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28625

1 OF 7

20625

NDA 20-625

Hoechst Marion Roussel, Inc.
P.O. Box 9627
Kansas City, MO 64134-0627

JUL 25 1996

Attention: Elaine Waller, Pharm.D.
Vice President,
U.S. Regulatory Affairs

Dear Dr. Waller:

Reference is made to your July 31, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Capsules, 60 mg.

We acknowledge receipt of your amendments dated September 5 and 27, October 6, 16, and 19, November 20 and 30, and December 8, 13, 21, and 22, 1995, January 19 and 26, February 9, 12, and 15, March 1, April 12, 26, and 29, May 2, 9, 10, 15, and 31, June 3, 4, 6, 7, 14, 18, 20, 21, and 26, and July 2 and 9, 1996.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the relief of symptoms associated with seasonal allergic rhinitis as recommended in the enclosed marked-up draft physician labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft physician labeling, and the June 26, 1996, final printed carton and container labels. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. All labels and labeling should be revised at the next printing, or within six months, whichever occurs first, to read "Allegra (fexofenadine hydrochloride) Capsules," remove the letters "BID" in association with the name, and include the moisture statement as amended on July 9, 1996.

Please submit 16 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 "FPL for approved NDA 20-625." Approval of this submission by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the 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 send one copy to the Division of Pulmonary 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.

We remind you of your agreement to perform full acceptance testing of the drug substance annually, and to add the statement "Protect from excessive moisture" to the packaging for aluminum foil blister packs printed after July 9, 1996. In addition, you are encouraged to characterize the mechanism of drug interaction between fexofenadine and ketoconazole and between fexofenadine and erythromycin, and to quantify the extent of any drug interaction between fexofenadine and other macrolide antibiotics, other azole antifungal agents, or cimetidine.

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.

NDA 20-625
Page 3

If you have any questions, please contact:

Ms. Gretchen Strange
Project Manager
(301) 827-1058

Sincerely yours,

 7/25/96

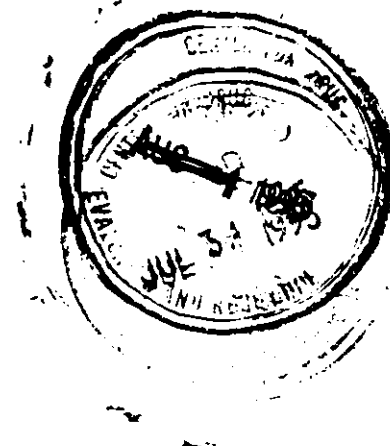
James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure



July 31, 1995

Food and Drug Administration
Office of Drug Evaluation and Research
Central Document Room
Park Building, Room 214
1240 ParkLawn Drive
Rockville, MD 20852



Subject: New Drug Application
Fexofenadine HCl Capsules
(MDL 16,455A)
NDA 20-625

Dear Madames/Messieurs:

In conformance with 21 CFR 314.1, Hoechst Marion Roussel, Inc. is submitting a New Drug Application (NDA) for fexofenadine HCl, 60 mg capsules. This NDA provides support for the use of fexofenadine HCl in the relief of symptoms associated with seasonal allergic rhinitis. The proposed dosage regimen for seasonal allergic rhinitis patients is 60 mg BID. The submission is 454 volumes in length. Contents of the submission include the following sections:

- 1) Index
- 2) Application Summary
- 3) Chemistry, Manufacturing and Control
- 4) Methods, Validation and Labeling
- 5) Nonclinical Pharmacology and Toxicology
- 6) Human Pharmacokinetics and Bioavailability
- 8) Clinical Data
- 10) Statistical Section
- 11) Case Report Tabulations
- 12) Case Report Forms
- 13/14) Patent Information and Certification

This submission is paginated to reflect the Section number (S), followed by Volume number (V), and by Page (P). A separate identical copy of Section 3, Chemistry, Manufacturing and Control has been issued to the local District Office.

Fexofenadine HCl development has been a product of collaborative efforts between the sponsor and Reviewing Division of the FDA. The free-base of fexofenadine HCl or MDL 16,455A (MDL 16,455) was identified as an active acid metabolite of terfenadine. Terfenadine has been marketed globally for over a decade for use in symptomatic relief of seasonal allergic rhinitis and is currently marketed in over 150 countries. While terfenadine has proven to be safe and effective when used under prescribed conditions elevated levels of terfenadine, whether due to hepatic dysfunction, concomitant medications or overdose,

have been associated with QTc interval prolongation. The acid metabolite of terfenadine, fexofenadine HCl, was found to exhibit antihistaminic properties without adverse cardiovascular side effects as observed in animal studies. As a result, Hoechst Marion Roussel, Inc. initiated clinical studies to determine safety and efficacy of the drug product in humans.

This NDA provides data to support the safety and efficacy of fexofenadine HCl (MDL 16,455A) in relief of symptoms of seasonal allergic rhinitis. Four adequate and well controlled clinical studies were conducted with fexofenadine HCl. All four studies were multicenter, randomized, double-blind, placebo-controlled, dose-response studies in patients with seasonal allergic rhinitis (SAR). Two studies were conducted in the spring (Protocol PJPR0009 and PJPR0010) and two studies were conducted in the fall (Protocols PJPR0023 and PJPR0024). Protocols PJPR0009 (962 intent-to-treat patients), PJPR0010 (995 intent-to-treat patients), PJPR0023 (570 intent-to-treat patients) and PJPR0024 (545 intent-to-treat patients) demonstrate effectiveness of fexofenadine HCl at doses ranging from 40 mg BID to 240 mg BID, in the treatment of the symptomatic relief of seasonal allergic rhinitis during both spring and fall seasons. Fexofenadine HCl reduced severity of individual symptoms (sneezing, rhinorrhea, itchy nose, palate and/or throat; and itchy, watery, red eyes) as well as total symptom scores. In addition, a study conducted to assess onset of action (PJPR0017) demonstrated effect one hour following a single dose of 60 mg. Analysis of the four adequate and well controlled studies shows the 60 mg dose had a faster onset of action than the 40 mg dose. Similar onset of effect was observed for doses of 60 mg to 240 mg BID of fexofenadine.

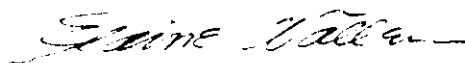
Under conditions of use defined in the proposed text of labeling, benefits of fexofenadine HCl 60 mg BID use in the relief of symptoms of seasonal allergic rhinitis outweigh any anticipated risk.

We look forward to your review of our New Drug Application for fexofenadine HCl. Please be advised that the information submitted is considered confidential under 21 CFR 314.430.

If you have any questions, please do not hesitate to contact:

Dr. Cynthia Kirk-Yourtee
Hoechst Marion Roussel, Inc.
P.O. Box 9707, Park A1
Kansas City, MO 64134-0707
(816) 966-5076

Sincerely,



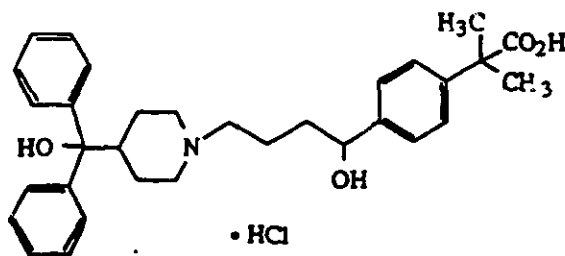
Elaine Waller, PharmD
Vice President,
U.S. Regulatory Affairs

Prescribing Information as of July 1996

ALLEGRA™
(fexofenadine hydrochloride) **Capsules**
60 mg capsules

DESCRIPTION

Fexofenadine hydrochloride, the active ingredient of ALLEGRA™, is a histamine H₁-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidiny]-butyl]-α,α-dimethyl benzeneacetic acid hydrochloride, (Refs. 3-9). It has the following chemical structure (Ref. 10):



The molecular weight is 538.13 (Ref. 11) and the empirical formula is C₂₂H₂₉NO₄•HCl (Ref. 12). Fexofenadine hydrochloride is a white to off-white crystalline powder (Ref. 13). It is freely soluble in methanol and ethanol, slightly soluble in chloroform and in water, and insoluble in hexane (Ref. 14). Fexofenadine hydrochloride is provided as a racemate and exists as a zwitterion in aqueous media at physiological pH (Refs. 15,16).

ALLEGRA™ is formulated as capsules for oral administration (Ref. 1). Each capsule contains 60 mg fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients (Ref. 2).

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H₁-receptor antagonist activity (Refs. 3-8). Fexofenadine inhibited antigen-induced bronchospasm in sensitized guinea pigs and inhibited histamine release from peritoneal mast cells in rats (Refs. 17,18). In laboratory animals, no anticholinergic or alpha₁-adrenergic-receptor blocking effects were observed (Refs. 4,19,20). Moreover, no sedative or other central nervous system effects were observed (Refs. 3,21). Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier (Ref. 35).

