPX for 2 years, and the probable involvement of endocrine mechanisms that are not relevant to humans."

Para. 4:

Para. 4:

The statements regarding the impact of PPX on fertility in rats and *potential* impact on fertility in humans should be reworded:

"In rat fertility studies, doses of 2.5 mg/kg/day pramipexole prolonged estrus cycles and inhibited nidation. These effects were associated with reductions of serum prolactin, a hormone necessary for implantation and maintenance of pregnancy in rats."

Pregnancy

The sponsor proposes that pramipexole should be placed in Pregnancy category B. Several factors argue against this proposal. The reproductive toxicology studies demonstrated a clear embryotoxic effect in rats at doses of 2.5 mg/kg/day. Because of the high rate of embryo loss, teratology information was very limited. The sponsor's contention that teratogenic effects were not observed is also disputable since 3 fetuses in the Segment II study (2 LD, 1 MD) had rare malformations. These facts are not clearly stated in the proposed labeling. In addition, the sponsor's statement that pups of pramipexole-treated dams developed normally, specifically referring to the Segment II study, is misleading since impairments of body weight development were observed in both the Segment I and Segment III studies. Therefore, the data presented only support a Pregnancy category C labeling:

"Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Pramipexole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 2.5 mg/kg (28 times the human dose) pramipexole to rats during gestation inhibited nidation. Administration of 1.5 mg/kg (17 times the human dose) to rats on days 7-16 post-coitum (p.c.) resulted in early resorption of embryos. Because of the pregnancy impairment and embryo lethality, limited teratogenicity data from the highest test dosages of pramipexole (mg/kg) were obtained. Rare malformations were observed in fetuses from dams treated on days post-coitum. Of 250 fetuses from dams treated with 0.1 mg/kg pramipexole, one fetus with atresia ani, and one fetus with sirenomelia and gastroschisis were found. Of 222 fetuses from dams treated with 0.5 mg/kg pramipexole, one case of cleft vertebra was noted. Body weight development was impaired in pups from dams treated with 2.5 mg/kg pramipexole through gestation and weaning, or 1.5 mg/kg from day 16 p.c. through weaning. Other developmental parameters including fertility were normal in F₁ pups.

Administration of up to 10 mg/kg/day to rabbits on days 6 through 18 p.c. did not result in any embryotoxic, fetotoxic, or teratogenic effects."

Nursing Mothers

Experimental support for the statement that PPX decreased lactation in rats is not in the section of the Integrated Summary (Vol. 1.26, p. 5.1/126) indicated in the labeling statement. This statement should be deleted.

ANIMAL TOXICOLOGY

1. Retinotoxicity

1st Para.:

Modify as follows:

"Pramipexole was retinotoxic in albino rats in a 2-year rat carcinogenicity study. The incidence of lesions was dose dependent in animals receiving 2 or 8 mg/kg/day. The first retinal lesions were observed during week 76 of the study."

2nd Para.:

Modify as follows:

"Pramipexole was not retinotoxic in a 2-year carcinogenicity study in mice treated with similar or higher doses (0.3, 2, or 10 mg/kg)."

3rd Para.:

Modify as follows:

"Limited evaluation of the retina in other long-term animal studies did not reveal signs of retinotoxicity in monkeys that received pramipexole (0.1, 0.5, or 2.0 mg/kg/day) for 12 months, or minipigs that received pramipexole (0.3, 1, or 5 mg/kg/day) for 13 weeks."

4th Para.:

Modify as follows:

"Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the retinal photoreceptor cells of albino rats. In a comparative study, retinal degeneration occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day pramipexole and constant light (100 lux), but not in pigmented rats exposed to the same dose and even higher light intensities."

Thus, the retina of albino rats may be uniquely sensitive to the damaging effects of pramipexole. The potential significance of this effect in humans has not been established, but cannot be disregarded since retinal disk shedding is a universal vertebrate mechanism."

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ANIMAL TOXICOLOGY (cont.)

2. Fibro-osseous proliferative lesion

"An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0 or 10 mg/kg. Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice, or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known."

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RECOMMENDATIONS

1. The NDA is approvable.
2. Labeling recommendations are in the preceding section. A major point of contention is the sponsor's proposed labeling of pramipexole in Pregnancy category B. The submitted data support category C labeling. The labeling could be amended if negative toxicological findings in appropriately designed Segment II and cross-fostering studies are obtained. An appropriate segment II design would involve either administration of pramipexole to rats on days 8-16 (after the prolactin-dependent stage on days 6-7), or the use of another species (hamster, mouse).

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/S/

Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20667

cc.: /Division File, HFD-120
/G. Fitzgerald, Ph.D.
/J. Feeney, M.D.
/J. Purvis
/T.D. Steele, Ph.D.

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Pharmacology/Toxicology Review
IND 34,850, Amendment No. 107
12/14/95

Drug: Pramipexole (SND 919) **Reviewer:** Thomas D. Steele, Ph.D.

Sponsor: The Upjohn Co.

Indication: Parkinson's Disease

Contents of Submission:

1. "Retinal Degeneration in Albino Rats" - a discussion of toxicological findings and scientific citations to support the safe use of pramipexole in humans
2. Expert Scientific Panel Report on retinal degeneration in the 2-year pramipexole carcinogenicity study
3. Two technical reports:
 - TR 7219-95-043: "SND 919 CL 2 Y: Influence on the Rod Outer Segment Disk-Shedding Mechanism in the Retina of Albino Rats"
 - TR 7219-95-048: "SND 919 CL 2 Y: Influence on Retinal Degeneration in the Albino Rat with and without Light as a Co-factor"
4. Draft protocol: "U-98528E: 21-Day Drug-in-Diet Toxicokinetic Study with Pramipexole in Male and Female Rats"

This review will primarily address the technical reports on Pramipexole-induced retinal degeneration.

Rationale:

Pramipexole (PRAM) is a D2 dopamine receptor agonist proposed for use in Parkinson's disease. An unexpected finding in the 2-year rodent carcinogenicity study was the development of retinal degeneration in rats treated with the middle (2.0 mg/kg/day, in diet) and high (8.0 mg/kg/day, in diet) doses of PRAM. The effect was dose-dependent (males: MD = 51%, HD = 90%; females: MD = 21%, HD = 77%). The degeneration was characterized microscopically by a bilateral loss of photoreceptor (PR) cells. In about two-thirds of the affected animals, the lesion was characterized as "mild"; it was restricted to the upper hemisphere of the eye, and the peripheral (outer) portion of the retina. In the "severe" form (remaining one-third of affected animals), PR cell loss occurred in both hemispheres, the entire retina was lesioned, and vessels penetrated the retinal pigment epithelium. These lesions were first observed in premature decedents at week 76 of the two-year study. The "No Effect" dose level for retinal degeneration

in the two-year rat carcinogenicity study was 0.3 mg/kg/day. In a parallel mouse two year study, a low incidence (8-28%) of retinal degeneration was observed in all dosage groups (0, 0.3, 2.0, 10 mg/kg/d, in diet; no dose-dependence).

Histopathological findings indicated that the outer portion of the retina, which contains the PR cells and the retinal epithelium, is affected most consistently and severely by PRAM. Thus, the speculated mechanism by which PRAM induces retinal degeneration should occur in this region rather than the inner (interplexiform and amacrine) cell layer where dopaminergic cells are found. One such mechanism is the PR cell "disk-shedding and renewal system", wherein the older, outermost disks of the rods and cones are shed and phagocytized in retinal pigment epithelial cells and replaced by new disks within the PR cell. The activity of this mechanism leads to the appearance of "phagosomes" containing digested disks in the retinal pigment epithelium. If the shedding/renewal system is disrupted, old disks are not shed and phagocytized, and degeneration of the retinal epithelium and PR cells may result. The disk-shedding/renewal system follows a circadian rhythm in rats and peaks shortly after the onset of light. Retinal melatonin appears to be a primary activator of disk-shedding, and its synthesis is inhibited by dopamine agonists and constant light. Therefore, the sponsor proposes that disruption of this disk-shedding/renewal system by PRAM is a possible mechanism of retinal degeneration. In addition, the sponsor contends that PRAM-induced retinal degeneration is a strain-specific effect and occurs only in albino (non-pigmented) rats, which are known to be susceptible to damage by light alone. Thus, pigmentation can be viewed as protective, and degeneration should not occur in pigmented animals, including humans.

These two hypotheses were the focal points of the experiments presented in this submission. The first experiment (TR 7219-95-043) was a combination of a model development/mechanistic study in which an inhibitory effect of PRAM (25 mg/kg, p.o. daily for 30 days) on disk-shedding in a "sensitive" albino strain (Wistar) of rats was established. In the second series of studies (TR 7219-95-048), the role of pigmentation in retinal degeneration was addressed by comparing the effects of daily treatments with PRAM (25 mg/kg, p.o. for 30 days), with light as a cofactor, on microscopic retinal changes in non-pigmented (Wistar) and pigmented (Brown Norwegian) rats. Based on the results of these studies, the sponsor concludes that PRAM-induced retinal degeneration is due to a direct D₂ receptor-mediated inhibitory effect on disk-shedding/renewal in non-pigmented animals, and is therefore not a safety risk in pigmented species (i.e., humans).

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TR 7219-95-043: "SND 919 CL 2 Y: Influence on the Rod Outer Segment Disk-Shedding Mechanism in the Retina of Albino Rats"

Study Design:

Results of two individual studies, a preliminary (I09) and a main study (I22), were presented.

Subjects: Male Wistar rats
I09: N = 25; 15 control, 10 PRAM
I22: N = 50; 25 control, 25 PRAM

Treatments:

PRAM animals were treated daily by gavage with 25 mg/kg for 30 days. The time of drug administration was 7-8 am (this was not reported in the submission; the information was obtained via a teleconference with the firm on 12/8/95). Animals were housed under "strict barrier conditions". The light intensity varied between 12-60 lux. The light cycle reported in the document text was 12:12 hr, but diagrams of the experimental design indicated "lights out" at 8 pm and "lights on" at 6 am.

Necropsy:

Animals were sacrificed on days 30/31 at the following time points:

8 pm, 5 am, 8 am, 10 am, 12 pm

These times were selected to establish the circadian pattern of disk-shedding. In the preliminary study, 3 control and 2 PRAM animals were sacrificed at each point. In the main study, five animals from each group were sacrificed at each time point.

Parameters:

Morphology: Eyes were removed, marked to distinguish upper and lower hemispheres, and sectioned for light and transmission electron microscopy. Toluidine blue-stained sections for light microscopy were evaluated for histopathological changes. Ultrathin EM sections were stained with uranyl acetate and lead citrate, and analyzed quantitatively for the number of phagosomes within the retinal pigment epithelial (RPE) cell layer.

Other Observations: Body weight and food intake were measured once weekly.

Results:

Morphology:

Light microscopy did not reveal any significant treatment-related changes. Quantitative EM analysis of phagosome numbers in RPE cells of control animals demonstrated a circadian pattern of disk-shedding. A small increase in phagosome number at 5 am was followed by a sharp rise at 8 am, 2 hrs after light onset. The peak number of phagosomes was approximately eight-fold greater than that at any other time point.

Pramipexole markedly blunted the peak rise in phagosome number at 8 am. The average reduction in phagosome number in PRAM-treated animals was 69% (combination of data from both studies). No significant differences in phagosome number were evident at any other time point.

A separate evaluation of phagosome numbers in the individual hemispheres did not reveal a striking hemispheric pattern of drug effect. The peak in phagosome number in both hemispheres was blunted by pramipexole, although statistical significance was achieved only in the upper hemisphere.

Other Observations:

As observed in the previously reported 13-week toxicity study, PRAM significantly reduced body weight throughout the study. The effect is probably secondary to a reduction of food intake, although PRAM-treated animals in the main study (I22) consumed significantly more food. These data were not elaborated since they were addressed in previous studies.

TR 7219-95-048: "SND 919 CL 2 Y: Influence on Retinal Degeneration in the Albino Rat with and without Light as a Co-factor"

Study Design:

Results of two individual studies, a preliminary (I10) and a main study (I31), were presented.

Subjects:

I10: N = 96 (48 M, 48 F) Wistar rats
N = 20 (10 M, 10 F) Brown Norway rats

I31: N = 64 (32 M, 32 F) Wistar rats
N = 64 (32 M, 32 F) Brown Norway rats

Treatments:

I10: This study was primarily to determine the appropriate light intensities for the main study. The Wistar rats were divided into three groups exposed to light intensities of either 60, 100, or 200 lux. The Brown Norway rats were exposed to 500 lux light. The groups were subdivided into control

and PRAM (25 mg/kg, p.o.) treatment groups. Animals were treated once daily (7-8 am) until the day before necropsy. The longest treatment duration was 13 weeks. Interim sacrifices were conducted at week 3, 5, and 9 (2M/2F) for Wistar rats, and week -1, 5, and 9 (1M/1F) for Brown Norway rats.

I31: Wistar rats were exposed to a light intensity of 100 lux, and Brown Norway rats were exposed to 500 lux. Thirty-two rats of each strain (16M/16F) received either PRAM (25 mg/kg, p.o.) or no drug once daily (7-8 am) until the day before necropsy. Eight rats (4M/4F) from each group were sacrificed at weeks 3, 5, 9, and 13.

Animals were housed under "strict barrier conditions". The lights were on 24 hr/day.

Necropsy:

Animals were sacrificed, eyes were marked to distinguish upper and lower hemispheres, removed and processed for light microscopy. H/E-stained sections were evaluated for histopathological changes to the retinae.

Other Observations:

Body weight and food intake were measured once weekly.

Results:

Morphology:

I10: Continuous exposure of albino Wistar rats to light for 3 months resulted in intensity-dependent retinal damage as assessed by loss of photoreceptor cell nuclei. PRAM caused more pronounced retinal degeneration, and shortened the latency for onset of degeneration compared to control animals. The effect was clearest in the 100 lux treatment groups; reduction in 100 lux/control animals were first apparent at week 5, whereas 100 lux/PRAM animals showed PR cell loss at week 3. All albino rats exposed to 200 lux light for 13 weeks were blind. Hence, the 100 lux intensity level was most appropriate for the main study.

None of the control or PRAM-treated Brown Norway rats exposed continuously to 500 lux light for 13 weeks showed any signs of retinal damage.

I31: Continuous exposure of **untreated** albino Wistar rats to 100 lux light resulted in PR cell degeneration. The severity of degeneration increased with exposure duration. PRAM treatment shortened the latency and increased the severity of damage. Both the upper and lower hemispheres of the eyes were lesioned.

None of the control or PRAM-treated Brown Norway rats exposed continuously to 500 lux light for 13 weeks showed any signs of retinal damage.

Other Observations:

Body weight and food intake data were collected but not evaluated by the sponsor. As a part of this review, these data were assessed to determine if there were strain differences in response to the drug other than retinal degeneration. Some interesting trends were noted, such as a PRAM-induced reduction of body weight gain in the Wistar, but not Brown Norway, rat. While such a finding suggests the possibility of strain differences in drug exposures/metabolism, the fact that the two strains were never subjected to similar light intensities prevents the evaluation of this hypothesis.

Summary and Conclusions:

The major finding of these studies was that daily treatment of albino Wistar rats, but not pigmented Brown Norway rats, with pramipexole (25 mg/kg, p.o.) produces retinal degeneration characterized by loss of photoreceptor cells. Duration and intensity of light exposure are critical co-factors for degeneration; lesion severity is increased and onset latency is shortened with increasing intensity of light. A drug effect can be observed with a treatment duration as short as 3 weeks in Wistar rats exposed to constant 100 lux light.

The proposed mechanism of PRAM-induced retinal degeneration is an inhibition of the circadian-controlled disk-shedding/renewal system, which is necessary for a constant supply of "fresh" disks in the PR cell. A reduction in disk-shedding is reflected by a decrease in phagosome number in the retinal epithelial cell layer. The disk-shedding/renewal mechanism is apparently activated shortly after light onset by melatonin. The biosynthesis of melatonin in vertebrate retina is inhibited by D₂ receptor activation. Thus, stimulation of D₂ receptors by pramipexole prevents melatonin-induced activation of disk-shedding leading to retinal degeneration.

The data presented support the sponsor's contention that: 1) pramipexole-induced inhibition of disk-shedding/renewal is a possible mechanism of degeneration, and 2) non-pigmented animals are more susceptible to the damaging effects of pramipexole than pigmented animals. The latter hypothesis is the basis for the sponsor's assertion that the risk of retinal damage in humans is minimized by pigmentation. However, some outstanding deficiencies in experimental support for this hypothesis remain:

1. A primary assertion is that pramipexole-induced retinal degeneration is due to D₂ receptor activation, and therefore may be a universal phenomenon for this class of drugs. However, there are no pharmacological data showing that the effect is blocked by D₂ antagonists or, more importantly, replicated by other DA agonists. A single citation that the MAO-A inhibitor clorgyline disrupts retinal rhythmicity is cited to support dopaminergic involvement. However, it is well-known that DA is metabolized by MAO-B; thus, the effect of clorgyline may have been due to elevation of retinal 5-HT rather than DA. In addition, the sponsor cites a study in which the D₂ agonist bromocriptine protected against light-induced retinal damage. If a clinically-important, positive control such as L-DOPA had been included in these studies and shown to

replicate the effect of pramipexole, than the retinal damage safety concerns would have been reduced.