Pharmacokinetics

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single dose of two 60 mg capsules to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours postdose (Ref. 31). After administration of a single dose of 60 mg as an oral solution to healthy subjects, the mean plasma concentration was 209 ng/mL (Ref. 32). Mean steady-state peak plasma concentrations of 286 ng/mL were observed when healthy volunteers were administered multiple doses of fexofenadine hydrochloride (60 mg oral solution every 12 hours for 10 doses) (Ref. 32). Fexofenadine pharmacokinetics were linear for oral doses up to 120 mg twice daily (Ref. 32). Although the absolute bioavailability of fexofenadine hydrochloride capsules is unknown, the capsules are bioequivalent to an oral solution (Ref. 31). The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, to steady-state in normal volunteers (Ref. 32).

Human mass balance studies documented a recovery of approximately 80% and 11% of the [¹⁴C] fexofenadine hydrochloride dose in the feces and urine, respectively. Approximately 5% of the total dose was metabolized (Refs. 33,34). Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients (Ref. 24).

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α_1 -acid glycoprotein (Refs. 36,37).

Special Populations

Special population pharmacokinetics (for age and renal and hepatic impairment), obtained after a single dose of 30 mg fexofenadine hydrochloride, were compared to those from normal subjects in a separate study of similar design (Ref. 38). While subject weights were relatively uniform between studies, these special population patients were substantially older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed in some of the special populations.

Effect of Age. In older subjects (≥ 65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in normal volunteers (<65 years old). Mean elimination half-lives were similar to those observed in normal volunteers (Refs. 38,41).

Renally Impaired. In patients with mild (creatinine clearance 41-80 mL/min) to severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤ 10 mL/min) were 82% greater and half-life was 31% longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See DOSAGE AND ADMINISTRATION.) (Refs. 38,40)

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects (Refs. 38,39).

Effect of Gender. Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine (Refs. 38,74).

Pharmacodynamics

Wheal and Flare. Human histamine skin wheal and flare studies following single and twice daily doses of 20 mg and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours (Refs. 22,23). There was no evidence of tolerance to these effects after 28 days of dosing (Ref. 23).

Effects on QTc. In dogs, (10 mg/kg/day, orally for 5 days) and rabbits (10 mg/kg ^{that} intravenously over one hour) fexofenadine did not prolong QTc at plasma concentrations ~~which~~ were at least 28 and 63 times, respectively, the therapeutic plasma concentrations in man (based on a 60 mg twice daily fexofenadine hydrochloride dose) (Refs. 24-26). No effect was observed on calcium channel current, delayed K⁺ channel current, or action potential duration in guinea pig myocytes, Na⁺ current in rat neonatal myocytes, or on the delayed rectifier K⁺ channel cloned from human heart at concentrations up to 1×10^{-5} M of fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on a 60 mg twice daily fexofenadine hydrochloride dose) (Refs. 24,27). ✓

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 seasonal allergic rhinitis patients (Ref. 73) given fexofenadine hydrochloride capsules in doses of 60 mg to 240 mg twice daily for two weeks or in 40 healthy volunteers (Ref. 29) given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days (Refs. 28,29).

Clinical Studies

In three, ~~two~~ week, multi-center, randomized, double-blind, placebo-controlled trials in patients 12-68 years of age with seasonal allergic rhinitis (n=1634), fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo (Refs. 75,76). Statistically significant reduction in symptom scores was observed following the first 60 mg dose, with the effect maintained throughout the 12-hour interval (Ref. 77). In general, there was no additional reduction in total symptom scores with higher doses of fexofenadine up to 240 mg twice daily (Ref. 42). Although the number of subjects in some of the subgroups was small, there was no significant difference in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, and race (Ref. 45). Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60 mg fexofenadine hydrochloride dose administered to patients with seasonal allergic rhinitis who were exposed to ragweed pollen in an environmental exposure unit (Ref. 43). ✓

INDICATIONS AND USAGE

ALLEGRA™ is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes (Refs. 7,8,46,47).

CONTRAINDICATIONS

ALLEGRA™ is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Drug Interactions

In two separate studies, fexofenadine hydrochloride 120 mg twice daily (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Co-Administration with Fexofenadine Hydrochloride 120 mg Every 12 Hours (twice recommended dose) in Normal Volunteers (n=24)

<i>Concomitant Drug</i>	<i>C_{max}</i> (Peak plasma concentration)	<i>AUC_{0-12h}</i> (Extent of systemic exposure)
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The mechanisms of these interactions are unknown, and the potential for interaction with other azole antifungal or macrolide agents has not been studied (Refs. 48,49). These changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole (Refs. 48,49).

Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Fexofenadine is an active acid metabolite of terfenadine.~~ The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were up to four times the human therapeutic value (based on a 90 mg twice daily fexofenadine hydrochloride dose) (Refs. 50,51).

In in-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in-vivo (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity (Refs. 53-56). ✓

In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose) (Ref. 52). ✓

Pregnancy

Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose), respectively (Refs. 57-59). ✓

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150 mg/kg of terfenadine; at these doses the plasma AUC values of fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60-mg twice-daily fexofenadine hydrochloride dose) (Ref. 52). ✓

Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ALLEGRA™ in pediatric patients under the age of 12 years have not been established. Across well-controlled clinical trials in patients with seasonal allergic rhinitis, a total of 205 patients between the ages of 12 to 16 years received doses ranging from 20 mg to 240 mg twice daily for up to two weeks. Adverse events were similar in this group compared to patients above the age of 16 years (Ref. 72).

Geriatric Use

In placebo-controlled trials, 42 patients age 60 to 68 years, received doses of 20 mg to 240 mg of fexofenadine twice daily for up to two weeks. Adverse events were similar in this group to patients under age 60 years (Refs. 7,8,46,47). ✓

ADVERSE REACTIONS

In placebo-controlled clinical trials which included 2461 patients receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients (Refs. 75,78). The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo (Ref. 79,80). All adverse events reported by greater than 1% of patients who received the recommended daily dose of fexofenadine hydrochloride (60 mg twice daily), and that were more common with fexofenadine than placebo, are listed in the following table.

Adverse Experiences Reported in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials at Rates of Greater Than 1%

<i>Adverse Experience</i>	<i>Fexofenadine 60 mg Twice Daily (n=679)</i>	<i>Placebo Twice Daily (n=671)</i>
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Adverse events occurring in greater than 1% of fexofenadine hydrochloride-treated patients (60 mg twice daily), but that were more common in the placebo-treated group, include headache and throat irritation (Ref. 78).

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride and placebo-treated patients (Ref. 63).

OVERDOSAGE

Information regarding acute overdosage is limited to experience from clinical trials conducted during the development of ALLEGRA™. Single doses of fexofenadine hydrochloride up to 800 mg (6 normal volunteers at this dose level), and doses up to 690 mg twice daily for one month (3 normal volunteers at this dose level), were administered without the development of clinically significant adverse events (Refs. 22,23).

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove terfenadine from blood (up to 1.7% removed) following terfenadine administration (Ref. 64)

~~An oral lethal dose in rodents could not be determined for (terfenadine hydrochloride). No~~
deaths occurred at oral doses up to 5000 mg/kg in mice (170 times the maximum recommended human daily oral dose based on mg/m²) and up to 5000 mg/kg in rats (330 times the maximum recommended human daily oral dose based on mg/m² Refs. 65,66). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (450 times the maximum recommended human daily oral dose based on mg/m² Refs. 67,68).

DOSAGE AND ADMINISTRATION

The recommended dose of ALLEGRA™ is 60 mg twice daily for adults and children 12 years of age and older (Refs. 7,8).

A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY.)

HOW SUPPLIED

ALLEGRA™ 60 mg capsules are available in (Ref. 69): high-density polyethylene (HDPE) bottles of 60 (NDC 0088-1102-41); HDPE bottles of 100 (NDC 0088-1102-47); HDPE bottles of 500 (NDC 0088-1102-55); and aluminum foil blister packs of 100 (NDC 0088-1102-49).

ALLEGRA™ capsules have a white opaque cap and a pink opaque body. The capsules are imprinted in black ink, with "60 mg" on the cap, and "1102" on the body (Ref. 70).

Store ALLEGRA™ capsules at controlled room temperature 20-25°C (68-77°F) (Ref. 71). Foil-backed blister packs should be protected from excessive moisture (Ref. 81).