2. Little explanation is provided for how pigmentation protects against PRAM-induced retinal damage. There is a very brief mention of the role of melanin in light absorption, but how the proposed mechanism (i.e., disk-shedding) is differentially affected in pigmented and non-pigmented animals is not examined. This is an important point, as indicated by the sponsor's Expert Panel, since disk-shedding is a universal vertebrate phenomenon, and if "alteration of this mechanism is the critical step in the development of retinal lesions in the albino rat given pramipexole, the Panel cannot exclude the possibility that a comparable retinal degeneration could occur in human beings chronically treated with the drug."
3. Although the "Pigmented versus Non-pigmented Rat" study provides evidence to support the hypothesis those strain differences in susceptibility to retinal damage exist, the question of whether this is a selectivity or sensitivity issue remains. A superficial perusal of the body weight and food intake data in TR7219-95-049 suggested the possibility of strain differences in response to pramipexole on these parameters, although the high light intensity the Brown Norway rats were exposed to could not be discounted as a factor. Thus, exposure level or mechanistic comparisons between the Wistar and Brown Norway strains would have been useful.
4. Also along the lines of species sensitivity, the argument is raised that pigmented animals in other long-term toxicity studies that were exposed to higher doses of PRAM than anticipated human exposure, did not show signs of degeneration. Results of a one-year monkey study (0.1, 0.5, 2 mg/kg/d, p.o.) and a 13-week minipig study (0.3, 1, and 5 mg/kg/d, p.o.) are cited. It is noted that in the 2-year rat carcinogenicity study, microscopic retinal changes were first observed at week 76. Using the argument that pigmentation is protective, degenerative changes in pigmented animals may not necessarily be expected until exposure durations greater than those conducted in the monkey or minipig studies are achieved.
5. The finding that albino mice in the 2-year carcinogenicity study did not incur dose-dependent retinal degeneration also argues against pigmentation as the sole or primary determining factor for susceptibility to PRAM-induced retinal damage.

Additional general comments on the submission are:

1. The sponsor repeatedly attempts to distinguish the retinal degenerative effects of pramipexole from retinotoxicity based on the following findings from the 2-year rat carcinogenicity study where the effects were first observed:
 - Higher doses of PRAM in toxicity studies of shorter duration did not cause photoreceptor cell damage in albino rats
 - The latency time for degeneration was greater than 52 weeks
 - The hemispheric pattern of degeneration differentiates it from retinotoxicity

which usually involves the entire retina

The data provided in this submission completely contradicts these arguments. Microscopic degenerative effects of 25 mg/kg PRAM (in combination with constant light) were observed as early as three weeks after treatment initiation. Even under normal lighting conditions, mechanistic endpoints (i.e., disk shedding) were affected after 30 days of treatment. The upper and lower hemispheres appear to be equally sensitive to the retinal degenerative effects of PRAM using the markers employed in these studies. Although this is primarily a semantic issue, the data for PRAM presented in this submission meet the sponsor's own criteria for a retinotoxic agent.

2. The "No Effect" level of PRAM for retinal degeneration in the 2-year rat carcinogenicity study was 0.3 mg/kg/d, and the expected human dose is 0.1 mg/kg/d. This represents a three-fold "safety margin". However, the target patient population (Parkinson's disease) is elderly, may have preexisting visual disturbances, and has a compromised dopaminergic system. Receptor supersensitivity is a well-established phenomenon in animals depleted of dopamine, and the possibility exists that D2 receptors in the retina of PD patients may have an exaggerated response to agonist administration. These factors may result in a narrowing of the safety margin for PRAM.

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Recommendations:

Several additional non-clinical questions have been raised by these studies:

1. Can the degenerative effects of PRAM be replicated by a clinically relevant dopaminergic agonist? Although using disk-shedding/phagosome number as a marker represents a shorter term study, assessing microscopic changes is probably a more appropriate index of degeneration since inhibition of the disk-shedding mechanism is hypothetical at this point.
2. How does pigmentation protect against PRAM-induced retinal degeneration? Does PRAM (or constant light) **not** inhibit the disk-shedding mechanism in pigmented animals? If strain differences were found, the validity of inhibition of disk-shedding as a degenerative mechanism would be supported.
3. Although strain differences in exposure levels may be a remote possibility as a contributing factor to the differences in response to pramipexole, they cannot be discounted and should be evaluated.
4. Is the effect of PRAM in pigmented and non-pigmented animals a sensitivity or selectivity issue? Does pigmentation merely prolong the latency to degeneration? Why were albino mice in the 2-year carcinogenicity not affected by pramipexole?
5. The timing of PRAM administration in these studies should be reevaluated. By administering the drug at the time of peak shedding (7-8 am), conditions are favorable for observing a drug effect by disrupting the normal circadian pattern, but do not accurately reflect the conditions under which the initial degenerative effects were observed/produced (drug-in-diet).

Appropriate experiments to address these issues should be considered to solidify the contention that pramipexole does not represent a serious risk of irreversible retinal degeneration in humans, which may lead to blindness.

/S/ 11/20/96

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Thomas D. Steele, Ph.D.

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Summary and Evaluation:

This amendment contains six additional non-clinical toxicology studies of putative pramipexole (PPX) degradative products. Acute toxicity/lethality was studied in mice following intravenous administration, and mutagenicity was evaluated in a standard Ames assay. The degradative products were designated BIII 786, BIII 820, Product V, and Products Z₁ and Z₂. BIII 786 and BIII 820 were tested in separate and independent experiments. The photochemical degradation products V, Z₁ and Z₂ were tested by preparing a defined mixture of PPX and these components. The chemical structures are as follows:

According to the chemistry reviewer, Dr. Zarifa, these impurities were not found in the batches.

The only significant toxicological findings were obtained with BIII 786. The LD₅₀ of this compound was times lower than that of PPX, and the signs of toxicity by the two compounds were similar. In addition, BIII 786 evoked a positive response

at amounts ≥ 5000 $\mu\text{g}/\text{plate}$ in the Ames assay with activation by either rat or hamster S9 in strain TA98. The sponsor contends that the results demonstrate a "very weakly positive" mutagenic response. Whether the descriptive modifiers "very weakly" accurately characterize the mutagenic response is debatable since the mutagenic response to the positive control (2-aminoanthracene, 2-AA, 0.5 $\mu\text{g}/\text{plate}$) in the presence of rat S9 was only 3-fold higher than that produced by BIII 786. However, 2-AA produced a far greater mutagenic response than the test compound in the presence of hamster S9.

The acute toxicity of BIII 820 was approximately equivalent to that of PPX in terms of potency and symptomology, and a mixture of PPX with the photochemical degradative products was less toxic than the parent compound. No other positive mutagenic responses were obtained.

The Ames tests conducted with BIII 786 and BIII 820 were deficient in that a strain sensitive to A-T mutations (*E. coli* WP2 uvrA or *S. typhimurium* TA102) was not included in the screen as set forth in the OECD Guidelines.

Since these impurities are not present at a level greater than 0.1%, additional testing is not required at this time. In the event that batches are submitted in which levels exceed this value, the Ames test deficiencies should be addressed.

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Study Results:

1. Compound BIII 786 BR3:

Acute toxicity:

This compound was tested in mice (Ico:OF1), and compared to PPX according to the following dosage regimen:

1. SND 919 C12 Y

ANIMALS/DOSE		DOSE	CONCENTRATION
male	female	(mg/kg)	(g/100 ml)
-	5	100	1
5	5	125	1.25
5	5	160	1.6

2. BIII 786 BR3

ANIMALS/DOSE		DOSE	CONCENTRATION
male	female	(mg/kg)	(g/100 ml)
5	-	12.5	0.125
5	5	16	0.16
5	5	20	0.2
-	5	25	0.25

Animals were observed for 14 days following treatment. Mortality was as follows:

Dose	BIII 786		PPX		Dose
	M	F	M	F	
12.5	0/5	-	-	0/5	100
16	1/5	0/5	0/5	1/5	125
20	4/5	0/5	5/5	3/5	160
25	-	3/5			

Calculated LD₅₀s were:

	<u>BIII 786</u>	<u>PPX</u>
Males:	17.9	141.4
Females:	23.4	150.9

All deaths occurred within 30 min. Similar signs of toxicity were observed with either compound (prone/lateral position, dyspnea, tachypnea, tonic-clonic convulsions). No delayed deaths occurred, and no gross pathological changes were evident at autopsy.

These studies indicate that the degradation product is times more toxic than PPX following i.v. treatment in mice.

Mutagenicity:

The mutagenicity of BIII 786 was tested in a standard Ames test (plate incorporation method) at concentrations ranging from 10-7000 µg/plate in the absence and presence of rat and hamster S9. The strains used were TA1535, TA1537, TA100 and TA98.

In the absence of S9, there were no increased mutation frequencies by BIII 786. However, a positive response (greater than doubling of control mutation frequency) was noted in the presence of either rat or hamster S9 in strain TA98:

BIII 786 BR3 concentration (µg/plate)	Relative mutation frequency*	
	Rat S9	Hamster S9
1500	-	-
3000	-	-
5000	-	-
6000	2.8	3.0
7000	2.7	3.1

Of note, is the marked species difference between the two S9 fractions with respect to responsiveness to the positive control 2-aminoanthracene (Tab. 1). With rat S9, 2-AA causes about an 8-fold increase in mutation frequency whereas hamster S9 causes at least a 90-fold increase in mutation frequency. Interestingly, little or no species difference is evident in mutagenic response to BIII 786 as increases were noted with S9 fractions from either species.

Since this rate of mutation frequency meets the sponsor's own criteria for a positive response in the Statistics section of the report, and the response in the presence of the rat S9 is only about 3-fold lower than the positive control response, it is difficult to agree with the sponsor's conclusion that BIII 786 "was very weakly mutagenic."

An apparent oversight in this study was the omission of a strain sensitive to A-T mutations (*S. typhimurium* TA102 or *E. coli* WP2 uvrA) as recommended in the OECD Guidelines.

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Table 8. Induction of mutations in the presence of a metabolizing system;
Experiment 3 (MUT 268/5, /6)

Substance ^a	Conc. (µg/pl.)	S9 ^b	Number of revertants per plate ^c		
			T198 S9 Rat	S9 Ham	
Solvent control (dist. water, 140 µl/pl.)		+	28	28	
			19	28	
			14	29	
			20 HV	28 HV	
			7 SD	1 SD	
BIII 786 ER3	10	+	n.t.	23	
				31	
				26	
				27 HV	
				4 SD	
	100	+	n.t.		27
					25
					26
					26 HV
					1 SD
	500	+	n.t.		26
					39
					36
					34 HV
					7 SD
1500	+	n.t.		47	
				47	
				49	
				48 HV	
				1 SD	
3000	+	n.t.		60	
				50	
				63	
				58 HV	
				7 SD	
5000	+			45	
				37	
				39	
				40 HV	
				4 SD	
6000	+			68	
				49	
				47	
				55 HV	
				12 SD	
BIII 768 ER3	7000	+		41	
				69	
				48	
				53 HV	
				15 SD	
2A	0.5	+		90	
				95	
				77	
				87 HV	
				9 SD	
				152	
				>2500	
				157	
				157 HV	
				5 SD	
Titer of the bacterial suspension (x10 ⁸ /ml)			2.6 (248, 246, 271) ^d	2.7 (288, 243, 276) ^d	

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2. Compound BIII 820 BS:

Acute toxicity:

This compound was tested in mice (Ico:OF1) according to the following dosage regimen:

ANIMALS/DOSE		DOSE	CONCENTRATION
male	female	(mg/kg)	(g/100 ml)
5	5	100	1.0
5	5	150	1.5
-	5	200	2.0

Mortality was as follows:

Dose	BIII 820	
	M	F
100	0/5	0/5
150	3/5	1/5
200	-	3/5

Calculated LD₅₀s were:

Males: 144.0
Females: 186.8

All deaths occurred within 3 min. Signs of toxicity were similar to those observed with PPX (prone/lateral position, dyspnea, tachypnea, tonic-clonic convulsions). There were no delayed deaths and no gross pathological findings in any animals at autopsy.

These studies indicate that the degradation product is approximately equipotent in acute toxicity to PPX following i.v. treatment in mice.

Mutagenicity:

The mutagenicity of BIII 820 was tested in a standard Ames test (plate incorporation method) at concentrations ranging from $\mu\text{g}/\text{plate}$ in the absence and presence of rat and hamster S9. The strains used were TA1535, TA1537, TA100 and TA98.

No cytotoxic or genotoxic effects were produced by BIII 820 under any conditions. As in the preceding study with BIII 786, a strain sensitive to A-T mutations (*S. typhimurium* TA102 or *E. coli* WP2 uvrA) was not tested.

3. Photochemical Degradation Products V, Z₁ and Z₂ in combination with PPX

For these experiments, a special compound mixture containing PPX and its photochemical degradative products was prepared. The final composition of the material on a percent basis was:

PPX (dihydrochloride salt)	-	83.1
Product V	-	9.5
Product Z ₁	-	2.5
Product Z ₂	-	4.9

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The rationale for this composition was not provided.

Acute toxicity:

The material was dissolved in saline and administered intravenously to mice (Ico:OF1) at doses of 150 and 225 mg/kg (5/sex/dose). Animals were observed for 14 days.

Three animals of each sex died within 2 minutes of receiving the 225 mg/kg dose. Signs of toxicity were prone/lateral position, tachypnea, exophthalmia, saltatory convulsions, and tremor. There were no delayed deaths and no gross pathological findings in any animals at autopsy. The calculated LD₅₀ was 216 mg/kg.

These studies indicate that the photochemical degradation products in this composition are less acutely toxic than PPX following i.v. treatment in mice.

Mutagenicity:

The mutagenicity of the photochemical degradative product mixture was tested in a standard Ames test (plate incorporation method) at concentrations ranging from 10-10000 µg/plate in the absence and presence of S9 from rat and hamster. The strains used were *S. typhimurium* strains TA1535, TA1537, TA100 and TA98, and *E. coli* WP2 uvrA.

No cytotoxic or genotoxic effects were produced by the mixture under any conditions.

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Recommendations

1. Since the potential impurities characterized in these studies have not been detected in batches at a level greater than 0.1%, additional testing is not required at this time. In the event that batches are submitted in which levels exceed this value, the Ames test deficiencies should be addressed.

/S/

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Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20667

cc.: /Division File, HFD-120
/G. Fitzgerald, Ph.D.
/J. Feeney, M.D.
/J. Purvis
/T.D. Steele, Ph.D.

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APPENDIX

Pathologist's Review of Retinal Degeneration Findings

Conducted by:

T.P. O'Neill, D.V.M., Ph.D
Armed Forces Institute of Pathology
Washington, D.C. 20306-0001



Memorandum

Date: 13 February 1996

From: Glenna Fitzgerald, Ph.D. /S/
Pharmacology Team Leader
Division of Neuropharmacological Drug Products

Subject: Consultative review of rodent retinal degenerative findings; NDA 20-667

To: Timothy O'Neill, D.V.M., Ph.D.
Dept. of Veterinary Pathology
Armed Forces Institute of Pathology
Building 54
16th and Alaska Ave., NW
Washington, D.C. 20306-6000

Thank you so much for agreeing to review the drug-induced retinal degeneration findings that you have discussed with Dr. Lois Freed. Enclosed please find several documents we would like evaluated.

To briefly summarize the issue, pramipexole is a relatively selective dopamine D2 receptor agonist under development by Upjohn for the treatment of Parkinson's disease. An unexpected finding in the two-year rat carcinogenicity study was retinal degeneration in mid- (2 mg/kg/day) and high- (8 mg/kg/day) dose rats. This finding was first made in premature decedents during weeks 76/78. The primary contention of the sponsor is that this finding is a species-specific effect in albino rats due to the lack of "protective" pigmentation. To support this contention, the sponsor has conducted a comparative study of retinal degeneration in non-pigmented (albino) and pigmented (Brown-Norway) rats. In addition, the sponsor has conducted a study on the possible mechanism by which pramipexole produces retinal degeneration in albino rats. According to their hypothesis, dopamine D2 receptor activation by pramipexole effectively mimics conditions of constant light, which is known to damage the retinae of albino rats. The sponsor's bottom line is that pigmented species (i.e., humans) should not be subject to similar retinal degenerative effects of pramipexole.

The following documents contain the material for review:

1. Boehringer Ingelheim Document #U93-0116 is a discussion of the initial retinal degeneration findings in the 2-year rat carcinogenicity study, and a literature review of retinal degeneration
2.
 - a. A literature review of retinal degeneration

- b. An Expert Panel Report regarding the drug-induced retinal degeneration findings and their possible relevance to humans
- c. A technical report (TR 7219-95-043) of a study in which a potential mechanism for drug-induced retinal degeneration (inhibition of disk shedding) was evaluated
- d. A technical report (TR 7219-95-049) of a study in which the degenerative effects of the drug were compared in pigmented and non-pigmented rats

Color photocopies from the Boehringer Ingelheim document (#93-0116, pages 32-34), and an original electron micrograph from the disk-shedding study (TR 7219-95-043) are provided. The histopathological evidence is rather limited, but according to the sponsor, this is the best they have at this point.

As you review the material, please consider the following questions:

- 1. In your opinion, has the sponsor provided convincing evidence that this is a species-specific effect that will occur only in non-pigmented animals? Bear in mind that albino mice did not show signs of retinal degeneration.
- 2. Are the retinal degeneration findings more likely a species-selective effect, as the sponsor contends, or a species-sensitive effect (i.e., does pigmentation merely prolong the latency for the degeneration)?
- 3. What are your recommendations for clinical monitoring for this effect, if any (type of monitoring, frequency)?
- 4. An issue that will arise during labeling is the description of the changes. The sponsor adamantly contends that the drug is not "retinotoxic", primarily citing the long latency for the changes. However, in the mechanistic and comparative studies, the retinal changes were produced in a much shorter period of time. Should the drug be considered retinotoxic? In non-pigmented rodents only?

If you have questions please contact me at (301) 594-5501, or speak directly to the pharmacology/toxicology reviewer of the NDA (who put this package together and knows the data better than anyone else) Thomas Steele, Ph.D., at (301) 594-5508.

cc: NDA 20-667
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THE REGISTRY OF COMPARATIVE PATHOLOGY

Armed Forces Institute of Pathology
Washington, D. C. 20306-0001

July 15, 1996

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Pharmacology Team Leader
Division of Neuropharmacological Drug Products
HFD-120
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Fitzgerald:

Thank you, once again, for the opportunity to assist the Division of Neuropharmacological Drug Products in the review of NDA 20-667. I very much appreciate the occasions to collaborate with your group in this and past reviews. I do, however, apologize for the delay in reporting this review summary to you, as my work here has been very demanding lately.