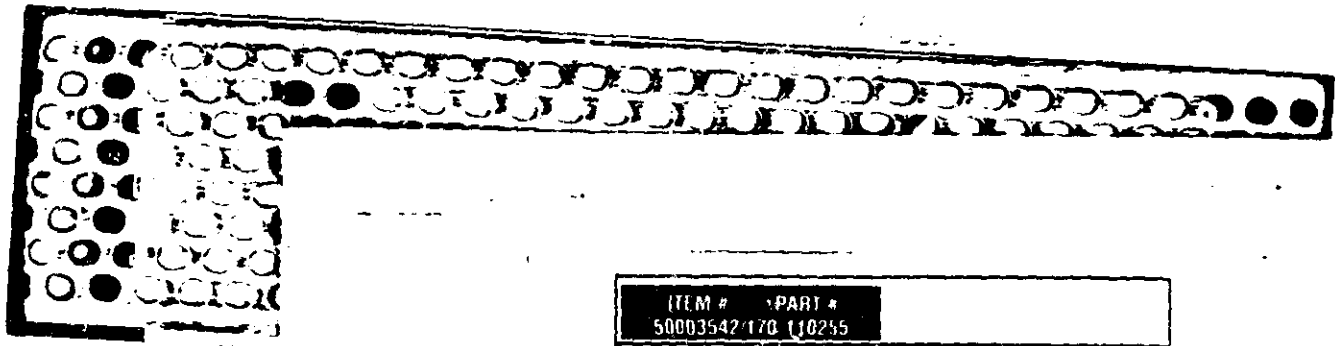
Prescribing Information as of July 1996

Hoechst Marion Roussel, Inc.

Kansas City, MO 64137 USA

Bottle Label, 500 count

BOTTLE LABEL
500 count



ITEM #	PART #		
50003542-170	110255		
DATE: 1/22/96 9:03 AM			
Pg. 1 of 1	CICERO JOB NO.: 15323		
PRODUCT: LABEL, ALLEGRA, CAPSULES, 60MG, 500 CT			
PRINTER: NEW JERSEY PACKAGING			
PMS 259	PMS 169	Black	40% Black

0088-1102-55

ALLEGRA™
(levamisole hydrochloride)

NDC 0088-1102-55



60 mg

Each capsule contains:
levamisole hydrochloride 60 mg
Strength and Administration: Read package insert for complete information.
CAUTION: Federal law prohibits dispensing without prescription.
Storage: Keep out of reach of children.
Presentation: Capsules in light, light-resistant container to contain 500 capsules.
N-77-102-55

ALLEGRA™
(levamisole hydrochloride)

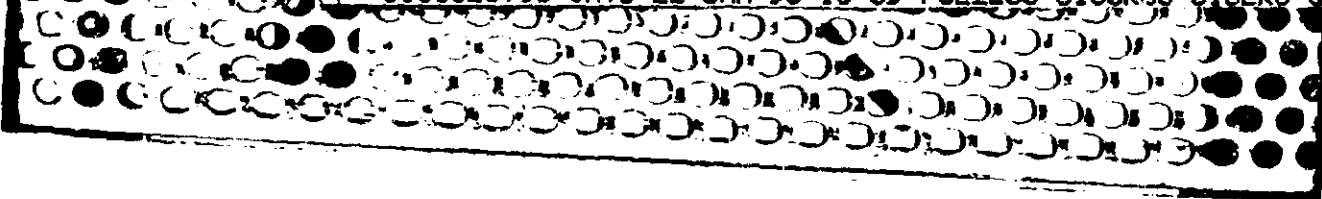
60 mg

Avoid excessive moisture.
© 1995 Watson Laboratories, Inc.
Watson City, MO 64137 USA

500 Capsules

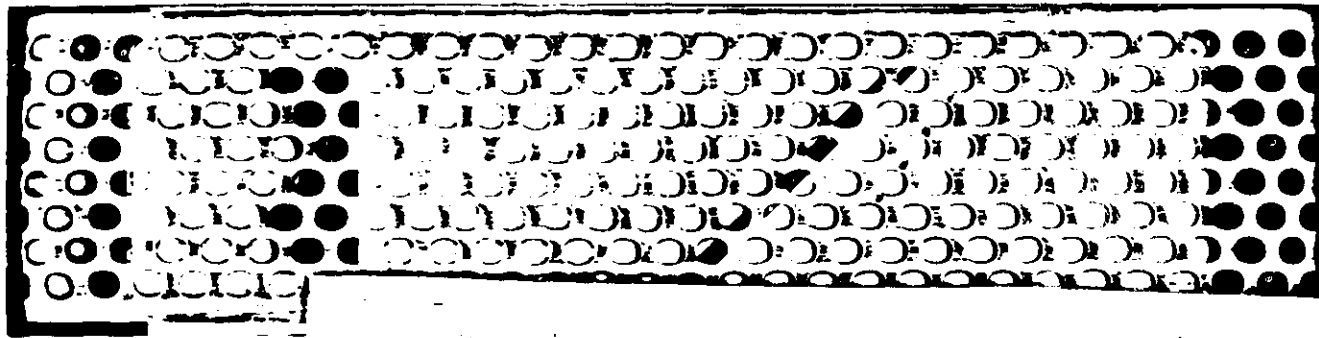
80003542

RS



Bottle Label, 100 count

DOTTIE LARUE
100 count



ITEM #	PART #		
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DATE: 2/11/86 1:34 PM			
Pg. 1 of 1	CICERO JOB NO.: 15322		
PRODUCT: LABEL, ALLEGRA, CAPSULES, 60 MG, 100 CT			
PRINTER: NEW JERSEY PACKAGING			
PMS 250	PMS 169	Black	40% Black

APPROVALS:
C Vogel 2-13-96
FUNCTIONAL
Korman 2-13-96
PROOFREADING
R Hopkins 2/14/96
REGULATORY

⊕ H NDC 0088-1102-47

60 Hoechst Marion Roussel

ALLEGRA™
 (terfenadine hydrochloride)

60 mg .

100 Capsules

⊕

⊕

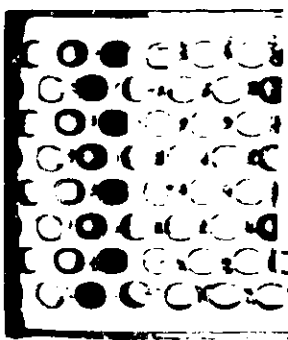
0088-1102-47

3 80003541

2/11/86 1:34 PM ITEM # PART #
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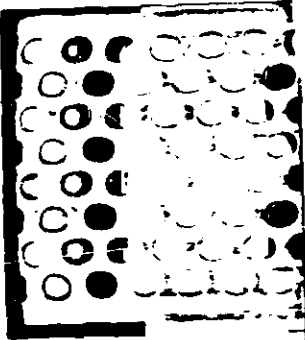
40% BLACK BLACK Cicero # 15322

Avoid excessive use. Do not use if you are taking other antihistamines. Do not use if you are taking other sedatives. Do not use if you are taking other drugs that may interact with terfenadine. Do not use if you are taking other drugs that may interact with terfenadine. Do not use if you are taking other drugs that may interact with terfenadine.



Bottle Label, 60 count

Dottle label for
60 count



ITEM #	PART #
50003540	170 110241
DATE: 2/13/96 11:42 AM	
Pg. 01 of 01	CICERO JOB NO.: 15433
PRODUCT: LABEL, ALLEGRA, CAPSULES, 60 MG, 60 CT	
PRINTER: NEW JERSEY PACKAGING	
PMS 259	Black 40% Black

APPROVALS:
C Vogel 2-15-96
 FUNCTIONAL
Kluman 2-15-96
 PROOFREADING
R. Anderson 2/15/96
 REGULATORY

NDC 0088-1102-41

60 mg Hoechst Marion Roussel

ALLEGRA™
(terfenadine hydrochloride)

60 mg

60 Capsules

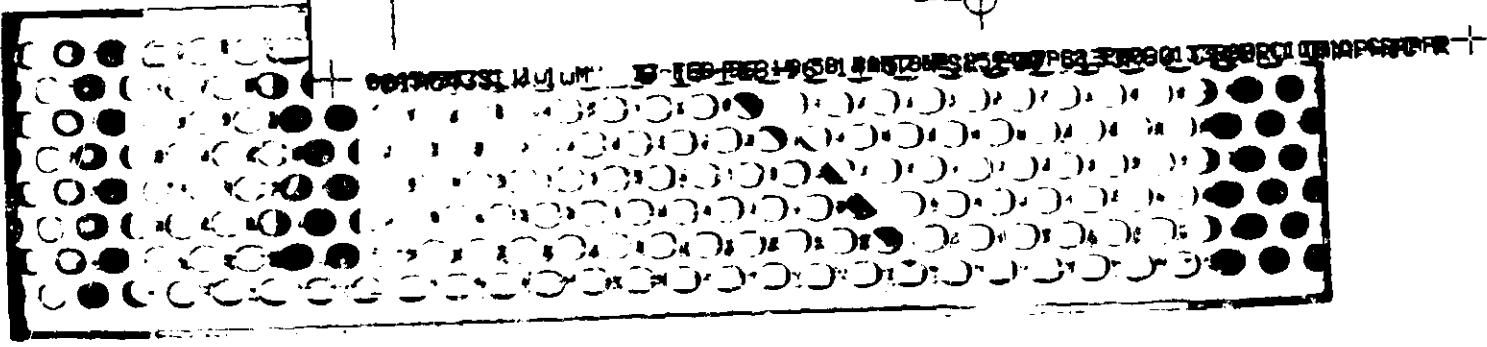
60 mg

3 0088-1102-41 2
 50003540

ITEM # PART #
 50003540/170-110241
 PMS 259 40% BLACK BLACK

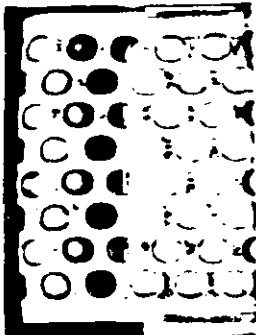
Cicero # 15433

AVOID EXCESSIVE
 moisture.