Enclosed along with this review of NDA 20-667 are the original documents sent to me for review on 15 Feb. 1996, to include:

1. Boehringer Ingelheim Document #U93-0116: discussion of the initial retinal degeneration lesions findings in the 2-year rat carcinogenicity study and literature review of retinal degeneration
2. containing:
 - a. Literature review of retinal degeneration
 - b. Expert Panel Report discussing the drug-induced retinal lesions and relevance to humans
 - c. Technical Report: TR 7219-95-043, SND 919 CL 2 Y: -Influence on the Rod Outer Segment Disk Shedding Mechanism in the Retina of Albino Rats
 - d. Technical Report: TR 7219-95-049, Pramipexole (SND 919 CL 2 Y) Influence on retinal degeneration in the albino rat with and without light as a cofactor

Phone: (202) 782-2440 ♦ Fax: (202) 782-9161/9150

3. Color photocopies and black and white photos of histological and electron microscopic images of control and drug-induced lesions in experimental animals.

The materials are returned in their entirety and original condition. In no instance was the material duplicated or reproduced and in no case was the proprietary nature of material disclosed.

As part of my review, in addition to review of the provided printed materials listed above, I conducted and reviewed information from fairly exhaustive MEDLARS[®] database searches from 1990 to the present on: retinal degeneration in rats and mice; dopamine and retina; dopamine receptors and retina; and dopamine or dopamine receptors and retinal degeneration. Moreover, I consulted with members of the Department of Ophthalmic Pathology, AFIP, on several questions I had regarding retinal pathology as they related to the lesions described in this NDA.

Before I specifically address the questions posed in your letter of 15 February 1996, I would like you to gain an appreciation for some of the assumptions I performed my review of the materials under. Defining these will aid in how I address these questions and arrived at my conclusions.

Firstly, The term retinal degeneration is ill defined in the documents. At times the term is applied to photoreceptor cell loss and at other times refers to, I assume, total loss of the retina.

Secondly, I did not find in the materials provided a detailed histological description of the retinal degeneration in the affected (treated) rats other than that described in the "Report of Expert Panel Evaluation...". In that report only a fairly general description of the light microscopic pathology was eluded to, i.e. "...loss of photoreceptor cells, inner layers of the retina had lesions and vessels penetrated the retinal pigment epithelium", and in TR 7219-95-049: "reduction of photoreceptor cell nuclei...". Little information regarding the genesis (e.g. the earliest lesion observed were nuclear pycnosis followed by cytoplasmic vacuolation, etc) of the photoreceptor cell loss was provided. Therefore, one has to assume these photoreceptor cells just disappeared without premonitory changes.

Thirdly, no mention was made of pathology secondary or ancillary to photoreceptor cell loss (i.e. retinal degeneration began with photoreceptor cell loss followed by inner nuclear layer cell loss, etc.), but rather terms such as "severe retinal degeneration" or "photoreceptor cells of the entire retina were completely degenerated". Therefore, one again assumes lesions were either restricted to photoreceptors or, as indicated, the entire retina (all layers) in the most severe form and were degenerated without a stepwise or pathogenesis to loss of the

other layers of the retina.

Lastly, the literature review and discussion material provided in the technical reports was at times confusing and contradictory in reference to dopamine action and metabolism and D2 (dopamine receptor) activation of the photoreceptor and inner nuclear layer cells. I gained ancillary information and clarification from the MEDLARS[®] searches previously mentioned.

In response to your questions regarding my review, I provide the following responses:

1. Within the context of the studies conducted and reference materials included (or lack of information showing D2 agonist-induced retinal degeneration in other species), the sponsor has provided evidence to support their contention that this is a species and strain-specific effect in non-pigmented (albino) rats. Detailed information on the conduct of the histopathological examination for both affected and non-affected species is not available in the materials and, therefore, I cannot assess what effort was put into looking for very early, inapparent or ultrastructural changes that may have been present in the other species/strains.

2. Again, within the context of the information provided or found, the absence of retinal degeneration in parallel 2-year studies in albino (non-pigmented) mice and pigmented rats would tend to support a strain-selective (i.e. Wistar rat) effect of the drug-induced retinal degeneration. As ultrastructural studies were not conducted in other species or 2-year studies using pigmented rats were not conducted the question of pigmentation prolonging latency of retinal degeneration cannot be answered.

3. Although this is not my area of expertise, I find the sponsor's plan for clinical monitoring of patients receiving the drug to be fairly inclusive of detecting untold effects on eyesight. A detailed clinical monitoring schedule to include parameters and periodicity of exams would be helpful.

4. From what I can conclude from the information on the drug, the drug is retinotoxic in Wistar rats. Albeit, the drug has not been shown to be retinotoxic in a limited number of other species of animals (including albino mice) or strains of rat, it is definitely toxic to the photoreceptor cells of the retina in Wistar rats.

In summary, after careful inspection and consideration of the provided and supplemental documentation I was able to retrieve on the subject matter, I conclude that the sponsor's claim: "that the retinal degeneration observed in association with pramipexole is species-specific and unique to albino rats" is correct within the limitations I have specified above. Without further information

regarding the histopathology of the retina in other species or future studies designed to better quantitate and characterize the effects of the drug on the retina in non-pigmented and pigmented species, I am unable to predict the effects of the drug in the human patient.

Once again, thank you very much for this opportunity to be of assistance to the FDA. Should you have any questions regarding this report or my conduct of the review, please do not hesitate to contact me directly at (202) 782-2442 or FAX at (202) 782-9150.

Respectfully Yours
/S/

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Timothy P. O'Neill, D.V.M., Ph.D.
Chief Pathologist
Diplomate, American College of Veterinary Pathologists

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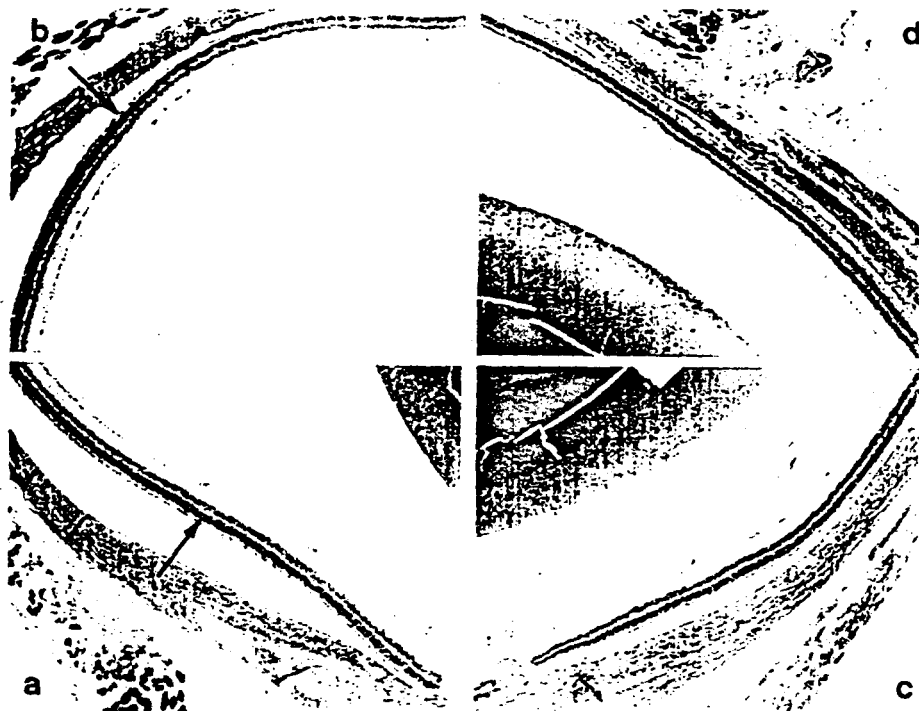


Fig. 1: SND 919 Cl 2 Y carcinogenicity study rat: control rat no. 0014
 a (central) and b (peripheral) represent one retinal hemisphere
 c (central) and d (peripheral) the second of the same eye, HE, 43 x
 —> = photoreceptor cell layer

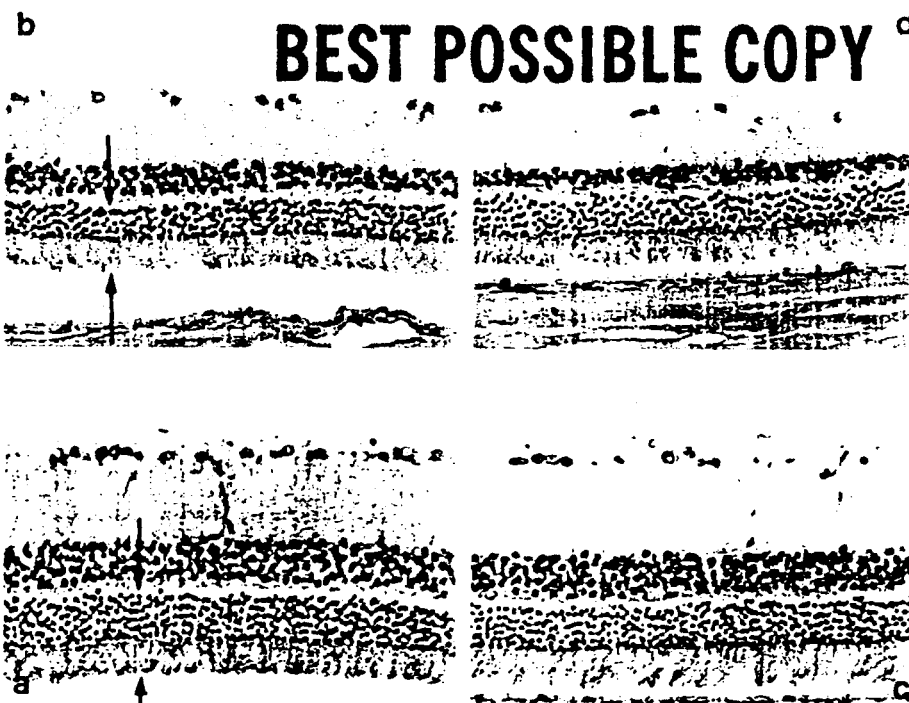


Fig. 2: The retinal localisations shown in Fig. 1 at higher magnification,
 HE, 260 x
 —> <— = photoreceptor cell layer

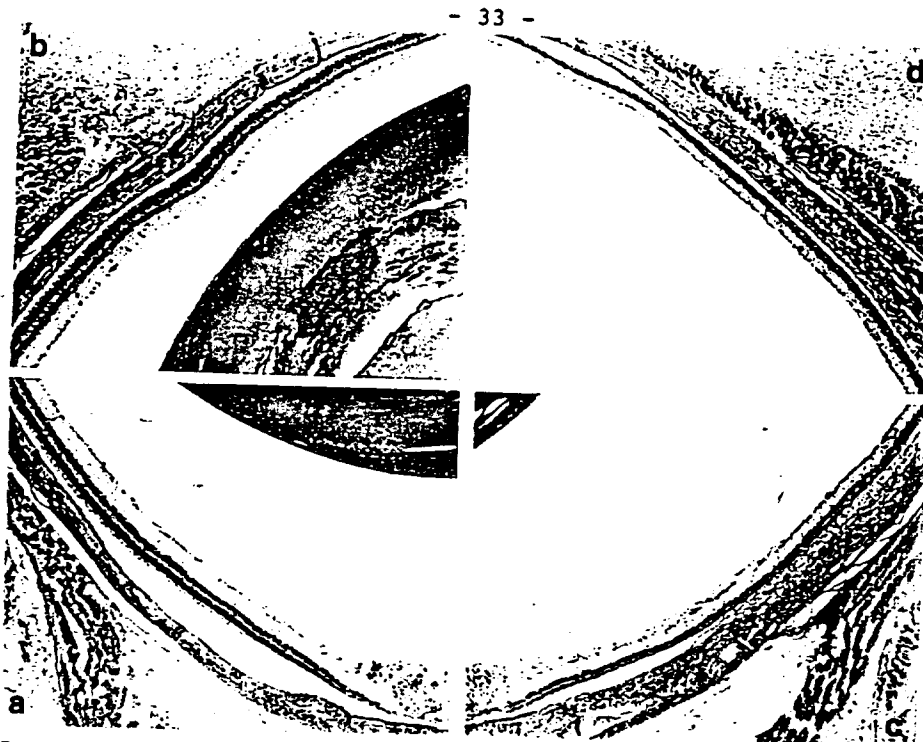


Fig. 3: SND 919 Cl 2 Y carcinogenicity study rat: high dose rat no. 3526
 a (central) and b (peripheral) represent one retinal hemisphere
 c (central) and d (peripheral) the corresponding, HE, 43 x,
 photoreceptor cell layer is present in one hemisphere
 nearly missing in the other one.

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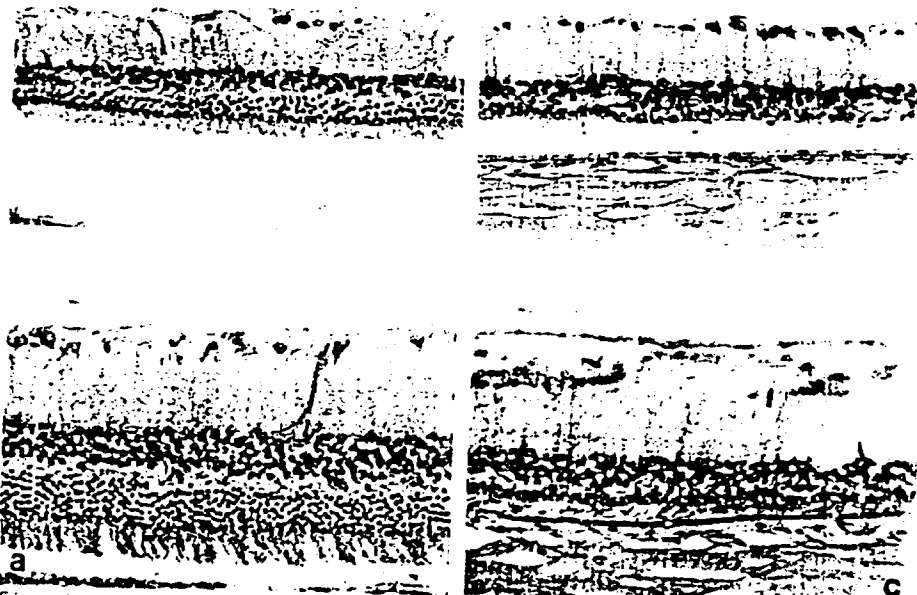


Fig. 4: The retinal localisations shown in Fig. 3 at higher magnification,
 HE, 260 x, intact and degenerated photoreceptor cell layer

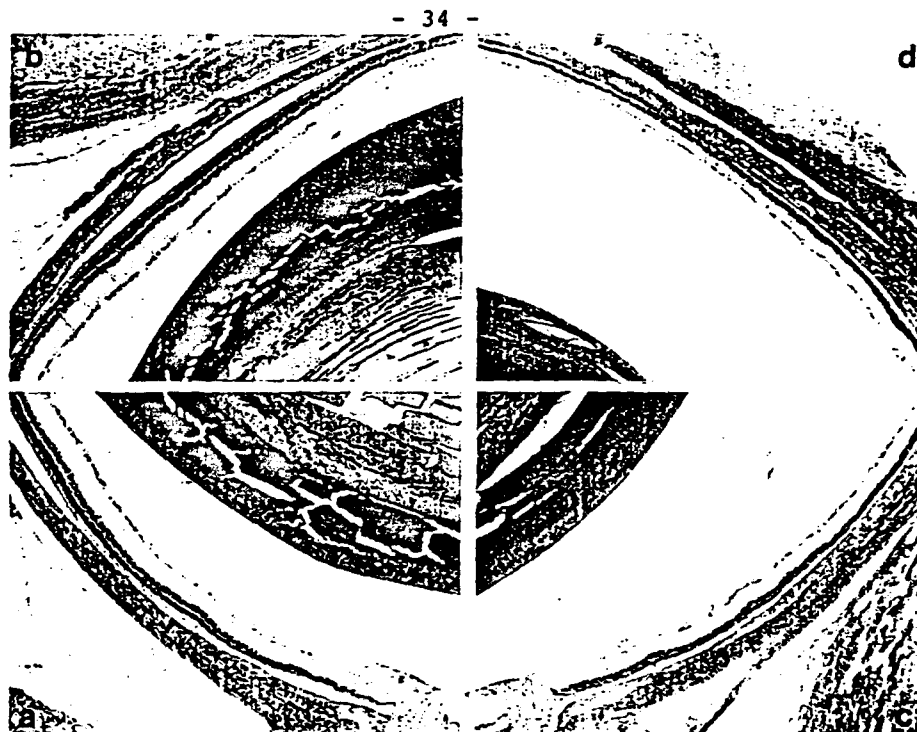


Fig. 5: SND 919 CL 2 Y carcinogenicity study rat: high dose rat no. 3535
 a (central) and b (peripheral) represent one retinal hemisphere
 c (central) and d (peripheral) the corresponding, HE, 43 x,
 photoreceptor cell layer is present in one hemisphere
 nearly missing in the other one.

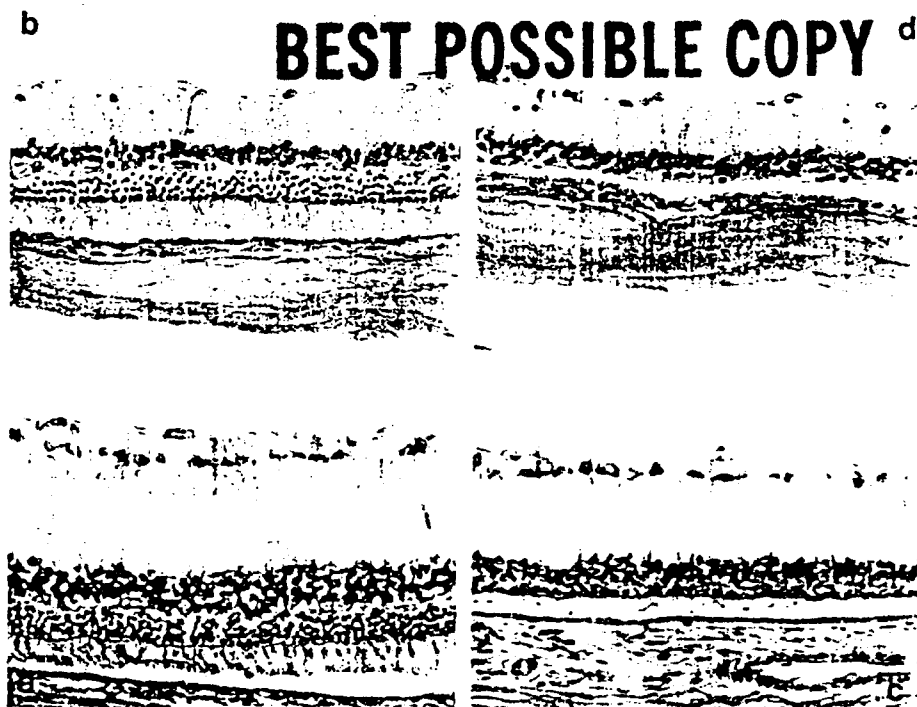


Fig. 6: The retinal localisations shown in Fig. 5 at higher magnification,
 HE, 260 x, intact and degenerated photoreceptor cell layer.

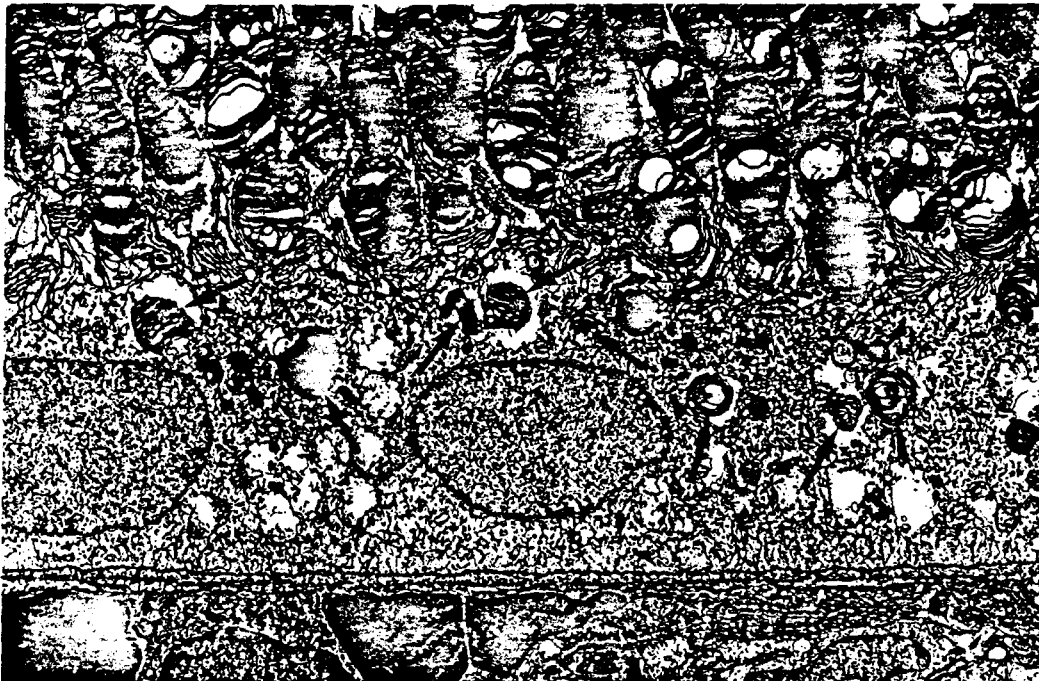


Figure 8: Electron micrograph of rod outer segments (ROS) and retinal pigment epithelium cells (RPE) from a control rat sacrificed at 8 am (early light phase). The RPE cells contain numerous phagosomes (←), magnification 5400 x

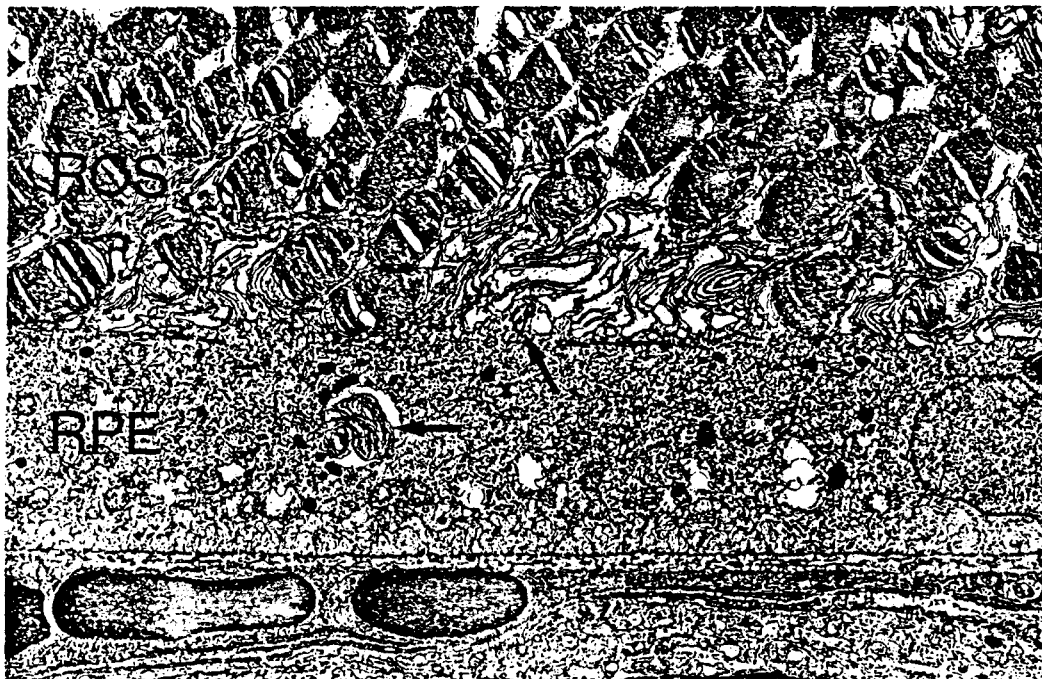


Figure 9: Electron micrograph of rod outer segments (ROS) and retinal pigment epithelium cells (RPE) from a SND 919 CL 2 Y-treated rat sacrificed at 8 am (early light phase). The RPE cells are nearly devoid of phagosomes (←), magnification 5400 x

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**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Amendments 039, 040, 043, 044**

NDA No.: 20667

Submission Date: 1/27/97

Drug: MIRAPEX (pramipexole) Oral Compressed Tablets

Sponsor: The Upjohn Co.
7000 Portage Rd.
Kalamazoo, MI 49001-0199

Reviewer: T.D. Steele

Indication: Parkinson's disease

Pharmacologic Class: Dopamine agonist

Background:

This amendment is revised labeling for MIRAPEX. Some of the revisions were in amendments 39, 40 and 43; thus, this review pertains to all these amendments.

Sponsor's text that should be deleted is indicated by ~~strikeout~~. Reviewer's revisions are redlined.

Review of Revised Labeling:

1. Page 1...Under **CLINICAL PHARMACOLOGY**

"Pramipexole is a nonergot dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D₂ subfamily of dopamine receptors.

"The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiological studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum. Animal studies have also shown that pramipexole depresses dopamine synthesis, release, and turnover

Comments:

- a. Inclusion of "full intrinsic activity" - According to the sponsor, pramipexole is distinct from other currently available dopamine agonists (bromocriptine, pergolide) by virtue of its "full intrinsic activity". Four of the five

studies cited by the sponsor to support this statement were electrophysiology studies, primarily assessing inhibition of neuronal cell firing in the substantia nigra pars compacta. Electrophysiology studies with dopamine agonists are not the best models for demonstrating full intrinsic activity because of the complexity of the neural pathways involved. *In vitro* studies assessing inhibition of adenylate cyclase by D₂ receptor agonists may be a more appropriate model. Nonetheless, the results were consistent with the conclusion that pramipexole possesses full intrinsic activity. Administration of bolus (but not cumulative) injections of pergolide suggested that this compound also possesses full intrinsic activity. Bromocriptine did not completely suppress cell firing, and was therefore not considered a full agonist. Bromocriptine has been considered a full agonist and a partial agonist in the literature. The lack of full intrinsic activity in the electrophysiology studies may have been due activation of other receptors by bromocriptine, which counteracted the effects of D₂ receptor activation. Thus, it is not clear from these studies that pramipexole is distinct from pergolide, and possibly bromocriptine, on the basis of full intrinsic activity. However, the sponsor's contention that pramipexole possesses full intrinsic activity appears accurate, and may be included in the label.

- b. D₃ receptor activity - As recognized by the sponsor, a full appreciation of the significance of D₃ receptors is currently lacking. This is particularly true in primates where a relatively low density of D₃ receptors is found. In view of the questionable clinical relevance of this pharmacological activity, references to it should be deleted.
- c. Reduction of neuronal degeneration - As detailed in the original review, this statement is of questionable clinical relevance and should be deleted.

2. Page 6... Under **PRECAUTIONS**

"Retinal degeneration in albino rats: Retinotoxicity (loss of photoreceptor cells, degeneration of retinal pigment epithelium) was observed in albino rats in the 2-year carcinogenicity study (see ANIMAL TOXICOLOGY). The significance of this effect in humans is not known, but cannot be disregarded since disruption of a universal vertebrate mechanism (i.e., disk-shedding) may be involved. If visual disturbances are suspected, a comprehensive ophthalmological examination including ERG and EOG should be conducted."

Comments:

- a. In the original labeling, the sponsor used "retinal degeneration" to describe the lesions in the 2-year rat carcinogenicity study. As recommended by the FDA consultant, Dr. Tim O'Neill, the term "retinotoxicity" was used in FDA Draft Labeling. The sponsor reinserted "retinal degeneration" for "retinotoxicity", claiming that this term is more descriptive of the lesion. The present revision

incorporates both views by parenthetically describing the nature of retinotoxicity with the same descriptions used by the sponsor's Expert Study Panel.

- b. An additional line incorporates the suggestions of the study panel regarding the use of ERG and EOG to detect retinal damage in humans.

3. Page 7... Under "**Information for Patients:**".

"Because animal teratogenicity information and human experience with MIRAPEX is limited, Ppatients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy)."

Comments:

- a. The original Pharmacology/Toxicology review detailed the inadequacies of the rat Segment II study in terms of its limited teratology information. The sponsor has not submitted any additional teratogenicity data to supplement their claim that pramipexole is not teratogenic in rats. The current revision is a slight modification of the FDA Draft Labeling.

4. Page 7... Under "Drug Interactions"...

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent K_i of 30 μ M, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Dopamine antagonists: Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX."

Comments:

- a. The sponsor has adequate data to support the claims that MIRAPEX does not inhibit cytochrome P450 isozymes at clinically relevant concentrations, and that dopamine antagonists may diminish the effectiveness of MIRAPEX.

5. Page 8...

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day (0.5,

3.4, and 17.2 times the highest recommended clinical dose [1.5 mg tid] on a mg/m² basis). In mice dosed at these levels, the plasma levels were at least 0.1, 0.49, and 4.4 times the observed C_{max} in humans dosed 1.5 mg tid. Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (0.8, 5, and 20 times the highest clinical dose on a mg/m² basis). In rats dosed at these levels, the plasma AUC was 0.3, 2.5, and 12.5 times the AUC in humans dosed at 1.5 mg tid.

Comments:

- a. The sponsor has modified the dosage conversions using factors from Casarett & Doull's Toxicology. The original dosage conversions (by the reviewer) were according to FDA standard conversions and based on a 50 kg body weight for humans. The sponsor's conversion is based on 70 kg human body weight. When the same human body weights (70 kg) were used for the conversion by both methods, the same values were obtained for rats, monkeys, and rabbits. Values for mice were slightly lower using the FDA conversion as compared to the sponsor's conversion. Thus, the conversions conducted by the sponsor are acceptable for all species.

"Testicular Leydig cell adenomas were found in male rats as follows: 13 of 50 control group A males, 9 of 60 50 control group B males, 17 of 50 males given 0.3 mg/kg/day, 22 of 50 males given 2 mg/kg/day, and 22 of 50 males given 8 mg/kg/day.

Leydig cell adenomas were not observed in mice after 2 years of treatment with MIRAPEX. Leydig cell hyperplasia and increased numbers of adenomas

in rats are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice, and the probable involvement of endocrine mechanisms that are not relevant to humans."

Comments:

- a. The Leydig cell tumor findings were omitted from FDA Draft Labeling because these tumors were not significant according to Agency criteria. The sponsor wishes to describe the tumor findings, and has reinserted them in the present labeling. This is acceptable to the reviewer. The text on the mechanism is modified since the sponsor has not clearly demonstrated that this mechanism applies to pramipexole.
- b. In line 2, the sponsor indicated (as in the initial submission) that 60 males were in control group B. The reviewer has been unable to identify the additional 10 animals claimed by the sponsor. The sponsor will need to clarify this discrepancy.

"Pregnancy: Pregnancy Category **B C**. When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (6.2 times the highest clinical dose on a mg/m² basis). In rats dosed at 2.5 mg/kg/day, the plasma levels were 19.3 times the observed C_{max} in humans dosed 1.5 mg tid. Administration of 1.5 mg/kg/day (3.7 times the highest clinical dose on a mg/m² basis) of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos

The plasma AUC in rats dosed at this level was 4.3 times the AUC in humans dosed at 1.5 mg tid. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of MIRAPEX could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day (47.2 times the highest clinical dose on a mg/m² basis) to pregnant rabbits during organogenesis. In rabbits dosed at 10 mg/kg/day, the plasma AUC was 71 times that in humans dosed at 1.5 mg tid. Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the highest clinical dose on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation. In pregnant rats dosed at 0.5 mg/kg/day, the plasma AUC was 1.5 times the AUC in humans dosed at 1.5 mg tid.

"There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus."

Comments:

- a. The sponsor deleted text from the FDA Draft labeling that indicated the inadequacies of the rat teratogenicity data. This text has been reinserted. The sponsor has argued that pramipexole should be labeled similar to bromocriptine as Pregnancy category B because the two drugs cause similar effects on early rat pregnancy. However, bromocriptine is labeled as B because substantial human experience exists with bromocriptine, and no reproductive or teratogenic effects have been associated with its use. It is also noted that the sponsor has identified pharmacological properties of pramipexole that are distinct from bromocriptine (i.e., full intrinsic activity, D₃ receptor selectivity). It is possible that these unique pharmacological properties of pramipexole may also convey unique toxicities to the compound.
- b. The sponsor modified the standard statement in FDA Draft labeling regarding the

benefit:risk assessment for fetal exposure. The original FDA statement has been reincorporated.

7. Page 19... ANIMAL TOXICOLOGY

Retinotoxicity in Albino Rats"

Retinotoxicity (loss of photoreceptor cells, degeneration of the retinal pigment epithelium) was observed in albino rats in the 2-year carcinogenicity study with pramipexole. Retinal lesions were first observed during week 76 and was dose dependent in animals receiving 2 or 8 mg/kg/day (5 and 20 times the highest clinical dose on a mg/m² basis). Lesions were not observed in that study at 0.3 mg/kg/day (0.8 times the highest clinical dose on a mg/m² basis). In rats dosed at 0.3, 2, or 8 mg/kg/day, the plasma AUC was 0.3, 2.5, and 12.5 times the AUC in humans dosed at 1.5 mg tid.

"Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, retinal degeneration occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (62 times the highest clinical dose on a mg/m² basis) and constant light (100 lux), but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats may be uniquely sensitive to the damaging effects of pramipexole and light. Retinotoxicity did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.5, 3.4, and 17.2 times the highest clinical dose on a mg/m² basis). Limited evaluation of the retinas in other long-term animal studies did not reveal signs of retinotoxicity in of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.5, 2.6, and 10.4 times the highest clinical dose on a mg/m² basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks

"The potential significance of this effect in humans has not been established, but cannot be disregarded since disk shedding is a universal mechanism of the vertebrate retina, and

Comments:

- a. The rationale for using "Retinotoxicity" rather than "Retinal degeneration" was described in a preceding section.
- b. According to the FDA consultant, Dr. Tim O'Neill, the evaluations of the retinas in other long-term animal studies were limited, and the labeling should reflect that position.
- c. The original FDA Draft Labeling, which emphasizes that the disk-shedding

mechanism also occurs, and may therefore be affected, in humans has been reincorporated.

/S/

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cc: Div. File N20667, HFD-120
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

STATISTICAL REVIEW(S)

OCT/1996
OCT 25 1996

Statistical Review and Evaluation

NDA: 20-667

Applicant: The Upjohn Company

OCT 24 1996

Name of Drug: Pramipexole Tablets

Documents Reviewed: Vols. 324-325, 344, 346, 355

Medical Officer: John Feeney, M.D., HFD-120

Background

The sponsor has submitted a total of five (5) controlled trials in support of Pramipexole (PX) for the treatment of Parkinson's disease. This review is restricted to the 3 large trials designated 'adequate and well-controlled' by the sponsor. The sponsor has designated the other 2 as 'supportive'. Trials 0001 and 0004 enrolled patients with early asymptomatic, idiopathic Parkinson's disease who were not receiving replacement levodopa therapy. Trial 0010 used PX as an adjunct to levodopa replacement therapy in patients with less than optimal response to levodopa as characterized by the presence of motor fluctuations.

Trial 0001 used stratified randomization (current selegiline use or not) among 26 centers in the US. Three hundred thirty-five (335) patients were randomized to either placebo or the PX group which experienced a 7 week dose escalation period (7 doses up to 4.5 mg/day) followed by a 24 week maintenance period.

The primary efficacy endpoint was the sum of scores of Parts II (13 activities each rated in increasing severity from 0-4) and III (14 components of physical status each rated in increasing severity from 0-4) of the UPDRS (Unified Parkinson's Disease Rating Scale). Secondary endpoints included 1) Time to Failure (worsening of disease or unsatisfactory therapeutic effect - time until patient requires levodopa), 2) Modified Hoehn and Yahr Scale, and 3) individual components (Parts II and III) of the UPDRS. The sample size of 150/arm was derived using Part III of the UPDRS results from DATATOP. The result follows from designing 90% power to find a treatment arm difference of change from baseline between 1.8 and 3.6 using a standard deviation of 5.0.

The primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The subset of those who actually entered the maintenance period was added before the data was unblinded and was intended to confirm the robustness of the results using primary data set. The primary analytic technique stated in the protocol was two-way ANOVA with interaction of treatment and center always in the model.