Bottle Label, 30 count (physician dispensing pack)

EDDIE Lauer #1
dispensing pack
30 count



ITEM # PART #	
50004021 170 110556	
DATE: 2/11/96 1:56 PM	
Pg. 1 of 1	CICERO JOB NO.: 14962
PRODUCT: LABEL, ALLEGRA, CAPSULES, 60 MG, 30 CT	
PRINTER: NEW JERSEY PACKAGING	
PMS 259	PMS 169 40% Black Black

APPROVALS:
 C Vogel 2-13-96
 PHARMACY
 K Wynn 2-13-96
 PHARMACY
 R Forberg 2/14/96
 REGULATORY

MDC 0088-1102-30

Hoechst Marion Roussel

ALLEGRA™
(lexafenodine hydrochloride)

60 mg DISPENSING PACK

30 Capsules

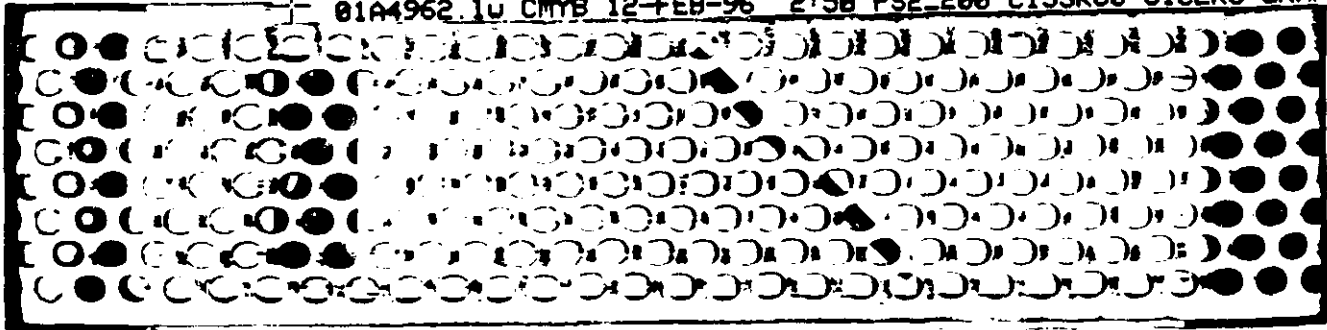
Avoid exposure to moisture.

3 0088-1102-02 3

85 80004021

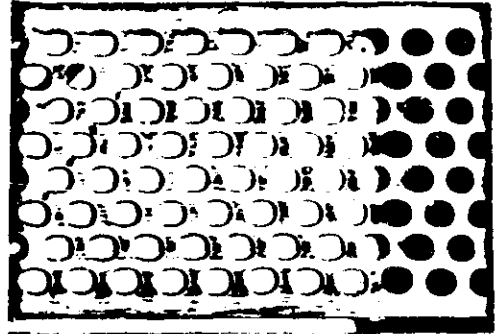
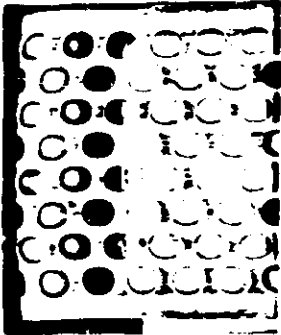
2/11/96 1:56 PM ITEM # PART #
 50004021/170-110556 Cicero # 14962
 PMS 259 PMS 169 40% BLACK BLACK

01A4962.1u CMYB 12-FEB-96 2:58 PS2_200 C133R80 CICERO GRAPHIC R



Unit Dose Carton, 100 count

UNIT CASE
100 count
page 1



NDC 0088-1102-49

60 mg

Hoechst Marion Roussel

ALLEGRA™
(fexofenadine hydrochloride)

60 mg

100 Capsules

NDC 0088-1102-49

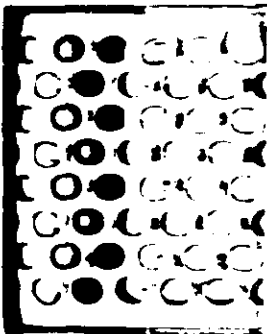
60 mg

Hoechst Marion Roussel

ALLEGRA™
(fexofenadine hydrochloride)

60 mg

100 Capsules



UDIP®
(Unit Dose Identification Past)

Each Capsule Contains:
fexofenadine hydrochloride 60 mg

Dosage and Administration: Read package insert
for prescribing information.

CAUTION: Federal law prohibits dispensing without
prescription.

Warning: Keep out of reach of children

Store at controlled room temperature
20-25°C (68-77°F)

AVOID EXCESSIVE MOISTURE

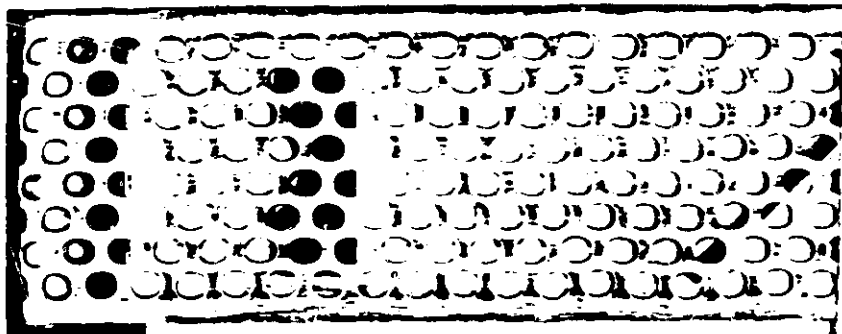
UDIP®
(Unit Dose Identification Past)

60 mg



3 0088-1102-49 8

unit dose
100 count
page 2



100 Capsules

60 mg

ALLEGRA™
(fexofenadine hydrochloride)

Hoechst Marion Roussel  
NDC 0088-1102-49

NDC 0088-1102-49

  Hoechst Marion Roussel

ALLEGRA™
(fexofenadine hydrochloride)

60 mg

100 Capsules

NDC 0088-1102-49

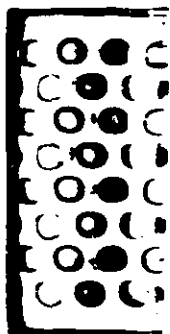
  Hoechst Marion Roussel

ALLEGRA™
(fexofenadine hydrochloride)

60 mg

100 Capsules

© 1995, Hoechst Marion Roussel, Inc.



This package is intended for institutional inpatient use only.

Hoechst Marion Roussel, Inc.
Kansas City, MO 64114 USA

Blisters for Unit Dose

Physician Sample Carton

Physician Sample
Carton
page 1

allegra
fexofenadine HCl^{60 mg}

See package insert
for prescribing information.