Trial 0004 randomized 264 patients among 20 centers in the US and Canada. Patients were randomized to either placebo or one of 4 doses of PX: 1.5, 3.0, 4.5 or 6.0 mg/day. The dose escalation phase lasted 6 weeks followed by a 4 week maintenance period.

The primary efficacy endpoint was the sum of scores of Parts I-III of the UPDRS. The secondary endpoints were the individual components of the UPDRS and the Hoehn and Yahr scale. The sample size of 50/arm was derived using the sum of parts II and II from a previous study. From a dose-response point of view, there was 80% power to detect a slope of 1.25 or, from a change from baseline point of view, there was 82% power to detect a difference of 5.8 between the 4.5 mg/day and placebo groups.

As in **Trial 0001**, the primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The subset of those who actually entered the maintenance period was added before the data was unblinded. With regard to the primary analytic technique, the protocol states only: "In this dose-response study, the primary variables will be analyzed by regression methods."

Trial 0010 (not conducted under an IND) randomized 360 patients among 26 centers in the US (22) and Canada (4). Patients were randomized to either placebo or the PX group which experienced a 7 week dose escalation period (from ng/day) followed by a 24 week maintenance period. Patients who dropped from the trial prior to completing at least one-half of the visits during the maintenance dose interval during the double-blind part of the trial were to be replaced unless the patient was dropped from the trial because of intolerable adverse events which included worsening of the underlying Parkinson's disease.

The primary efficacy endpoints were the following: 1) Part II of the UPDRS for both 'on' and 'off' periods and 2) Part II for 'on' periods, only. Secondary endpoints included 1) Part II 'on' and 'off' separately), 2) Modified Hoehn and Yahr Scale for 'on' and 'off' periods and a myriad of other analyses. As with **Trial 0001**, the protocol-specified sample size of 150/arm was derived using Part III of the UPDRS results from DATATOP.

The primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The primary analytic technique was two-way ANOVA with interaction of treatment and center always in the model. AUC was also conducted as a longitudinal analysis. The timed walking test (50 feet) was analyzed using change from baseline.

Note: All figures and graphs were produced by the sponsor.

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Results

In general, all reported results are for the LOCF analysis at the last visit during the maintenance period. This review reports only the intent-to-treat (ITT) results since similar results are obtained using only patients who entered the maintenance period.

There was no evidence of treatment by center interaction in any trial.

Trial 0001

Two (2) patients did not have any post-baseline measurements. Thus the ITT data set consists of 333 patients.

Table 1 displays the baseline characteristics of all randomized patients. There were no important treatment imbalances.

Table 2 displays the numbers of patients completing each phase of the trial. Approximately 80% of the patients completed the maintenance period.

Tables 3, 4, and 5 display the changes from baseline and statistical results for Parts II, III, and by selegiline and anti-cholinergic status, respectively. Patients treated with PX clearly improved their symptoms relative to those on placebo. On average, the LOCF change from baseline of patients who discontinued from the PX arm (N=16) was better than that of dropouts from the placebo arm (N=24): -.94 on PX, 1.58 on PBO for Part II, and -.63 on PX, 5.04 on PBO for Part III.

Tables 6 and 7 display the changes from baseline for the separate components of Parts II and III, respectively.

The distribution of **Hoehn and Yahr scale scores** also reflected a treatment effect: improvement from baseline: 27% PX, 16.5% PBO, worsening from baseline: 16.7% PX, 23.5% PBO.

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The time to treatment failure analysis using the logrank test ($p=.0015$) also indicates a treatment benefit: 5 patients failed in the PX group while 22 failed in the PBO group.

There was no indication of differential treatment effect by age, race or gender.

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Trial 0004

Table 8 displays the treatment group baseline characteristics and Table 9 displays the numbers of patients completing each phase of the trial. Approximately 90% of the patients completed the maintenance phase.

Table 10 displays the statistical results for the primary endpoint using the assigned dose as the treatment group: sum of all 3 parts of the UPDRS. Each dose was statistically different from placebo using even a conservative multiple comparison rule such as a simple Bonferroni adjustment. The sponsor states that "there was no dose-response relationship for efficacy apparent across the range of pramipexole doses studied".

With placebo in the analysis, a linear dose-response trend was detected with a p-value of .03 using the assigned dose group and .005 using the dose actually received.

When Parts II and III were analyzed separately, the overall test was statistically significant in favor of PX for part III but not for part II. See Tables 11 and 12.

Table 13 displays the results for the individual components of Parts II and III which showed the greatest average change from baseline.

Table 14 displays the distribution of patients who improved or worsened from baseline on the Hoehn and Yahr Scale. Approximately twice the number of patients on the 3 highest doses of PX improved from baseline compared to the number who improved on placebo.

Comment

The obvious question about this trial is why there was no statistical difference between drug and placebo for Part II of the UPDRS unlike the result in Trial 0001. The standard deviations are the same in both trials (3.0). Comparing Table 3 to Table 11 indicates that the average treatment difference was approximately 2.3 units in Trial 0001 as opposed to 1.5 in Trial 0004. The average change from baseline on drug was 0.5 units less in the latter trial. The slightly smaller overall sample size in Trial 0004 contributed to some extent.

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Trial 0010

Table 15 displays the baseline information for the treatment groups.

Table 16 displays the number of patients who completed each stage of the study. Approximately 80% of the patients completed the trial, a completer being one who "completed at least half of the visits during the maintenance-dose interval (i.e., through Visit 15) or any patient who discontinued trial medication because of intolerable adverse events".

Figure 1 and **Table 17** display the results when averaging the 'on' and 'off' periods for Part II of the UPDRS using LOCF.

Figure 2 and **Table 18** display the results of Part III of the UPDRS using LOCF. The sponsor did not report the results for just the 'on' period as it stated it would in the report. However, the protocol makes no mention of restricting Part III to the 'on' period.

Figures 3 and **4** display the results over time for the two respective primary endpoints. The profiles are very similar to those using LOCF, indicating that there is little effect of dropouts on the LOCF analyses.

In summary, the LOCF analyses were statistically significant on both primary endpoints.

Secondary endpoints which reached nominal significance were Part II 'off' periods ($p < .001$), Part II 'on' periods ($p = .004$), average percentage 'off' time calculated from patient diaries ($p < .001$, see **Table 19** and **Figure 5**), levodopa dosage ($p < .001$), Schwab-England Disability Scale ($p < .001$) for 'off' periods and $P = .01$ for 'on' periods, and Modified Hoehn and Yahr Scale ($p < .001$). The timed walking test was not statistically significant.

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Subgroup analyses

The sponsor investigated demographic subgroups and the possibility of an interaction between selegiline (l-deprenyl) and pramipexole. The demographic analyses did not produce any evidence of interactions between treatment difference and age, race or gender. In **Trials 0001, 0004 and 0010**, 67%, 61% and 54% of the patients were taking selegiline, respectively. **Table 20 (Trial 0004)** displays the mean changes from baseline for active drug groups and placebo for patients who were and were not taking selegiline on study. **Table 21 (Trial 0010)** displays results for only patients taking selegiline and for the full data set. In **Trial 0004**, the differences from placebo were larger among patients who did not take selegiline at the two highest doses of pramipexole. This may be partially explained by the larger placebo effect among the selegiline-taking patients. None of the trials provide substantial evidence of an interaction between pramipexole and selegiline use.

Conclusion

Trials 0001 and 0004 provide statistically significant evidence of efficacy in patients with early PD. Trial 0001 was dose ranging up to 4.5mg/day. In trial 0004, although 6.0mg/day was slightly numerically superior to 1.5mg/day on the total UPDRS, there was no statistical evidence that it is in fact more effective than 1.5mg/day.

Trial 0010 provides statistical evidence of efficacy of a dose-ranging regimen of PX of up to 4.5mg/day as an adjunct to l-dopa therapy in patients with motor fluctuations.

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TABLE 1

Demographic Characteristics of Patients at Screen

Patient Data	Number (%) of Patients		
	Pramipexole (N=164)	Placebo (N=171)	P-Value
Age (yrs)			
<65	76 (46.3)	87 (50.9)	0.183
≥65	88 (53.7)	84 (49.1)	
Mean	63.4	62	
S.E.	0.78	0.88	
Min	33	30	
Max	85	85	
Sex			
Male	105 (64.0)	98 (57.3)	0.185
Female	59 (36.0)	73 (42.7)	
Race			
White	156 (95.1)	161 (94.1)	0.740
Black	2 (1.2)	4 (2.3)	
Other	6 (3.7)	6 (3.5)	
Weight (lbs)			
Mean	168.6	168.2 (N=169)	0.856
S.E.	2.48	2.79	
Min	101	96	
Max	260	282	
Height (in)			
Mean	67.1	66.9 (N=170)	0.631
S.E.	0.3	0.33	
Min	58	54	
Max	75	76	
Smoking History			
Nonsmoker	79 (48.2)	98 (57.3)	0.010
Ex-smoker	76 (46.3)	56 (32.8)	
Smoker	9 (5.5)	17 (9.9)	
Use of Alcohol			
Never Drinks	55 (33.5)	66 (38.6)	0.689
Average Consumption	108 (65.9)	104 (60.8)	
Excessive Consumption	1 (0.61)	1 (0.58)	
Duration of Parkinson's Disease			
Mean	2	1.7	0.097
S.E.	0.16	0.12	
Min	0	0	
Max	11.6	7.2	
UPDRS Part II (ADL) Total Score			
Mean	8.2 (N=163)	8.2	0.982
S.E.	0.31	0.33	
Min	1	1	
Max	20	22	
UPDRS Part III (Motor Examination) Total Score			
Mean	18.8 (N=162)	18.7 (N=170)	0.958
S.E.	0.71	0.71	
Min	1	3	
Max	63	53	
Modified Hoehn & Yahr Scale			
Mean	1.9 (N=163)	1.9	0.643
S.E.	0.04	0.05	
Min	1	1	
Max	3	3	
Current L-deprenyl Use			
Yes	112	113	0.480
No	52	58	
Current Anti-cholinergic Use			
Yes	19	24	0.511
No	145	147	

Source: Appendix C: Table 3.
Abbreviations: ADL = Activities of Daily Living.

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TABLE 2

Disposition of Patients Enrolled in the Study

Disposition	Treatment Group	
	PPX	FBO
No. of Patients Randomized	N=164	N=171
No. (%) of ITT ^a Patients	163 (99)	170 (99)
No.(%) of Patients Completing Ascending-dose Phase	152 (93)	161 (94)
No.(%) of Patients Completing Maintenance Phase	136 (83)	137 (80)
No.(%) of Patients Discontinuing Study	28 (17)	34 (20)
Reason for Discontinuation		
Adverse Events		
Worsening of Disease ^b	4 (2)	15 (9)
Worsening of Other Pre-existing Disease	0 (0)	1 (1)
Other	18 (11)	8 (5)
Unsatisfactory Therapeutic Effect ^c	1 (1)	7 (4)
Protocol Violation	1 (1)	0 (0)
Lost to Follow-up	2 (1)	0 (0)
Withdrawal of Consent	2 (1)	2 (1)
Other	0 (0)	1 (1)

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Source: Appendix C: Table 2.1.

^a Intent-to-treat, the number of patients in each treatment group is the number randomized who received at least one dose of study drug and with at least one post-baseline follow-up.

^b Defined as worsening of Parkinson's disease.

^c Defined as no deterioration but still unsatisfactory therapeutic effect.

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TABLE 3

Adjusted^a Mean Change from Baseline in UPDRS Part II Total Score^b,
Maintenance Interval
Intent-to-Treat - All Patients, LOCF

Treatment Group	Baseline ^c	Maintenance Week					
		0 ^d	4	8	12	16	24
PPX (N=163)	8.2	-2.5	-2.5	-2.4	-2.3	-2.4	-1.9
PBO (N=170)	8.3	-0.9	-0.7	-0.4	-0.2	0	0.4
P-Value	-	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 9.2.

^a Adjusted by investigator and investigator-by-treatment interaction.

^b Sum of 13 components of UPDRS Part II.

^c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^d Week 0 is the endpoint of the ascending-dose interval.

TABLE 4

Adjusted^a Mean Change from Baseline in UPDRS Part III Total Score^b,
Maintenance Interval
Intent-to-Treat - All Patients, LOCF

Treatment Group	Baseline ^c	Maintenance Week					
		0 ^d	4	8	12	16	24
PPX (N=162)	18.8	-6	-5.4	-5.2	-5.2	-5.1	-5
PBO (N=168)	18.8	-2.6	-2.3	-1.6	-0.9	0.4	0.8
P-Value	-	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 10.2.

^a Adjusted by investigator and investigator-by-treatment interaction.

^b Sum of 14 components of UPDRS Part III.

^c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^d Week 0 is the endpoint of the ascending-dose interval.

TABLE 5

Mean Change From Baseline in UPDRS
Parts II and III, Total Score by L-deprenyl and Anti-cholinergic Usage;
All Patients

Concomitant Therapy	Treatment Group	Part II ^a				Part III ^b			
		N	Yes	N	No	N	Yes	N	No
l-deprenyl	PPX	112	-1.9	51	-1.5	111	-4.6	51	-4.6
	PBO	112	0.3	58	0.7	112	1.3	57	1.5
Anticholinergic	PPX	19	-1.3	144	-1.9	19	-4.5	143	-4.6
	PBO	24	0.1	146	0.4	24	1.4	145	1.4

Source: Appendix C: Tables 11.1A & 12.1A.

^a Sum of 13 components of UPDRS Part II.

^b Sum of 14 components of UPDRS Part III.

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TABLE-6
UPDRS Part II Individual Components
Mean Change From Baseline to Endpoint
All Patients

UPDRS Component	Treatment Group	
	PPX N=163	PBO N=170
Speech	0.0	0.0
Salivation	0.0	-0.1
Swallowing	0.0	0.0
Handwriting	-0.3	0.0
Cut food/handling utensils	-0.2	0.0
Dressing	-0.2	0.1
Hygiene	-0.1	0.0
Turning in bed/adjusting clothes	-0.3	0.1
Falling	0.0	0.0
Freezing when walking	0.0	0.1
Walking	-0.1	0.0
Tremor	-0.4	0.0
Sensory complaints related to Parkinsonism	-0.1	0.1

TABLE 7

UPDRS Part III Individual Components
Mean Change From Baseline to Endpoint
All Patients

UPDRS Component	Treatment Group	
	PPX N=163	PBO N=170
Speech	-0.1	0.1
Facial expression	-0.1	0.0
Tremor at rest (face)	-0.1	0.0
Tremor at rest (Left Hand)	-0.2	0.0
Tremor at rest (Right Hand)	-0.3	0.0
Tremor at rest (Left Foot)	-0.1	0.0
Tremor at rest (Right Foot)	-0.1	0.0
Action or postural tremor of hands (Left Hand)	0.0	0.0
Action of postural tremor of hands (Right Hand)	-0.1	0.0
Rigidity (neck)	-0.1	0.0
Rigidity (left upper extremity)	-0.3	0.0
Rigidity (right upper extremity)	-0.3	0.0
Rigidity (left lower extremity)	-0.1	0.1
Rigidity (right lower extremity)	-0.1	0.0
Finger taps (left)	-0.4	0.1
Finger taps (right)	-0.4	0.1
Hand movements (left)	-0.4	0.1
Hand movements (right)	-0.3	0.1
Rapid alternating movements (Left Hand)	-0.2	0.1
Rapid alternating movements (Right Hand)	-0.3	0.1
Leg agility (left)	-0.1	0.1
Leg agility (right)	-0.2	0.1
Arising from chair	0.0	0.2
Posture	0.0	0.1
Gait	-0.1	0.0
Postural stability	-0.1	-0.1

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TABLE 8

SELECTED DEMOGRAPHIC AND BASELINE FACTORS

Parameter	Pramipexole - assigned dose				Placebo n=51	p value
	1.5 mg/day n=54	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55		
age (mean years)	60.2	62.2	62.7	62.8	60.4	0.67
sex (% male)	64.8	62.0	63.0	69.1	62.8	0.90
race (% caucasian)	96.3	98.0	96.3	98.2	96.1	0.58
duration of disease (mean years)	1.8	2.0	1.9	2.3	1.6	0.16
current selegiline use (% yes)	55.6	66.0	66.7	58.2	58.8	0.65
UPDRS total score (mean points)	29.0	28.3	27.3	32.9	28.7	0.08
Hoehn and Yahr score (mean points)	1.8	1.9	1.8	1.9	1.8	0.52

TABLE 9

PATIENT DISPOSITION AND TOLERABILITY - NUMBER PATIENTS (%)

Endpoint	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
Number randomized	54	50	54	55	51
number (%) completing ascending dose	47 (87.0)	48 (96.0)	52 (96.3)	47 (85.5)	51 (100.0)
number (%) completing maintenance	44 (81.5)	48 (96.0)	50 (92.6)	46 (83.6)	50 (98.0)
number (%) completing at assigned dose - tolerability	44 (81.5)	46 (92.0)	43 (79.6)	37 (67.3)	49 (96.1)
number (%) completing with one or no dose reductions	44 (81.5)	48 (96.0)	50 (92.6)	44 (80.0)	50 (98.0)
number (%) dose limited during ascending dose interval due to clinical intolerance	2 (3.7)	3 (6.0)	7 (13.0)	10 (18.2)	1 (2.0)

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TABLE 10

UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	28.5	28.3	27.3	32.9	28.7
mean change*	-6.1	-5.8	-6.6	-7.1	-1.2
pairwise p value vs placebo	0.0027	0.0057	0.0008	0.0003	--
overall p value	0.0022	--	--	--	--

*Adjusted for center effect and treatment by center interaction

TABLE 11

UPDRS PART II - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	8.0	8.0	7.3	8.8	8.2
mean change*	-1.8	-1.9	-1.8	-1.8	-0.3
pairwise p value vs placebo**	N.D.	N.D.	N.D.	N.D.	N.D.
overall p value	0.0613	--	--	--	--