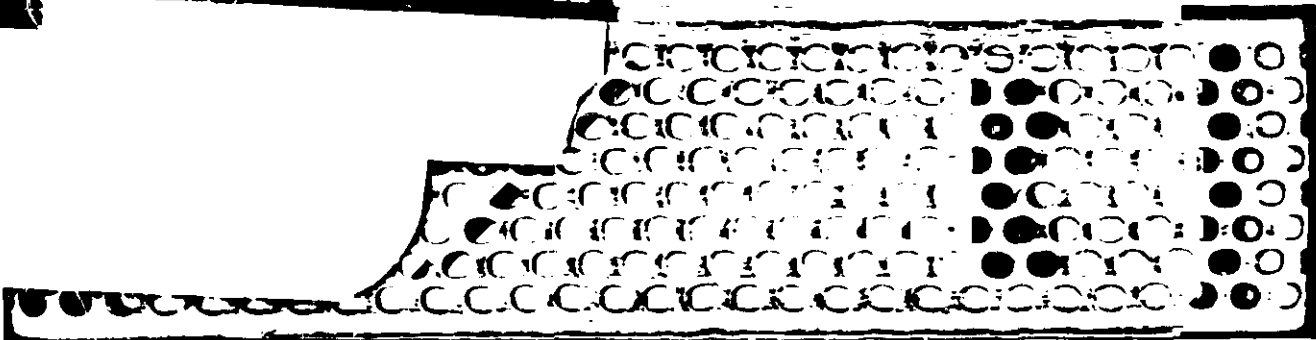
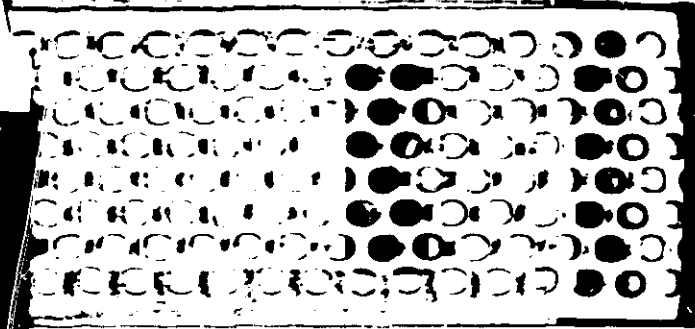
PHYSICIAN SAMPLE—NOT TO BE SOLD

for seasonal allergy sufferers
allegraTM
fexofenadine HCl^{60 mg}
bid

Store at controlled room temperature

AVOID EXCESSIVE MOISTURE

CAUTION
FEDERAL LAW PROHIBITS DISPENSING
WITHOUT PRESCRIPTION



WARNING: Keep out of reach of children.
Dosage and administration.
Read package insert for prescribing information.



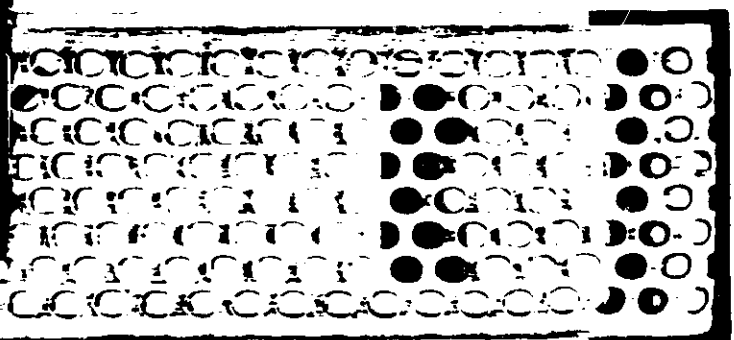
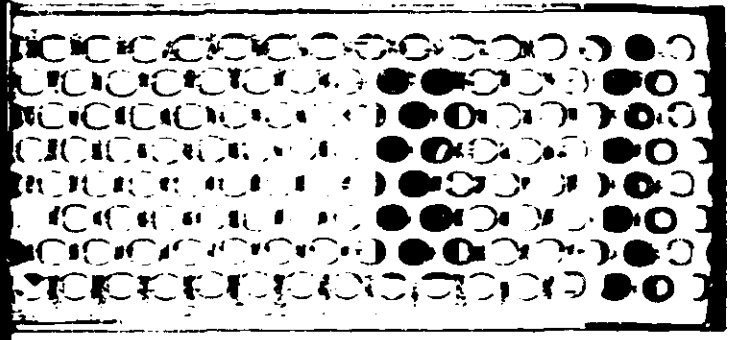
3-DAY STARTER SAMPLE
Net contents: 6 capsules,
60 mg each.

PHYSICIAN SAMPLE—NOT TO BE SOLD

For seasonal allergy sufferers
allegra™
fexofenadine HCl 60 mg
bid

Hoechst Marion Roussel, Inc.
Kansas City, MO 64114 USA

Exp
Lot #



Blister for Physician Sample

physician sample
blister

For seasonal allergy sufferers:
Fexofenadine HCl 60 mg BID



Day 1
Morning

Day 1
Evening

Day 2
Morning

Day 2
Evening

Day 3
Morning

Day 3
Evening

Fexofenadine HCl 60 mg BID PHYSICIAN SAMPLE—NOT TO BE SOLD

front

For seasonal allergy sufferers
Fexofenadine HCl 60 mg BID
Contains: 6 Capsules
PHYSICIAN SAMPLE—NOT TO BE SOLD

Each capsule contains:
fexofenadine hydrochloride.. 60 mg

Dosage and administration:
Read package insert for
prescribing information.

CAUTION:
Federal law prohibits dispensing
without prescription.

WARNING:
Keep out of reach of children.
Package not child-resistant.

Store at controlled room temperature
68-77°F (20-25°C)

Hoechst Marion Roussel, Inc.
Kansas City, MO 64114 USA
50004780 R5

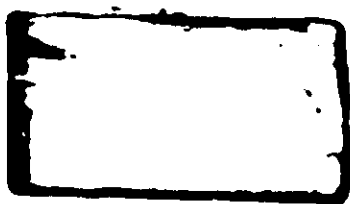
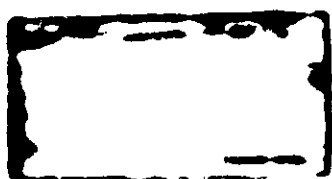
back



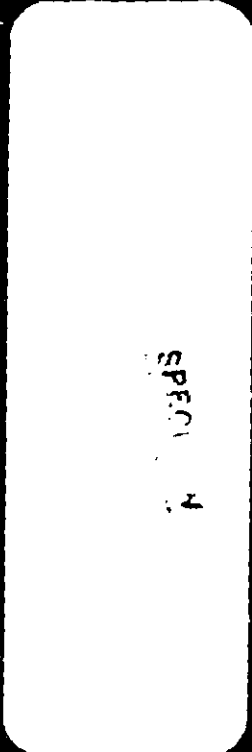
fexofenadine HCl 60 mg
bid

For more information, please contact
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936 USA

۸۸۸ ۸



For seasonal allergy sufferers.
Fexofenadine HCl 60 mg BID



SPECI
H

Day 1
Morning

Day 1
Evening

Day 2
Morning

Day 2
Evening

Day 3
Morning

Day 3
Evening

Fexofenadine HCl 60 mg BID PHYSICIAN SAMPLE NOT TO BE SOLD

For seasonal allergy sufferers
Fexofenadine HCl 60 mg BID

Contains 6 Capsules

PHYSICIAN SAMPLE NOT TO BE SOLD

Each capsule contains:
fexofenadine hydrochloride 60 mg

Dosage and administration:

Read package insert for
prescribing information.

CAUTION:

Federal law prohibits dispensing
without prescription.

WARNING:

Keep out of reach of children.
Package not to be recycled.

Store at controlled room temperature
20° to 25° C (68° to 77° F).

Howell-Miller, Inc.
A Division of Hoechst-Roussel, Inc.
Raritan, NJ 08869



NDC 0088-1102-49

60 mg

Hoechst Marion Roussel

ALLEGRA™
(fexofenadine hydrochloride)

60 mg

100 Capsules

NDC 0088-1102-49

60 mg

Hoechst Marion Roussel

ALLEGRA™
(fexofenadine hydrochloride)

60 mg

100 Capsules

UDIP™
(Unit Dose Identification Pack)

Each Capsule Contains
fexofenadine hydrochloride 60 mg

Dosage and Administration: Read package insert
for prescribing information.

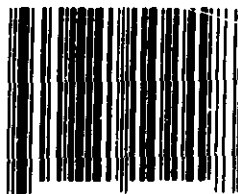
CAUTION: Federal law prohibits dispensing without
prescription.

Warning: Keep out of reach of children.

Store at controlled room temperature
20-25°C (68-77°F).

UDIP™
(Unit Dose Identification Pack)

60 mg



3 0088-1102-49 8

EXP :

3 0088-1102-55 9



50003542

ALLEGRA™
(lexofenadine hydrochloride)

60 mg

Each capsule contains
lexofenadine hydrochloride 60 mg
Dosage and Administration: Read package insert for prescribing information.
CAUTION: Federal law prohibits dispensing without prescription.
Warning: Keep out of reach of children.
Precautions: Discontinue in light sensitivity reaction.
Store in controlled room temperature 68-77°F (20-25°C).

© 1995 Hoechst Marion Roussel, Inc.
Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

R5

NDC 0088-1102-55

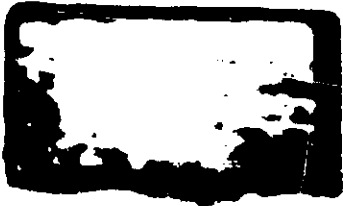


SPEC

ALLEGRA™
(lexofenadine hydrochloride)

60 mg

500 Capsules



B

3 DAY STARTER SAMPLE
Net contents: 6 capsules,
60 mg each

For seasonal allergy sufferers
allegra[™]
fexofenadine HCl 60 mg

WARNING: Keep out of
reach of children.
Dosage and administration:
Read package insert for
prescribing information.

PHYSICIAN SAMPLE - NOT TO BE SOLD

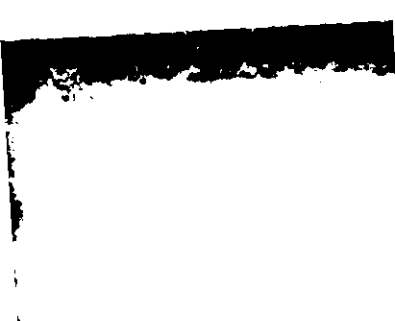
For seasonal allergy sufferers
allegra[™] SPECIMEN
fexofenadine HCl 60 mg
bid



Howell Laboratories, Inc.
Kirkland, MO 64584 USA







C



Hoechst Marion Roussel

Hoechst Marion Roussel

June 26, 1996

Hoechst Marion Roussel, Inc.

Ms. Gretchen Strange
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Products (HFD-570)
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

10216 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Subject: NDA 20-625 ALLEGRA™
(fexofenadine HCl)
Response to FDA Request

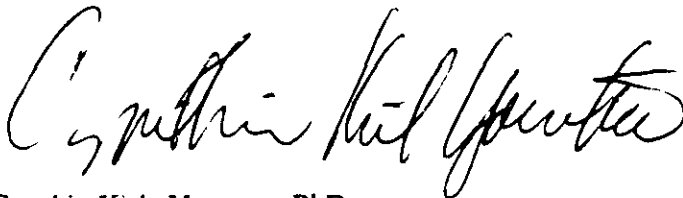
Dear Ms. Strange:

In reference to our conversation today. These are the items you requested.

If you should have any questions or concerns, please don't hesitate to contact me at the number listed below.

Sincerely,

HOECHST MARION ROUSSEL, INC.
(816) 966-5076



Cynthia Kirk-Yourtee, PhD
Director, U.S. Regulatory Affairs

Hoechst Marion Roussel
A member of the Hoechst Group

Hoechst 

DATE: 2/11/96 1:34 PM PMS 259 PMS 169 Black 40% Black	
PRODUCT: LABEL, ALLEGRA, CAPSULES, 60 MG, 100 CT PRINTER: NEW JERSEY PACKAGING	
CICEERO JOB NO.: 15322	

APPROVALS:
 C. Lopez 2-13-96
 K. Lopez 2-13-96
 R. Lopez 2/11/96

H 1102 47

 Ciceero (Marion Roussel)

ALLEGRA™
 (excitatory hydrochloride)

60 mg

100 Capsules

0088-1102-47
 6 08 63003641
 License # 15322

01A5322.1u CMYB 12-FEB-96 2:58 P52_200 S133R80 CICEERO GRAPHIC R

ITEM # PART # 50003540 170 110241	
DATE: 2/13/96 11:42 AM	
Pg. 1 of 1	CICERO JOB NO.: 15533
PRODUCT: LABEL, ALLEGRA, CAPSULES, 60 MG, 60 CT	
PRINTER: NEW JERSEY PACKAGING	
PMS 259	Black 40% Black

APPROVALS:
 C. Vogel 2-15-96
 FUNCTIONAL
 Klamma 2-15-96
 PROOFREADING
 B. Toliver 2/15/96
 REGULATORY

MCC 0088-1102 41
 60 mg

Hoechst Marion Roussel

ALLEGRA™
 (levamisole hydrochloride)

60 mg

60 Capsules

⊕

1. The information on this label is intended to provide you with the most accurate and complete information available. It is not intended to be used as a substitute for professional medical advice. Always consult your physician before using any medicine.

2. This medicine is intended to be used only in the treatment of the condition for which it is prescribed. Do not use it for any other condition.

3. This medicine may cause drowsiness. Do not drive or operate machinery until you know how this medicine affects you.

4. This medicine may cause dizziness. Do not drink alcohol while taking this medicine.

5. This medicine may cause dry mouth. Drink plenty of fluids to avoid dehydration.

6. This medicine may cause constipation. Eat a high-fiber diet and drink plenty of fluids.

7. This medicine may cause blurred vision. Do not drive or operate machinery until you know how this medicine affects you.

8. This medicine may cause fatigue. Rest when you feel tired.

9. This medicine may cause weakness. Avoid strenuous activity until you know how this medicine affects you.

10. This medicine may cause headache. Take over-the-counter pain relievers if needed.

11. This medicine may cause dizziness. Do not drink alcohol while taking this medicine.

12. This medicine may cause dry mouth. Drink plenty of fluids to avoid dehydration.

13. This medicine may cause constipation. Eat a high-fiber diet and drink plenty of fluids.

14. This medicine may cause blurred vision. Do not drive or operate machinery until you know how this medicine affects you.

15. This medicine may cause fatigue. Rest when you feel tired.



60 MG 50003540

2/13/96 11:42 AM
 PMS 259

ITEM # PART #
 50003540 170-110241

40% BLACK BLACK

Close # 15433

001974331412 UNIT 13-15888 19 6561 9A040525288P62.328801 130801 130801 000000000000

ITEM #	PART #
50004021	170-110556
DATE:	2/11/96 1:56 PM
Pg. 1 of 1	CICERO JOB NO.: 14962
PRODUCT:	LABEL, ALLEGRA, CAPSULES, 60 MG, 30 CT
PRINTER:	NEW JERSEY PACKAGING
PMS 259	PMS 169 40% Black
	Black

APPROVALS:
 C. Vogel 2-13-96
 FUNCTIONAL
 K. Moon 2-13-96
 PROGRAMMER
 B. Anagn... 2/14/96
 REGULATORY

NDC 0088-1102-30



ALLEGRA™
 (lexofenodine hydrochloride)

60 mg DISPENSING
 PACK

30 Capsules

2/11/96 1:56 PM
 PMS 259 PMS 169 40% BLACK

ITEM # PART #
 50004021/170-110556
 Cicero # 14962

0088-1102-02

50004021

NDA 20-625

fexofenadine hydrochloride capsule

13/14. Patent Information Certification

13/14. Patent Information/Certification

Patent information relevant to fexofenadine HCl is defined in Attachments A and B.

These attachments are copies of Patent Information Declarations issued separately to NDA 20-625. These declarations apply to:

- 1) United States Patent No. 4,254,129 (Attachment A).
- 2) United States Patent No. 5,375,693 (Attachment B).

Marion Merrell Dow Inc.
Kansas City, Missouri 64134

NDA 20-625

fexofenadine hydrochloride capsule

13/14. Patent Information Certification

Attachment A: United States Patent No. 4,254,129



MARION MERRELL DOW INC.

Marion Park Drive
MAIL P.O. Box 9627
Kansas City, Missouri 64134-0627
Telephone 816 966-5000

July 31, 1995

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission for Fexofenadine HCl
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Fexofenadine HCl:

PATENTS NUMBER(S): United States Patent No. 4,254,129
EXPIRATION DATE(S): April 10, 1999
PATENT OWNER: Merrell Dow Pharmaceuticals, Inc.
2110 E. Galbraith Road
Cincinnati, OH 45215
Marion Merrell Dow Inc.
9300 Ward Parkway
Kansas City, MO 64114-3321
TYPE OF PATENT: Drug Substance, Drug Product Composition and Method of Use

The undersigned declares that United States Patent No. 4,254,129 covers Fexofenadine HCl, the drug substance of the drug product for which the above-referenced NDA is being submitted for approval, even date herewith, for use in treating allergic reactions, as well as the drug product (composition) containing the drug substance and a method of using said drug substance in treating allergic reactions. Merrell Dow Pharmaceuticals, Inc. is a wholly-owned subsidiary of Marion Merrell Dow Inc. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President,
U.S. Regulatory Affairs

Marion Merrell Dow Inc.
Kansas City, Missouri 64134

NDA 20-625

fexofenadine hydrochloride capsule

13/14. Patent Information Certification

Attachment B: United States Patent No. 5,375,693



MARION MERRELL DOW INC.