*Adjusted for center and treatment by center interaction

**N.D. - not done since overall p value not significant

TABLE 12

UPDRS PART III - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	19.4	19.3	19.2	22.9	19.6
mean change*	-4.2	-3.8	-4.7	-5.1	-0.6
pairwise p value vs placebo	0.0052	0.0151	0.0016	0.0005	--
overall p value	0.0048	--	--	--	--

*Adjusted for center and treatment by center interaction

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TABLE 13

**UPDRS PART II - INDIVIDUAL ITEMS WITH
GREATEST MEAN CHANGE FROM BASELINE**

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
handwriting	-0.4	-0.4	-0.4	-0.4	0.0
dressing	-0.1	-0.3	-0.3	-0.3	-0.1
tremor	-0.1	-0.3	-0.2	-0.3	-0.1

**UPDRS PART III - INDIVIDUAL ITEMS WITH
GREATEST MEAN CHANGE FROM BASELINE**

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
tremor - left hand	-0.2	-0.3	-0.2	-0.4	0.0
tremor - right hand	-0.1	-0.2	-0.3	-0.4	0.0
tremor - left foot	0.0	-0.1	-0.3	0.0	0.0
rigidity - neck	-0.1	0.0	-0.2	-0.3	0.1
rigidity - left upper extremity	-0.2	-0.2	-0.4	-0.2	-0.1
rigidity - right upper extremity	-0.2	-0.3	-0.3	-0.3	-0.1
rigidity - right lower extremity	0.0	-0.3	-0.2	-0.1	0.0
finger taps - left	-0.4	-0.2	-0.3	-0.3	-0.1
finger taps - right	-0.6	-0.2	-0.2	-0.3	0.0
hand movements - left	-0.2	-0.2	-0.3	-0.2	0.1
hand movements - right	-0.3	-0.1	-0.3	-0.3	0.0
rapid alternating movements - left	-0.2	-0.3	-0.2	-0.1	0.2
rapid alternating movements - right	-0.4	-0.2	-0.2	-0.2	0.1
bradykinesia	-0.3	-0.2	-0.2	-0.3	0.0

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TABLE 14

MODIFIED HOEHN AND YAHR SCALE - PERCENT CHANGE

Category	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
improved from baseline (%)	19.2	36.7	25.0	30.2	13.7
worsened from baseline (%)	17.3	6.1	5.8	9.4	25.5

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TABLE 15

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Characteristics	Placebo N=179	Pramipexole N=181	Total N=360
Age (yrs)			
N	179 (100%)	181 (100%)	360 (100%)
< 65	90 (50.3%)	85 (47.0%)	175 (48.6%)
≥ 65	89 (49.7%)	96 (53.0%)	185 (51.4%)
Mean	179	181	360
S.E.	63.3	63.4	63.3
Range	0-72	0-72	0-81
Sex			
Male	116 (64.8%)	119 (65.7%)	235 (65.3%)
Female	63 (35.2%)	62 (34.3%)	125 (34.7%)
Race			
White	172 (96.1%)	172 (95.0%)	344 (95.6%)
Black	4 (2.2%)	3 (1.7%)	7 (1.9%)
Other	3 (1.7%)	6 (3.3%)	9 (2.5%)
Height (cm)			
N	179	179	358
Mean	170.3	170.8	170.6
S.E.	0.75	0.77	0.84
Range			
Weight (kg)			
N	179	180	359
Mean	72.9	73.7	73.3
S.E.	1.23	1.06	0.82
Range			
Duration of Parkinson's Disease (yrs)			
N	179	181	360
Mean	5.0	5.4	5.2
S.E.	0.39	0.45	0.39
Range			
Smoking History			
Non-smoker	95 (53.1%)	103 (56.9%)	198 (55.0%)
Ex-smoker	69 (38.5%)	70 (38.7%)	139 (38.6%)
Smoker	15 (8.4%)	8 (4.4%)	23 (6.4%)
Use of Alcohol			
Never Drinks	61 (46.4%)	76 (42.0%)	137 (44.2%)
Average Consumption	96 (53.6%)	105 (58.0%)	201 (55.8%)
Current L-deprenyl Use			
No	85 (47.5%)	80 (44.2%)	165 (45.8%)
Yes	94 (52.5%)	101 (55.8%)	195 (54.2%)
Current Anticholinergic Use			
No	158 (88.3%)	155 (85.6%)	313 (86.9%)
Yes	21 (11.7%)	26 (14.4%)	47 (13.1%)
UPDRS Part II 'on' Total Scores			
N	179	181	360
Mean	7.7	7.3	7.5
S.E.	0.40	0.40	0.28
Range			
UPDRS Part II 'off' Total Scores			
N	177	181	358
Mean	17.4	17.4	17.4
S.E.	0.48	0.62	0.56
Range			
UPDRS Part III Total Scores			
N	179	181	360
Mean	23.3	22.8	23.0
S.E.	0.94	0.97	0.67
Range			
Modified Hoehn and Yahr Scale 'on'			
0	1 (0.6%)	1 (0.6%)	2 (0.6%)
1	3 (1.7%)	2 (1.1%)	5 (1.4%)
1.5	6 (3.4%)	3 (1.7%)	9 (2.6%)
2	95 (53.1%)	97 (53.6%)	192 (53.5%)
2.5	37 (20.7%)	25 (13.8%)	62 (17.2%)
3	34 (19.0%)	38 (21.0%)	72 (20.1%)
4	2 (1.1%)	5 (2.8%)	7 (1.9%)
N	178	181	359
Mean	2.3	2.3	2.3
S.E.	0.04	0.04	0.03
Range			
Modified Hoehn and Yahr Scale 'off'			
1	3 (1.7%)	1 (0.6%)	4 (1.1%)
1.5	36 (20.2%)	27 (14.9%)	63 (17.6%)
2	37 (20.7%)	63 (34.8%)	100 (28.1%)
2.5	68 (38.2%)	62 (34.3%)	130 (36.5%)
3	22 (12.3%)	29 (16.0%)	51 (14.3%)
4	2 (1.1%)	9 (5.0%)	11 (3.1%)
5	11 (6.2%)	11 (6.1%)	22 (6.2%)
N	178	181	359
Mean	2.9	2.9	2.9
S.E.	0.06	0.06	0.04
Range			
Chest X-ray Findings			
Normal	125 (70.2%)	114 (64.0%)	239 (67.1%)
Abnormal	53 (29.8%)	64 (36.0%)	117 (32.9%)

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TABLE 16

Disposition for Patients Randomized Into the Trial

	Number of Patients (%)		
	PRAMIPEXOLE	PLACEBO	TOTAL
Number of Patients Randomized	181 (100)	179 ¹ (100)	360 (100)
Number of Patients Treated	181 (100)	178 ¹ (99.4)	359 (99.7)
Number of Patients Who Completed the Trial	151 (83.4)	140 (78.2)	291 (80.8)
Number of Patients Who Prematurely Discontinued	30 (16.6)	39 (21.8)	69 (19.2)
Discontinued Due To:			
Adverse Events			
Worsening of Disease Under Trial	3 (1.7)	9 (5.0)	12 (3.3)
Worsening of Pre-Existing Diseases	0 (0.0)	3 (1.7)	3 (0.8)
Other Adverse Events	21 (11.6)	18 (10.1)	39 (10.8)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Administrative Reasons			
Protocol Violation	1 (0.6)	0 (0.0)	1 (0.3)
Lost to Follow-up	0 (0.0)	2 (1.1)	2 (0.6)
Withdrawal of Consent	4 (2.2)	3 (1.7)	7 (1.9)
Other	1 (0.6)	4 (2.2)	5 (1.4)

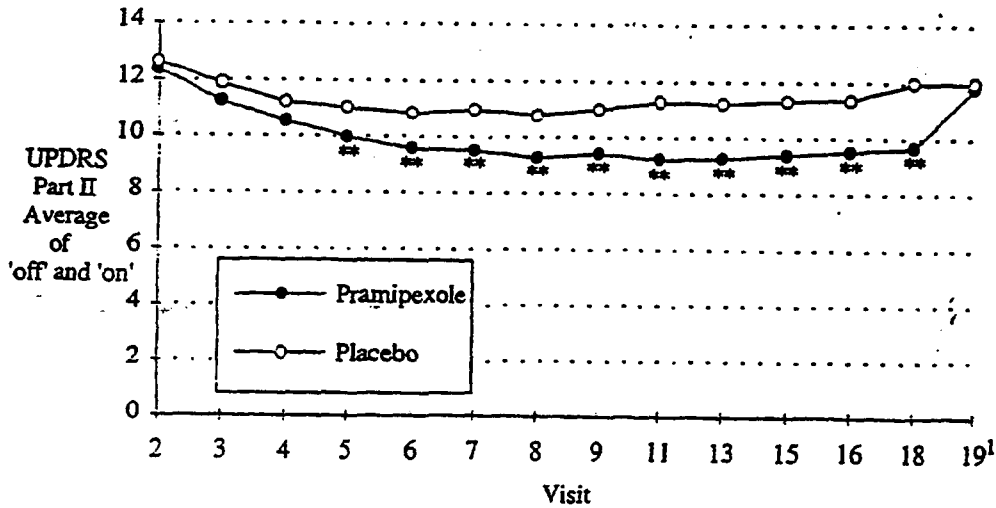
Source Data: Appendices 15.12 LISTING 1.1, 15.12 LISTING 7.1, 15.12 LISTING 7.2

¹ One patient (1054, Center 7) was randomized into the placebo treatment group but discontinued prior to receiving drug.

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FIGURE 1



Average UPDRS Part II 'off' and 'on' Means by Visit.
Last Observation Carried Forward Analysis

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TABLE 17

Adjusted¹ UPDRS Part II Average of 'off' and 'on' Period Means, Sample Sizes, and p-values for Change from Baseline and Area Under the Curve.

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (11-18)	OC Area Under the Curve over Maintenance Visits (11-18)
Pramipexole	-2.72 n = 179	-2.83 n = 171	-56.86 n = 179	-54.29 n = 134
Placebo	-0.47 n = 171	-0.46 n = 156	-17.63 n = 171	-17.36 n = 124
p-value	≤ 0.0001	≤ 0.0001	≤ 0.0001	≤ 0.0001

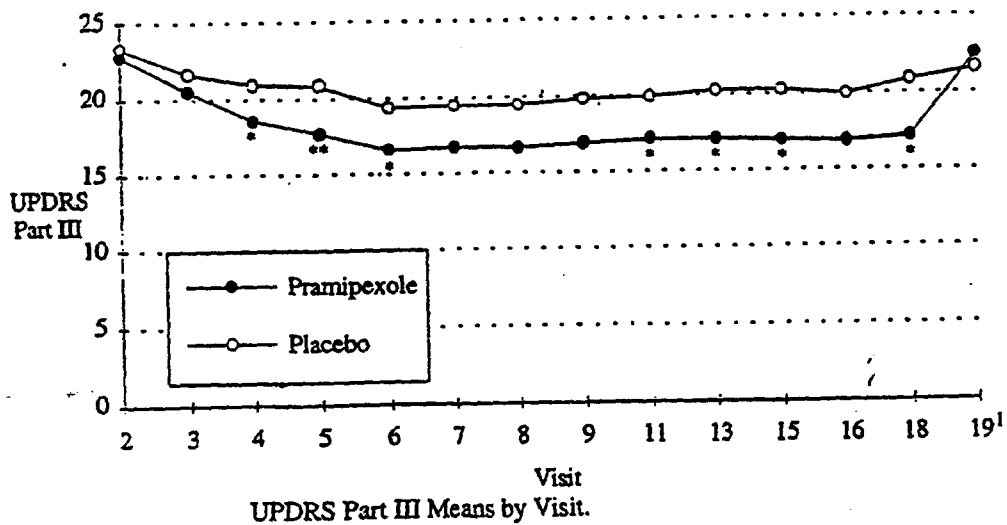
Source Data: Appendix 15.9.2 STATDOC 4.1.3.1, 4.1.3.2, 4.1.5.1 & 4.1.5.2

¹ Adjusted by center and center-by-treatment interaction (as per protocol).

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FIGURE 2



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UPDRS Part III Means by Visit.
Last Observation Carried Forward Analysis

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TABLE 18

Adjusted¹ UPDRS Part III Means, Sample Sizes, and p-values for Change from Baseline and Area Under the Curve.

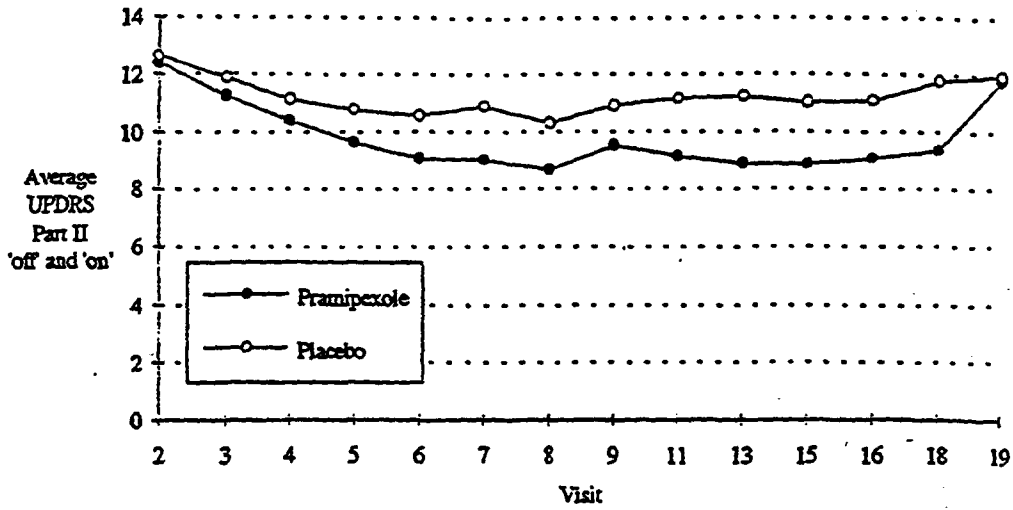
	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (11-18)	OC Area Under the Curve over Maintenance Visits (11-18)
Pramipexole	-5.64 n = 179	-5.73 n = 170	-113.84 n = 179	-125.60 n = 148
Placebo	-2.79 n = 171	-3.65 n = 157	-63.53 n = 171	-74.78 n = 133
p-value	0.01	0.08	0.01	0.02

Source Data: Appendix 15.9.2 STATDOC 4.2.3.1, 4.2.3.2, 4.2.5.1 & 4.2.5.2

¹ Adjusted by center and center-by-treatment interaction (as per protocol).

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FIGURE 3

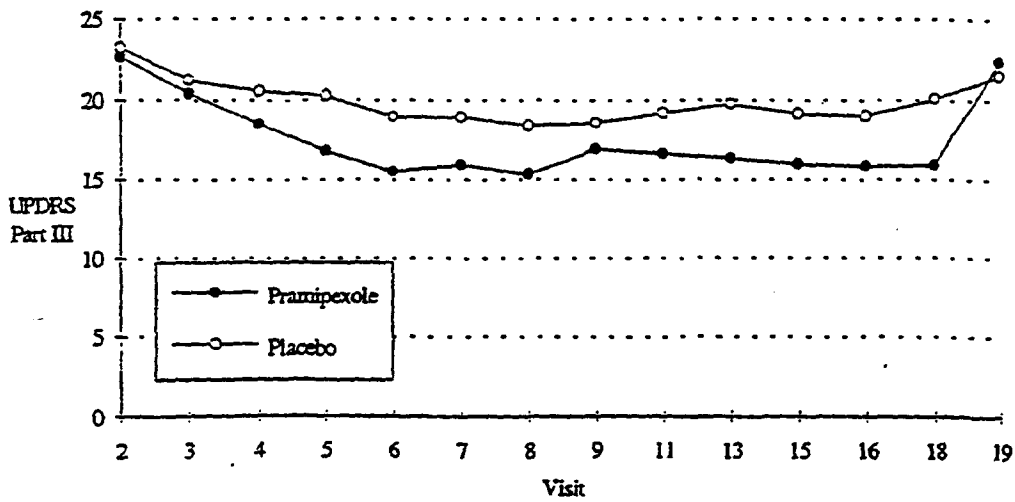


Average UPDRS Part II 'off' and 'on' Means by Visit.

Observed Cases Analysis

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FIGURE 4



UPDRS Part III Means by Visit.

Observed Cases Analysis

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TABLE 19

Unadjusted Means, Standard Deviations, and Sample Sizes for Average Percentage of 'off' Period Time by Visit.

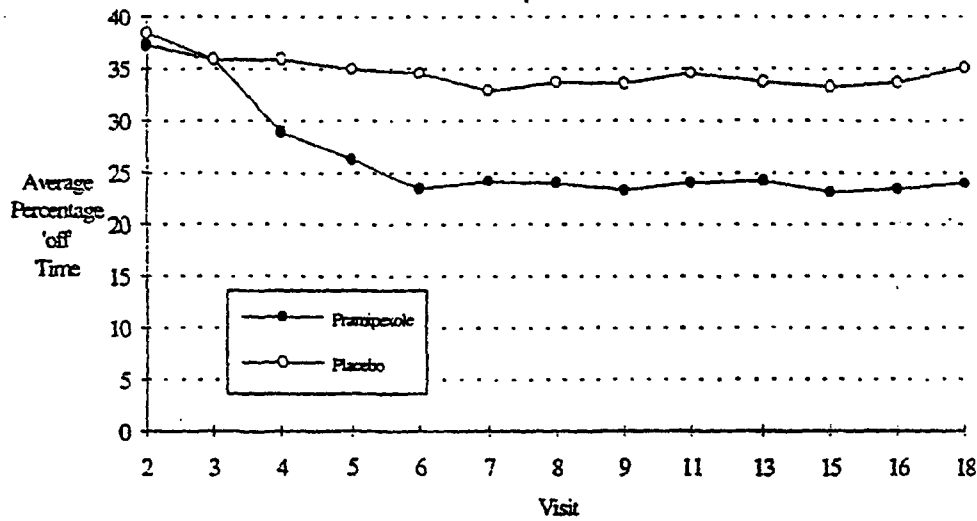
Last Observation Carried Forward Analysis

Group	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Pramipexole:							
Mean =	37.30	35.88	28.85	26.24	23.46	24.22	24.02
S.D. =	19.91	21.06	20.42	20.43	20.43	22.32	21.59
n =	173	173	173	173	173	173	173
Placebo:							
Mean =	38.28	35.91	35.88	34.92	34.54	32.79	33.61
S.D. =	20.35	18.88	19.80	20.71	21.20	21.07	21.64
n =	172	172	172	172	172	172	172

Group	Visit 9	Visit 11	Visit 13	Visit 15	Visit 16	Visit 18
Pramipexole:						
Mean =	23.31	24.06	24.24	23.08	23.39	24.01
S.D. =	21.46	22.75	22.28	21.25	20.79	22.45
n =	173	173	173	173	173	173
Placebo:						
Mean =	33.48	34.55	33.70	33.18	33.59	35.13
S.D. =	21.99	22.32	22.76	23.69	24.63	24.24
n =	172	172	172	172	172	172

Source Data: Appendix 15.9.2 STATDOC 4.5.1

FIGURE 5



Average Percentage 'off' Time by Visit.

Last Observation Carried Forward Analysis

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TABLE 20

Protocol M/2730/0004
 UPDRS I-III TOTAL SCORE+
 BY L-DEPRENYL AND ANTICHOLINERGIC USE AT BASELINE
 MEAN CHANGE FROM BASELINE TO ENDPOINTS - ALL PATIENTS

			FPX 1.5 mg	FPX 3.0 mg	FPX 4.5 mg	FPX 6.0 mg	Placebo
L-Deprenyl	Yes	N	30	33	36	32	30
		Mean Baseline	27.9	26.7	25.2	29.9	25.3
		Mean Endpoint	20.3	19.2	19.1	24.3	23.4
		Mean Change	-7.6	-7.5	-6.1	-5.7	-1.9
		S.E.	1.32	0.98	0.99	1.17	1.49
	No	N	23	17	18	23	21
		Mean Baseline	29.3	31.3	31.5	37.0	33.6
		Mean Endpoint	24.5	28.4	24.0	26.0	34.2
		Mean Change	-4.8	-2.9	-7.5	-9.0	0.6
		S.E.	2.28	1.66	2.71	1.98	2.24
Anticholinergic	Yes	N	35	37	41	37	34
		Mean Baseline	28.2	27.1	26.8	31.5	25.3
		Mean Endpoint	20.9	20.5	20.3	25.3	24.0
		Mean Change	-7.4	-6.6	-6.5	-6.2	-1.3
		S.E.	1.26	0.99	0.91	1.14	1.37
	No	N	18	13	13	18	17
		Mean Baseline	29.0	31.5	29.1	35.7	35.5
		Mean Endpoint	24.5	27.6	22.9	26.9	35.5
		Mean Change	-4.5	-3.9	-6.8	-8.8	0.0
		S.E.	2.71	2.04	3.71	2.38	2.71

+ Sum of the 31 components of UPDRS Parts I, II and III (Range = 0 - 176).
 @ Values taken at the baseline visit, Visit 2 (Week 0).
 @@ Last visit, prior to dose-reduction.
 Treatment groups are classified by assigned (target) dose.

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TABLE 21

UPDRS Part II Average of 'off' and 'on' Periods Change from Baseline to Final for L-Deprenyl Users Only and All Patients.

Last Observation Carried Forward Analysis

	Intent-to-Treat Data Set	L-Deprenyl Users
Pramipexole	-2.72 n = 179	-2.97 n = 97
Placebo	-0.47 n = 171	-0.82 n = 93
p-value	≤0.0001	0.0005

UPDRS Part III Change from Baseline to Final for L-Deprenyl Users Only and All Patients.

Last Observation Carried Forward Analysis

	Intent-to-Treat Data Set	L-Deprenyl Users
Pramipexole	-5.64 n = 179	-6.82 n = 97
Placebo	-2.79 n = 171	-3.06 n = 93
p-value	0.01	0.01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20667

Submission Dates: Dec. 26, 1995

SPONSOR: Upjohn

Feb. 9, 1996

Kalamazoo MI

March 20, 1996

DRUG: Pramipexole (0.125, 0.25, 1.0, 1.25, and 1.5 mg tablets)

INDICATION: Parkinson's Disease

SECTION

TYPE OF SUBMISSION: NME

REVIEWER: Robert Harris, Ph.D.

JUL 31 1996

SYNOPSIS:

Pramipexole is a dopamine receptor agonist used in the treatment of Parkinson's Disease. The sponsor plans on marketing 0.125, 0.25, 1.0, 1.25, and 1.5 mg tablets. The recommended starting dose is 0.125 mg administered tid. Patients are gradually titrated up to the lowest effective dose. The maximum dose described in labeling is 4.5 mg/day. Pramipexole can be administered in monotherapy or in combination therapy with carbidopa/levodopa.

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. Over 90% of an oral dose reaches systemic circulation, indicating that pramipexole is almost completely absorbed and does not undergo first pass metabolism. Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of approximately 500 L (cv = 20%). It is only about 15% bound to plasma proteins, binding primarily to albumin. Pramipexole distributes into red blood cells, having an erythrocyte to plasma ratio of approximately 2.

Pramipexole displays linear kinetics over the labeled dosing range. The terminal half life is about 8 h (cv = 20%) in young healthy volunteers and about 12 h (cv = 20%) in elderly volunteers. Steady state concentrations are achieved within 2 days of dosing.

Approximately 90% of a pramipexole dose is recovered in the urine, almost all as unchanged drug. Non-renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in the plasma or urine. The clearance of pramipexole is approximately 400 mL/min (cv = 25%), which is about three times higher than GFR. Thus, pramipexole is probably secreted via the renal organic cation transport system. Pramipexole clearance correlates moderately well with creatinine clearance.

Pramipexole clearance is about 30% lower in women than in men. This gender difference is primarily due to differences in body weight, and is greatly reduced after weight normalization.

Pramipexole clearance is also about 30% lower in the elderly compared to the young, indicating that pramipexole clearance, like creatinine clearance, decreases with age. This age related decline in pramipexole elimination is potentially noteworthy because the majority of Parkinson's patients are elderly. Pramipexole clearance also appears to be additionally reduced, by about 30%, in Parkinson's patients compared to healthy elderly volunteers. The reason for this is unknown, but may be related to the generally poorer overall health of Parkinson's patients. The effect of race on pramipexole elimination is unknown. Because the dosage of pramipexole is titrated up from a low starting dose, no specific alterations in pramipexole dosing based on gender, age, or the presence of Parkinson's disease are necessary.

Pramipexole clearance is reduced in renally impaired patients. The clearance of pramipexole was about 75% lower in patients with severe renal impairment ($Cl_{cr} \approx 20 \text{ mL/min}$) and about 60% lower in patients with moderate impairment ($Cl_{cr} \approx \text{mL/min}$) compared to healthy volunteers. There is a good correlation between creatinine clearance and pramipexole clearance in patients with decreased renal function. Thus, creatinine clearance can be used as a predictor of the degree of impairment of pramipexole clearance. Because of the decreased pramipexole clearance in patients with renal disease, lower daily doses should be administered. In addition, because of the increase in pramipexole half-life in these patients, it is possible to administer the drug less frequently. Pramipexole is eliminated extremely slowly in hemodialysis patients, making it virtually impossible to predict plasma concentration versus time profiles in these individuals. Very little pramipexole is eliminated by the dialysis process.

Hepatic impairment would not be expected to have a significant effect on the elimination of pramipexole, although this has not been studied.

Pramipexole clearance is reduced by concomitant administration of drugs that inhibit organic base secretion in the kidneys. Cimetidine, a known inhibitor of basic drug secretion caused a 35% reduction in pramipexole clearance. Probenecid, an agent that primarily inhibits organic acid secretion, but also may slightly inhibit base secretion, caused a 10% decrease in pramipexole clearance. Levodopa, carbidopa, and selegiline did not affect the pharmacokinetics of pramipexole. Pramipexole did not affect the systemic elimination of levodopa or carbidopa, although it did alter the rate of levodopa absorption as indicated by T_{max} decreasing from about

Drugs that inhibit or induce CYP enzymes would not be expected to alter pramipexole pharmacokinetics. It is possible that pramipexole inhibits CYP enzymes, although this possibility was not investigated by the sponsor.

The sponsor has adequately linked the to be marketed tablets to the tablets used in the clinical trials. The to be marketed tablets are manufactured in Puerto Rico. The dissolution methodology and specification submitted by the sponsor are acceptable.

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COMMENTS:

1. Pramipexole elimination is so slow in patients with very severe renal impairment (creatinine CL < 10 mL/min) and in those undergoing hemodialysis that it is virtually impossible to predict the plasma levels upon multiple dosing to these patients. Thus, when writing labeling, the Medical Officer may want to put strong warnings about the use of pramipexole in renally impaired subjects. Please see review of Study 0060, starting on p. A30, for a detailed analysis of renal impairment data.
2. A maximal dose of 1.5 mg/TID was given to patients in the clinical efficacy studies. The table provided in the Renal Impairment subsection of the Dosage and Administration section of labeling (p.11 of this review) assumes that the Agency will decide to limit dosing to this amount within labeling. The third column of this table can be removed if it is decided that a maximum dose will not be given in labeling. Alternatively, the table could be replaced with a sentence instructing BID administration to patients with moderate renal impairment and QD administration to patients with severe renal impairment.
3. In the future, in addition to presenting separate gender analyses for phase I/II studies, the sponsor should also present mean data.
4. Pramipexole may inhibit certain cytochrome P-450 enzymes despite the fact it is not metabolized by these enzymes in vivo. The sponsor is requested to utilize in vitro methodologies to determine whether pramipexole inhibits any of the major P-450 enzymes.
5. The sponsor should analyze their population PK database to determine whether race affects pramipexole pharmacokinetics. In addition, if possible, they should examine whether the population PK database can provide any additional information regarding drug interactions.

RECOMMENDATION: The submission (NDA 20,667) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable. Please convey Comments 1-2 to the Medical Officer, and Comments 3-7 to the firm.

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SUMMARY

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ABSORPTION

Rate: After administration of pramipexole, the time to reach maximal plasma concentration is approximately 2 hours (0065, 0069).

Extent: Over 90% of a pramipexole dose is absorbed from the GI tract (0030). Over 90% of the absorbed dose reaches systemic circulation (0030). Thus, pramipexole is almost completely bioavailable.

Food effect: Food does not affect the extent of pramipexole absorption, although T_{max} is increased by about one hour when the drug is taken with food (0065).

DISTRIBUTION

Volume of distribution: The volume of distribution is about 500 L ($cv = 20\%$), indicating that pramipexole distributes into tissues (0065, 0069, 0047).

Protein and red blood cell binding: Pramipexole is only about 15% bound to plasma proteins, binding primarily to albumin (0030). Pramipexole distributes into red blood cells, having an erythrocyte to plasma ratio of approximately 2 (0030).

METABOLISM AND ELIMINATION

Route: About 90% of a pramipexole dose is excreted in the urine as unchanged drug (0030). About 5% of a dose may be excreted in the urine as metabolites (0030), although no specific metabolites have been identified in the urine or plasma. In some pharmacokinetic studies submitted in the NDA (e.g. 0069, 0047), there appears to be a significant amount of nonrenal clearance (contributing up to 1/3 of the total clearance in study 0069). However, this may be largely due to fact that renal clearance was computed as CL_{po} multiplied by the fraction of the dose that was not recovered as unchanged drug in the urine. Thus, any drug that was not recovered unchanged in the urine, including drug that was not absorbed from the GI tract, was considered to be eliminated by nonrenal routes. Because it is often technically very difficult to recover 100% of a dose, a majority of what is called nonrenal clearance may simply be due to experimental limitations in accurately quantifying renally excreted drug. This concept is supported by the observation that the calculated nonrenal clearance of pramipexole decreases with renal impairment (0060, see discussion of renal impairment below).

Rate: The clearance and terminal half-life of pramipexole in healthy volunteers are about 400 ($cv = 25\%$) mL/min and 8 h respectively ($cv = 20\%$; 0061, 0065, 0069). These parameters are altered in certain special populations (see below). Pramipexole displays linear kinetics over the labeled dosing range (0047, 0017, 0062). The renal clearance of pramipexole is about three

times higher than creatinine clearance (130 mL/min), suggesting that pramipexole is extensively secreted via the renal organic cation transport system (0061).

SPECIAL POPULATIONS

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General note: Pramipexole displays a moderate amount of intersubject variability (cv= 30% from population analysis). Certain factors such as age and gender account for a portion of this variability (see below), although most of this variability is unpredictable (see graphs from population analysis). Because the dose of pramipexole is titrated up from a low dose for each patient, the effects of covariates such as weight, age and gender should not affect the dosing of the drug. An exception is with patients who have moderate to severe renal impairment because pramipexole clearance is greatly reduced in these individuals. In these patients, a lower starting dose and less frequent dosing may be necessary (see below).

Gender: Pramipexole clearance is about 25% higher in men than in women (0064, 0063, 0047, 0009, population analysis). This gender difference is primarily due to differences in body weight, and is greatly reduced when data is weight normalized.

Age: Pramipexole clearance decreases with age (0069, population analysis). The half-life and clearance are about 40% longer and 30% lower respectively in the elderly (0069). Consistent with this result, creatinine clearance is also known to decrease with age.

Parkinson's Disease patients: Parkinson's disease patients are usually elderly, so they would be expected to eliminate pramipexole more slowly than did the young subjects studied in the phase III studies. In addition, a comparison of population pharmacokinetic data (patients) to data obtained in healthy elderly volunteers suggests that the clearance of pramipexole is further reduced, by about 30%, in Parkinson's patients compared to healthy elderly individuals (300 mL/min vs 425 mL/min). The reason for this additional decrease in clearance is unknown, but may be related to the poorer general health of Parkinson's patients. Because the clinical studies were performed in Parkinson's patients, and because doses are titrated for each patient, no dosage adjustments on account of Parkinson's disease are necessary.

Renal impairment: Pramipexole clearance is reduced in renally impaired patients. The clearance of pramipexole was about 75% lower in patients with severe renal impairment (CLcr $\approx$ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr $\approx$ 40 mL/min) compared to healthy volunteers. In patients with varying degrees of renal impairment, pramipexole clearance correlates very well with creatinine clearance (0060). Thus, creatinine clearance can be used as a predictor of the degree of impairment of pramipexole clearance. For example, if creatinine clearance is $\frac{1}{2}$ normal then pramipexole clearance would be expected to be $\frac{1}{2}$ normal. Because of the decrease in clearance in renally impaired patients, a lower or less frequent initial dose is necessary, and the maximal allowable doses must also be adjusted (see review of Study 0060 on page A30 and the OCPB labeling / Dosing and Administration section). Pramipexole is removed extremely slowly in patients who are undergoing dialysis, and it is very

difficult to predict plasma drug concentrations in these patients. Very little pramipexole is removed by the dialysis process.

Hepatic impairment: The effect of hepatic impairment on pramipexole pharmacokinetics has not been investigated. Because the drug is predominantly renally excreted, hepatic impairment would not be expected to have a notable effect on pramipexole elimination.

Race: The effect of race on pramipexole kinetics is unknown. The population pk database may contain information about this topic although the sponsor has not yet organized this information. Again, because the dose is titrated, racial differences in pramipexole kinetics, if present, are not likely to be clinically important.

DRUG INTERACTIONS

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Effects of drugs on pramipexole renal elimination: Drugs that affect renal filtration or secretion would be expected to affect pramipexole elimination.

Cimetidine (300 mg, Q 6 h), a well characterized inhibitor of the renal organic cation transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (0061).

Probenecid, a drug that primarily inhibits organic anion transport, caused a 10% increase in pramipexole AUC, and half-life was not affected (0061). The small increase in AUC could be due to the fact that probenecid may weakly inhibit cation secretion.

Interactions with other drugs used in Parkinson's disease: *SINEMET 25/250* (carbidopa/levodopa) administered as a single dose, did not affect pramipexole kinetics. Pramipexole (1.5 mg tid) did not affect the systemic elimination of carbidopa or levodopa, although it did appear to increase the rate of levodopa absorption (T_{max} decreased by about 2 hr and C_{max} increased by about 600 ng/mL)(0063). The sponsor speculates that this increase in the rate of absorption is due to a decrease in GI transit time caused by pramipexole binding to dopamine receptors in the GI tract.

Selegiline (5 mg bid) did not have a significant effect on pramipexole elimination when data from male (n=6) and female (n=5) subjects was combined. If the data was analyzed by gender, selegiline appeared to increase pramipexole clearance in women, and decrease pramipexole clearance in men. Due to the small number of subjects studied, it is inappropriate to make conclusions about gender differences based on this study. The effect of pramipexole on selegiline pharmacokinetics was not examined.

Effects of pramipexole on the elimination of other drugs: Pramipexole could potentially cause increases in the concentrations of drugs that are eliminated via renal secretion such as ranitidine, procainamide and quinidine. In addition, although pramipexole is not significantly metabolized by CYP enzymes in vivo, it could nonetheless inhibit these enzymes. The sponsor has not performed in vitro studies to examine the potential for pramipexole to inhibit CYP mediated drug

metabolism.

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LABELING

CLINICAL PHARMACOLOGY

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Pharmacokinetics

Pramipexole is rapidly absorbed reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90% indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although T_{max} is increased by about one hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (cv = 26%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte to plasma ratio of approximately 2.

Pramipexole displays linear kinetics over the clinical dosing range. Its terminal half-life is about 8 h in young healthy volunteers and about 12 h in elderly volunteers (see Pharmacokinetics in Special Populations). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination

Urinary excretion is the major route of pramipexole elimination with 90% of a pramipexole dose recovered in the urine, almost all as unchanged drug. Non renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The clearance of pramipexole is approximately 400 mL/min (cv = 25%), which is about three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Special Populations

Because the pramipexole dose is gradually titrated upward, no dosage adjustments based on gender, weight or age are necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see Renal Insufficiency).

Gender: Pramipexole clearance is about 30% lower in women than in men, although most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower respectively in elderly (ages 65 years or older) compared to young healthy volunteers (ages less than 40 years). This difference is likely due to a reduction in renal function with age.