Marion Park Drive
MAIL P.O. Box 9627
Kansas City, Missouri 64134-0627
Telephone 816-967-5000

July 31, 1995

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parktown Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission for Fexofenadine HCl
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Fexofenadine HCl:

PATENTS NUMBER(S): United States Patent No. 5,375,693
EXPIRATION DATE(S): August 3, 2012
PATENT OWNER: Sepracor Inc. and Georgetown University
33 Locke Drive Washington, D.C.
Marlborough, MA 01752-1146
TYPE OF PATENT: Method of Use

The undersigned declares that United States Patent No. 5,375,693 covers a method of using Fexofenadine HCl and drug product containing the same in treating allergic rhinitis. Marion Merrell Dow Inc. is licensed under United States Patent 5,375,693, which has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: 
Elaine Waller
Vice President,
U.S. Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 20-625

SUPPL# _____

Trade Name Allegra

Generic Name fexofenadine hydrochloride 60 mg

Applicant Name Hoechst Marion Roussel

HFD# 570

Approval Date If Known _____

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 question 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:

d) Did the applicant request exclusivity?

YES / X / NO / /

Spanish sent request dated 7/11/96
if not ok 7/12/96

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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 and route of administration, previously been approved by FDA for the same use?

YES / / NO / X /

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 LFSI upgrade?

YES / / NO / X /

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).

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 _____

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.)

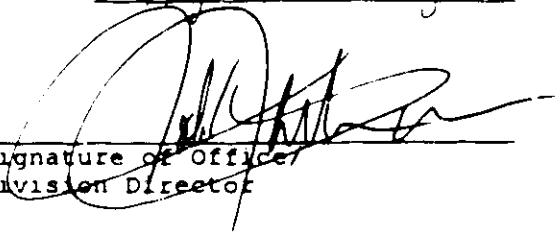
YES / _ / NO / _ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA _____
NDA _____
NDA _____

W. H. Stone
Signature
Title: Project Manager

June 6 1996
Date


Signature of Officer
Division Director

7/8/96
Date

cc: Original NDA

Division File

HFD-84

Page
Purged

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-625 Trade (generic) names Allegra (fexofenadine HCl)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. 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 do not need to be encouraged because the drug product has little potential for use in children.

x 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

~~This drug product has some potential for use in children, however alternative products are currently available. The Division has not at this time requested pediatric studies, nor has the sponsor requested pediatric labeling. However, the sponsor is in the process of developing a pediatric formulation, and is working on drafting a pediatric protocol.~~

[Signature]
Signature of Preparer

7/18/96
Date

cc: Orig NUA
HFD-510/Div File
NUA Action Package

Debarment Certification

Hoescht Marion Roussel, Inc. hereby certifies that we did not and will not, in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

Elaine Waller
Elaine Waller, Pharm D
Vice President, US Regulatory Affairs

7. 31. 95.
Date

JUL 9 1996

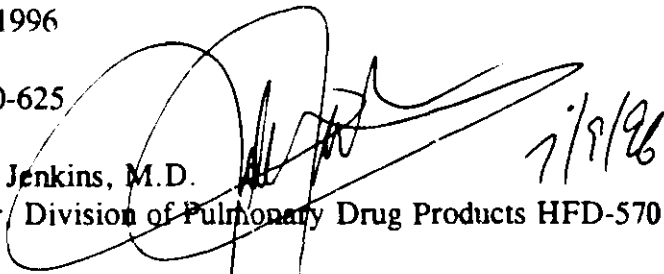
MEMORANDUM

DATE: July 9, 1996

TO: NDA 20-625

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues



Administrative

NDA 20-625 for Allegra (fexofenadine HCL) Capsules was originally submitted by Marion Merrell Dow (now Hoechst Marion Roussel) on July 31, 1995. Fexofenadine is a metabolite of terfenadine and is considered to be a New Molecular Entity. The User Fee Goal Date for NDA 20-625 is July 31, 1996.

Clinical

The proposed indication for Allegra is relief of symptoms associated with seasonal allergic rhinitis. In support of this indication, the sponsor submitted four multicenter, randomized, double-blind, placebo-controlled, two week trials of Allegra at doses of 20 to 240 mg BID versus placebo (Studies 09, 10, 23, and 24). Studies 23 and 24 are considered the pivotal demonstrations of efficacy for the proposed dose of 60 mg BID (see the MO review by Dr. Sevka and the Memo by Dr. Himmel for more complete details on the design/results of these studies). In these studies, there was little evidence of additional symptomatic relief at doses of Allegra greater than 60 mg BID. The 40 mg BID dose was statistically superior to placebo in Study 23, however, it provided numerically less relief than the 60 mg BID dose. Studies 09 and 10 are considered supportive of the efficacy of Allegra at the proposed dose of 60 mg BID, however, as detailed in Dr. Sevka's review neither of the studies is considered pivotal; i.e., in study 09 the 60 and 80 mg BID Allegra doses performed worse than the 40 mg BID dose and in study 10 a treatment by baseline effect made interpretation of the results difficult. The absolute magnitude of the effect size for Allegra versus placebo was small, however, the treatment effect was consistently statistically significantly greater than that of placebo and the effect size was typical of that observed with other antihistamines in SAR.

The safety database for Allegra for inhalation includes data available from over 2800 normal volunteers and patients with allergic rhinitis treated with fexofenadine HCL at doses up to 690 mg BID in clinical pharmacology studies and at doses up to 240 mg BID in well-controlled clinical trials. The vast majority of patient exposures were for durations of less than 30 days. Since fexofenadine is the major human metabolite of terfenadine, the safety database also includes the extensive clinical exposure to fexofenadine which has occurred in patients treated with terfenadine. Please refer to Dr. Sevka's review of the Integrated Summary of Safety for more detailed information on the Allegra safety database. The safety database demonstrates that Allegra is generally well tolerated with an adverse effect profile that is very similar to

placebo. There were no deaths reported in any of the clinical trials and none of the serious adverse events reported in volunteers or patients treated with fexofenadine HCL appeared to be plausibly related to the drug.

Given the recognized potential for terfenadine in certain clinical situations to produce serious and potentially fatal cardiac arrhythmias, the sponsor conducted an extensive preclinical and clinical evaluation of the cardiac effects of fexofenadine HCL. The clinical trials included; 1) exposure of small groups of normal volunteers (4 per dose group) to doses of fexofenadine HCL up to 690 mg BID for 28 days in a dose escalating design, 2) complete crossover trials in which normal volunteers were exposed to doses of fexofenadine HCL of up to 400 mg BID for 6 days, 3) drug interaction trials in which normal volunteers were exposed to fexofenadine HCL at doses of 120 mg BID and concomitant ketoconazole or erythromycin for 6 days, and 4) large clinical trials in which patients with SAR were exposed to fexofenadine HCL at doses up to 240 mg BID for two weeks. All of the trials in normal volunteers included very detailed assessments of serial ECGs at baseline and on treatment; the studies in patients with SAR included baseline ECGs and ECGs on the last visit at approximately the time of Cmax of fexofenadine HCL. As detailed in Dr. Sevka's review, there was no evidence of a clinically important effect of fexofenadine HCL on the QT interval in these studies despite the fact that doses up to 11 times the recommended clinical dose were studied. Some of the studies included a positive control of terfenadine which demonstrated the expected prolongation of QT interval at doses of only 3 times the recommended clinical dose. See comments below regarding additional supportive data from the preclinical studies conducted to explore the effect of fexofenadine HCL on cardiac conduction.

This NDA was not presented for discussion to the Pulmonary and Allergy Drugs Advisory Committee. This decision was based on the recognized efficacy of terfenadine which is primarily due to fexofenadine since terfenadine undergoes nearly complete first pass metabolism in the gut/liver, the clear demonstration of efficacy of fexofenadine HCL at the proposed dose of 60 mg BID in the clinical trials submitted to the NDA, and the extensive safety database which failed to demonstrate any significant safety concerns related to exposure to fexofenadine HCL at the proposed dose of 60 mg BID.

Allegra is considered clinically approvable for the relief of symptoms of seasonal allergic rhinitis with labeling as reflected in the final draft labeling as submitted by the sponsor on July 2, 1996.

Preclinical

The sponsor submitted only limited (14 and 30 day studies in dogs) toxicology studies for fexofenadine HCL. These studies demonstrated that fexofenadine HCL is less toxic than terfenadine. As detailed in the Dr. Sancilio's review and Dr. Sun's Team Leader Memo, the systemic bioavailability of fexofenadine in rats following oral administration of terfenadine was greater than that observed following oral administration of fexofenadine HCL. Therefore, the chronic toxicity studies that were conducted in support of the approval of terfenadine provide an adequate assessment of the toxicity of fexofenadine HCL. There is no evidence from these studies that fexofenadine HCL is carcinogenic, teratogenic, or impairs fertility in rats and/or

rabbits. There is also no evidence that fexofenadine HCL is mutagenic.