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Parkinson's Disease Patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's patients compared to healthy elderly volunteers. The reason for this decrease is unknown, but may be related to the poorer general health of Parkinson's patients. Because the dosing regimen is based on clinical efficacy studies performed in Parkinson's patients, no dosage adjustments are necessary.

Pediatric: The pharmacokinetics of pramipexole in the pediatric population has not been evaluated.

Race: The influence of race on pramipexole pharmacokinetics has not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. However, because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have large effect on pramipexole elimination.

Renal Insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment ($CL_{cr} \approx 20$ mL/min) and about 60% lower in patients with moderate impairment ($CL_{cr} \approx 40$ mL/min) compared to healthy volunteers. A less frequent starting dose is recommended in these patients (see Dosage and Administration). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed in the dialysis process. Caution should be exercised when administering pramipexole to patients with renal disease.

Drug Interactions

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Carbidopa/Levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (n=10). Conversely, pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from _____ hr.

Selegiline: In healthy volunteers (n=11), selegiline did not influence the pharmacokinetics of pramipexole.

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (n=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter did not notably influence pramipexole pharmacokinetics (n=12).

Other drugs eliminated via renal secretion: Drugs that interact with the renal organic cation

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ranitidine, procainamide, and quinidine could potentially limit pramipexole elimination. Likewise, pramipexole could potentially inhibit the elimination of these drugs.

CYP Interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo. The ability of pramipexole to inhibit CYP enzymes has not been examined.

Patients with renal impairment:

Pramipexole Dose in the Renally Impaired		
Renal status	Starting Dose (mg)	Maximum Dose (mg) ?
Normal-mild impairment (Creatinine CL > 60 mL/min)	0.125 TID	1.5 TID
Moderate impairment (Creatinine CL = 35-59 mL/min)	0.125 BID	1.5 BID
Severe impairment (Creatinine CL = 15-34 mL/min)	0.125 QD	1.5 QD
Very severe impairment (Creatinine CL < 15 mL/min and hemodialysis patients)	WARNING	

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Biopharm Day: June 18, 1996

/S/

Robert Z. Harris, Ph.D.
Division of Pharmaceutical Evaluation I

FT initialed by Raman Baweja, Ph.D.

/S/

cc: NDA 20667, HFD-120, HFD-860 (Harris, Baweja, Malinowski), HFD-340 (Viswanathan),
Chron. Reviewer, Drug (Clarence Bott HFD-870, PKLN RM. 13B-31). HFD-19 (FOI) .

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SECTION

OCT 25 1996

OCT 25 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-667

Submission Date: August 1, 1996

Name, Strength(s), and Formulation: Pramipexole 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg Immediate-Release Tablets For Oral Administration.

Sponsor: The Upjohn Company
Kalamazoo, MI

Indication: Parkinson's Disease

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Population PK Analysis

REVIEW OF POPULATION PK ANALYSIS

This submission contains an updated study report for the population pharmacokinetic (PK) analysis of sparse plasma data that were obtained from patients who participated in Phase III clinical trials of pramipexole (Protocols M/2730/0001, M/2730/0004, and M/2730/0010).

Method:

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(Attachment 1 presents the detailed population PK method used in the analysis of pramipexole data).

Briefly, data obtained from 484 patients with pramipexole concentrations ranging from _____ ng/mL at doses ranging from _____ mg/day (given TID) were used in the analysis. The patient population in the database ranged in age from _____ / years, in weight from _____ kg. Sixty-five percent of the population was male and 35 % female. Ninety-seven percent was white, 1.3 % black, and 1.7 % classified as 'other'. Creatinine clearance values ranged from _____ mL/min. Figure 1 shows the frequency distribution of pramipexole concentrations and sampling times. Figure 2 shows the frequency distribution of age, weight, and creatinine clearance values.

Table 1 shows the number of patients and pramipexole samples for each study for each medication coadministered with pramipexole. The medications included in the analysis were selegiline, trihexyphenidyl, cationic and anionic transport system medications, estrogen, bztropine, levodopa, and amantadine.

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Using NONMEM computer program, a 1-compartment open model with first-order absorption and elimination was found to best describe the steady-state plasma concentration/time data of pramipexole. Interindividual variability (% CV in Cl and Ka) variability was modeled using the proportional error model. % CV in Vd could not be estimated due to numerical difficulties within NONMEM. Residual variability was modeled using the proportional error model.

Basic Model:

$$\begin{aligned} Cl &= \Theta_{Cl} \cdot (1 + \eta_j^{Cl}) \\ Vd &= \Theta_{Vd} \\ Ka &= \Theta_{Ka} \cdot (1 + \eta_j^{Ka}) \end{aligned}$$

Parameter estimates, standard error of the estimates (%SEM), and interindividual and residual variabilities for the basic structural model (no covariates added) are shown in Table 2.

As pramipexole is eliminated almost entirely unchanged by the kidneys, creatinine clearance was added to the basic model as a linear predictor of pramipexole clearance. In order to obtain a more precise and more meaningful estimate for the intercept parameter, Θ_{Cl} , creatinine clearance values were centered by subtracting the minimum CrCl value (25.6 mL/min) for this population from each observation.

Table 3 shows the parameter estimates, % SEM, interindividual variability, and residual variability after accounting for creatinine clearance. Addition of CrCl decreased interindividual variability by 9 % from the basic model.

Basic Model with creatinine clearance:

$$\begin{aligned} Cl &= \Theta_{Cl} + \Theta_{Cl}^{CrCl} (CrCl_j - 25.6) \cdot (1 + \eta_j^{Cl}) \\ Vd &= \Theta_{Vd} \\ Ka &= \Theta_{Ka} \cdot (1 + \eta_j^{Ka}) \end{aligned}$$

Various covariates (demographics and comedications) were then tested in the above model (i.e. basic model with CrCL) to determine their effect on the oral clearance of pramipexole. Age and weight were modeled as linear continuous variables. Gender, race, obesity, comedications were modeled as dichotomous variables. The results of this modeling are presented in Tables 4-7. Covariates having significant effect on pramipexole Cl were incorporated in the final model (Table 8).

Results: (See also Attachment 1)

Table 4 shows the effect of demographics (weight, age, gender, race, and obesity) on the oral clearance of pramipexole. Gender, race, and obesity were found to be significant covariates affecting pramipexole Cl. Backward elimination of these covariates from the model (Table 5) showed that only gender and race affect pramipexole Cl.

The effect of concomitant medications on the oral clearance of pramipexole is shown in Tables 6. Initially, amantadine, drugs that are secreted by the cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine), and drugs that are secreted by the anionic transport system (cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide), were found to be significant covariates affecting pramipexole Cl. Backward elimination of these comedications from the model (Table 7) showed that amantadine and drugs that are secreted by cationic transport system were significant covariates affecting pramipexole Cl.

The **final model** describing the population Pk model of pramipexole is as follows:

$$Cl = \theta_{Cl} + \theta_{Cl}^{CrCl} (CrCl_j - 25.6) * (1 + SEX * \theta_{Cl}^{SEX}) * \\ (1 + RACE1 * \theta_{Cl}^{RACE1}) * (1 + RACE2 * \theta_{Cl}^{RACE2}) * \\ (1 + X_j * \theta_{Cl}^X) * (1 + \eta_j^{Cl})$$

$$Vd = \theta_{Vd}$$

$$Ka = \theta_{Ka} * (1 + \eta_j^{ka})$$

where X_j = concomitant medication in the jth patient.

Final parameter estimates (%SEM), interindividual variability, and residual variability are shown in Table 8 (Attachment 1). Figure 3 shows the scatterplots of predicted versus observed pramipexole concentrations, and weighted residuals versus predicted pramipexole concentration for the final PK model including patients demographics and concomitant medications.

For a white male patient with normal renal function ($CrCl = 120$ mL/min) and not taking any comedication, the oral clearance of pramipexole would be:

$$Cl = 480 \text{ mL/min}$$

which is close to the value obtained in healthy volunteers, 400 mL/min.

In conclusion, population PK modeling of steady state plasma concentration data revealed that the oral clearance of pramipexole increased by 17 % in black patients and by 28 % in patients classified as 'Other' compared to white male patients. Drugs which are secreted by the cationic transport system decreased the oral clearance of pramipexole by 18 %. The effect of these covariates may not be clinically important as the dose of the drug is individually titrated to response.

COMMENTS

Reference is made to the labeling provided for pramipexole in the OCPB review of July 26, 1996:

1. Under **Special Populations/Race** (on Page 10), the statement: "The influence of race on pramipexole pharmacokinetics has not been evaluated" should be written as:

"Population PK analysis revealed that oral clearance of pramipexole was 17 % higher in black male patients and was 28 % higher in male patients classified as 'Other' than in white male patients"

2. Under **Drug Interactions** on page 10, the following statement should be added:

"Amantadine: Population PK analysis showed that amantadine does not alter the oral clearance of pramipexole (n=54 patients)."

3. Under **Drug Interactions** on page 10, the statement, "Other drugs eliminated via renal secretion: Drugs that interact with the renal....." should be modified to the following:

"Other Drugs Eliminated Via Renal Secretion: Population PK analysis revealed that coadministration of drugs that are secreted by the cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreased the oral clearance of pramipexole by 18 % while those secreted by the anionic transport system (cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) had no effect on the oral clearance of pramipexole.

COMMENT (To the Clinical Division):

New additional information from population PK analysis relates to race and drug interactions issues as mentioned in Comments 1-3 above. The technical aspects of the above Comments should be included in the labeling for pramipexole.

APPEARS THIS WAY

/S/

Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by R. Baweja, Ph.D.

/S/

- 10/25/96

cc: NDA # 20-667 (Suppl.), HFD-120, HFD-860 (Ibrahim, Baweja, Malinowski), Chron, Drug, and Reviewer Files (Clarence Bott, HFD-870, Parklawn, Rm 13B-31).

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APR 30 1997

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,667

Pramipexole 0.125, 0.25, 1.0, 1.25 and 1.5 mg Tablets

Submission Dates: January 6, 1997; January 7, 1997;

January 24, 1997; January 27, 1997

Indication: Parkinson's Disease

Reviewer: Raman Baweja, Ph.D.

Pharmacia and Upjohn

Kalamazoo, MI 49001

RETURN

APR 30 1997

REVIEW OF RESPONSES TO APPROVABLE LETTER

An Approvable letter was sent to the sponsor on December 23, 1996 for their drug, pramipexole, which is indicated for the treatment of Parkinson's disease. From an OCPB standpoint the two main items in the letter were labelling and the sponsor's acceptance of the dissolution method and specification. The sponsor has now responded to the approvable letter and the review below will address their responses.

I. Labelling:

(A) Essentially the sponsor has accepted entire portions of OCPB's version of labelling that was sent to them in the approvable letter of December 23, 1996. Current labelling is attached to this review as Appendix I. There are two issues that need to be discussed, viz., Drug Interactions, and Dosing and Administration to the very severely renally impaired group. These follow:

(B) In the Drug Interactions section of labelling the sponsor was requested to expand the subsection on CYP Interactions. More specifically, it had been mentioned in the Agency's labelling that "The ability of Pramipexole to inhibit CYP enzymes has not been examined". It should be mentioned that pramipexole is about 90 % recovered in the urine as unchanged drug, and therefore, the issue was not whether it would be a substrate for CYP enzymes; instead the issue was if pramipexole would inhibit CYP enzymes.

The sponsor mentions that Pramipexole does not inhibit enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Further, the drug will not inhibit CYP2D6. All this is correct and can be placed in the labelling. Substantiation for this is provided in Appendix II which shows the percent inhibition of CYP P450 activity by various concentrations of pramipexole. These CYP P450 isoform activities were refractory to inhibition by pramipexole in its concentrations of 1µM and 10 µM (relevant concentrations), and 100 µM (very high and irrelevant concentration).

Appendix II also shows the Dixon plot of pramipexole's inhibition of debrisoquin 4-hydroxylation (CYP 2D6). Inhibition of CYP2D6 was observed with an apparent Ki of 30 µM indicating that pramipexole will not inhibit this enzyme even after administration of the highest recommended clinical dose of 1.5 mg t.i.d.

Overall then, it can be concluded that pramipexole will not inhibit the CYP P450 enzymes and this information can be placed in the labelling.

(C) Dosage and Administration section/Patients with Renal Impairment: A table was made in the labelling for dosing recommendations to this population. The sponsor has accepted these dosing recommendations as they pertain to the normal-mild group (starting dose: 0.125 mg tid), the moderately impaired group (starting dose: 0.125 mg bid), and the severe group (starting dose: 0.125 mg qd). However, it is with regard to the 'very severe impairment group (Creatinine Clearance < 15 ml/min and hemodialysis patients)' where a change has been made by the sponsor. We had written that for this group this be a "Warning"; instead the sponsor has written -- 'the use of Mirapex is not recommended.' The statement from the sponsor appears to be the stronger of the two, and the Medical Officer is requested to look into this.

Comment to the Clinical Division: OCPB accepts the labelling as provided by the sponsor in their latest response. The Medical Officer is requested to note Item I (C) above -- Dosing in the 'very severely renally impaired group'.

/S/

APPEARS THIS WAY
ON ORIGINAL

Raman Baweja, Ph.D. 4/28/97
Team Leader
DPE I

RD/FT Initialed by M.Mehta, Ph.D. /S/ 4/30/97

cc: NDA 20,667, HFD-120, HFD-860 (Baweja, Mehta, Malinowski), Drug files (Barbara Murphy, Central Documents Room)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

ADMINISTRATIVE DOCUMENTS

PRAMIPEXOLE TABLETS NDA 20-667

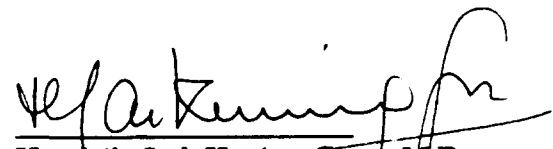
XIII. PATENT INFORMATION

PATENT CERTIFICATION

1.	Active Ingredient	Pramipexole
2.	Strength(s)	0.125, 0.25, 1.0, 1.25 and 1.5 mg
3.	Trade Name	To be determined
4.	a. Dosage Form	Compressed Tablets
	b. Route of Administration	Oral
5.	Applicant Firm Name	The Upjohn Company
6.	NDA Number	20-667
7.	NDA Approval Date	To be determined
8.	Exclusivity - Date first ANDA could be approved and length of exclusivity period	Five (5) years after date of NDA approval / December 12, 2006 / or date of any patent extension -- whichever date occurs last.
9.	Applicable patent numbers and expiration date of each	4,886,812 - compound patent Expiration date - December 12, 2006 4,843,086 - use in Parkinson's disease Expiration date - June 27, 2006

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ON ORIGINAL**

This is to certify that the above information is correct to the best of my knowledge.


Hendrik J. deKoning Gans, M.D.
Regulatory Liaison

EXCLUSIVITY SUMMARY for NDA # 20-667 SUPPL # _____

Trade Name Mirapex[®] Generic Name Pramipexole Tablets 0.125; 0.25; 1.0; 1.25; & 1.5 mg.

Applicant Name Pharmacia & Upjohn HFD- 120

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / X / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

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If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

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- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / ___ / ! NO / ___ / Explain: _____

Investigation #2

IND # _____ YES / ___ / ! NO / ___ / Explain: _____

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- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____

NO / ___ / Explain _____

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Investigation #2

YES / ___ / Explain _____

NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ /

NO / ___ /

If yes, explain: _____

/S/ _____ ^{^^} 11/20/96
Signature _____ Date
Title: PMO

/S/ _____ 7/1/97
Signature of Division Director _____ Date

APPROVED THIS DAY

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-667

Supplement # Circle one: SE1, SE2, SE3, SE4, SE5, SE6

HFD-120 Trade (generic) name/dosage form: Mirapex (Pramipexole) Tablets Action: AP AE NA

Applicant Pharmacia & Upjohn Therapeutic Class 1S

Indication(s) previously approved: None

Pediatric labeling of approved indication(s) is adequate inadequate *Drug is intended*

Indication in this application: *largely for elderly population; no use yet in pediatric population.*

(For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.
2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
- c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.
4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/
Dir ODEI
Signature of Preparer and Title (PM, CSO, MD, other)

APPEAR THIS WAY
ON ORIGINAL
7/1/97
Date

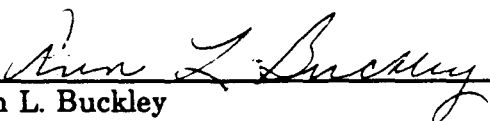
cc:Orig NDA
HFD-120/Div File
NDA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

DEBARMENT CERTIFICATION FOR NDA 20-667**Pramipexole Tablets**

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.


Ann L. Buckley
Executive Director,
Worldwide Regulatory Compliance


Date

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

11041
~~CONFIDENTIAL~~

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 12, 1996

FROM: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

RETURN
AUG 26 1996

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Daniel Boring, Chair
Labeling and Nomenclature Committee
HFD-600, Metropark North II

APPEARS THIS WAY
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Proposed Trademark: MIRAPEX (Pramipexole) Tablets NDA 20-667

Established name, including dosage form: Pramipexole Tablets 0.125, 0.25, 1.0
1.25, 1.5

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):

treatment of the signs and symptoms of idiopathic Parkinson's disease

Initial comments from the submitter: (concerns, observations, etc.)

See attached copies of the "Description, Indications and Usage, Overdosage, and Dosage and Administration" Sections of the package insert.

Any questions call Jack Purvis, 4-5525.

cc: ORIG NDA 20-667, HFD-120, HFD-120/SBlum/Zarifa, HFD-120/JPurvis/rd4/22/96

JS/ 7/12/96

APPEARS THIS WAY
ON ORIGINAL

Consult #641

MIRAPEX

pramipexole tablets

The LNC noted the following look alike/sound alike conflicts with the trademark: MIRASEPT (OTC contact lens solution) and minaprine (antipsychotic unavailable in the U.S.) however, the Committee believes there is a low potential for confusion with these names given the different storage environments for each product. The Committee found no misleading or fanciful aspects in the proposed proprietary name.

The Committee has no reason to find the proposed name unacceptable.

/S/ 8/22/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

END

MD