As noted above, the sponsor also conducted or submitted the results of a substantial battery of preclinical studies to evaluate the potential of fexofenadine HCL to alter cardiac conduction as has been demonstrated with terfenadine. Please see Dr. Sancilio's review for a detailed description of the results of these studies. The preclinical studies included in-vitro studies (blockade of human delayed rectifier K⁺ channel, blockade of delayed rectifier K⁺ current in feline myocytes, blockade of delayed rectifier K⁺ current using embryonic cells cloned from human heart) and in-vivo studies (analysis of QT interval following intravenous infusion in anesthetized rabbits, analysis of QT interval in unanesthetized dogs following oral administration twice daily for 5 days). These studies demonstrated that fexofenadine HCL possesses little or no effect on cardiac conduction.

On March 28, 1996 the FDA received a draft copy of a study conducted under the auspices of the Canadian Health Protection Branch, by Dr. Gregory Beach, which examined the pro-arrhythmic potential of several antihistamines in an animal model. For more details on the methods and results of this study please see Dr. Sevka's Safety Overview and the consult review from Dr. Koerner from the Division of Cardio-renal Drug Products (HFD-110) which is included in the preclinical section of the action package. The author reported that fexofenadine induced arrhythmias in 3/10 high dose animals while terfenadine induced arrhythmias in only 1/10 high dose animals. High dose fexofenadine and terfenadine did not prolong the QT interval in this study and the arrhythmias observed in the high dose fexofenadine group were monomorphic and appear to be AV junctional in origin. Terfenadine failed to induce polymorphic ventricular tachycardia (VT) in this study which suggests that the sensitivity of the rabbit model utilized in this study is limited for detection of polymorphic VT. The high dose fexofenadine dose was 10 fold greater than the terfenadine high dose and the AUC for fexofenadine observed in the high dose animals was comparable to the AUC observed in human volunteers exposed to 200 mg BID of fexofenadine HCL for one week in study 07; no prolongation of the QT interval was observed in this study. I concur with the conclusions reached by Drs. Sevka, Koerner, and Himmel that this study is flawed and does not provide evidence of a potential arrhythmogenic effect of fexofenadine in humans.

Allegra is considered approvable from a preclinical standpoint with labeling as reflected in the final draft labeling submitted by the sponsor on July 2, 1996.

CMC

Allegra is formulated in capsules containing 60 mg of fexofenadine HCL as a racemic mixture. The capsules will be packaged in HDPE bottles of 60, 100 and 500 capsules and aluminum foil blister packs of 100. The chemistry reviewer has noted dissolution failures in capsules packaged in the aluminum foil blister packs when stored at 40°C/75%RH for 6 months. Similar failures were not observed for products stored in the HDPE bottles which suggests that the failures with the aluminum foil blisters are related to moisture. The reviewer has recommended that all packaging associated with the foil blisters should include the statement that the blisters packs should be protected from excessive moisture. This statement has been included in the how supplied section of the final draft package insert submitted on July 2,

1996, however, the statement is not included on the mock ups of the cartons and foil backing to be utilized for packaging the foil blister packs. The sponsor reports that in anticipation of launch that they have printed and packaged a large number of blister packs/cartons which do not contain the moisture statement and have requested that they be allowed to utilize these packages provided they commit to add the required statement to all future packaging for the blister packs (see letter dated July 9, 1996). The Division has decided to grant this request based on the fact that the dissolution failures only occurred at high temperatures/humidity, the packaging already recommends storage at controlled room temperature, and the fact that the dissolution failures which occurred in the stability studies would likely result in decreased plasma levels of fexofenadine which would not result in a safety problem, albeit the efficacy of the capsule might be reduced. There are no outstanding CMC issues and the application is considered approvable from a CMC standpoint with labeling as reflected in the final draft labeling submitted by the sponsor on July 2, 1996. The sponsor will be reminded of their commitments to perform full acceptance testing of the drug substance annually and to include the "protect from excessive moisture" statement on all future packaging for the foil blister packs.

Biopharmaceutics

Fexofenadine HCL is rapidly absorbed following oral administration of Allegra Capsules with a Tmax of approximately 2.6 hours and a mean elimination half-life of 14 hours. The pharmacokinetics of fexofenadine are linear up to 120 mg BID. Fexofenadine is minimally metabolized and primarily excreted unchanged in the feces. In elderly subjects the fexofenadine Cmax is increased by 99% as compared to younger subjects, however, the mean elimination half-life is unchanged. Since the half-life is unchanged in elderly subjects and the NDA includes adequate data to support the safety of the increased Cmax, no dosage adjustment in the elderly is necessary. Both the Cmax and half-life of fexofenadine are increased in patients with renal impairment (87-11% and 59-72%, respectively), therefore, the recommended starting dose in patients with renal impairment is 60 mg once daily. Formal interaction studies with ketoconazole and erythromycin demonstrated increased fexofenadine Cmax (135% and 82%, respectively) and AUC (164% and 109%, respectively). The mechanisms of these interactions are unclear, particularly given the fact that only 5% of the total fexofenadine dose appears to undergo metabolism prior to excretion. There was no pharmacodynamic effect on the QT interval observed in the interaction studies and since there are adequate data to support the safety of these increased plasma concentrations of fexofenadine, no dosage adjustment is necessary. While not a formal Phase 4 commitment, the sponsor will be encouraged to further investigate the mechanism(s) of these interesting interactions and the potential for an interaction between fexofenadine and other antifungals/antibiotics in the action letter.

Allegra is considered approvable from a biopharmaceutics standpoint with labeling as reflected in the final draft labeling as submitted by the sponsor on July 2, 1996.

Data Verification

The Division of Scientific Investigations (DSI) completed audits at a total of 6 clinical sites from the pivotal efficacy trials. All of the audits were listed as NAI. The audit reports were

reviewed by Dr. Sevka who agreed that only minor problems were identified at the audited sites. Based upon the results of the 6 audits for this NDA and Dr. Sevka's audit of selected case report forms and data during his NDA review, there are no concerns regarding the integrity of the overall NDA database.

Labeling

The proposed trade name, Allegra Capsules, is acceptable to the Division and was reviewed and found acceptable by the Labeling and Nomenclature Committee. The final draft package insert, patient instructions for use, and the container and carton labels submitted by the sponsor on July 2, 1996 have been reviewed by the appropriate discipline(s) and are acceptable.

Conclusion

There are no outstanding issues from any discipline with regard to this application and the application can be APPROVED with labeling that is identical to the final draft labeling submitted by the sponsor on July 2, 1996. There are no formal Phase 4 commitments for additional studies.

cc:

NDA 20-625

HFD-570 Division Files

HFD-570/Jenkins

HFD-570/Schumaker

HFD-570/Strange

HFD-570/Himmel

HFD-570/Sevka

MAY 9 1996

NDA 20-625

PRODUCT: FEXOFENADINE CAPSULES 60MG

SUBMITTED: JULY 31, 1995

SPONSOR: HOECHST MARION ROUSSEL, INC

REVIEW TEAM MEMBERS:

Michael J. Sevka, M.D.	Medical Officer
Lawrence F. Sancilio, Ph.D.	Pharmacologist
Barbara Bono, M.S.	Statistician
Brad Gillespie, Pharm.D.	Biopharmaceutics Reviewer
Craig Bertha, Ph.D.	Drug Product Chemist
Brian Rogers, Ph.D.	Drug Substance Chemist

NDA 20-625

SUMMARY REVIEW CONCLUSIONS AND SIGN-OFF

PRODUCT: FEXOFENADINE CAPSULES 60MG
SUBMITTED: JULY 31, 1995
SPONSOR: HOECHST MARION ROUSSEL, INC

1. Fexofenadine is clinically approvable as a safe and effective treatment for the reduction of symptoms of seasonal allergic rhinitis at a dose of 60mg twice a day in patients 12 years of age and older, provided:
 - a) the sponsor makes changes to the proposed package insert recommended in the attached labeling review; and
 - b) the sponsor agrees to characterize more accurately in Phase IV trials the pharmacokinetics of fexofenadine in patients with severe renal and hepatic failure.

2. The sponsor should be encouraged to conduct Phase IV investigations:
 - a) to characterize the mechanism of drug interaction between fexofenadine and ketoconazole and between fexofenadine and erythromycin;
 - b) to quantify the extent of any drug interaction between fexofenadine and other macrolide antibiotics, between fexofenadine and other antifungal agents, and between fexofenadine and cimetidine.

Michael J. Seyka, M.D. 4/25/96
Michael J. Seyka, M.D.
Medical Officer
Division of Pulmonary Drug Products
HFD-570

see supervisor memo on Himmel 5/1/96
Martin H. Himmel, M.D.
Deputy Director
Division of Pulmonary Drug Products
HFD-570

see Div Dir overview of Review issues memo in Action package 5/19/96
John K. Jensen, M.D.
Division Director
Division of Pulmonary Drug Products
HFD-570

James M. Bilstad, M.D.
Office Director
Office of Drug Evaluation II

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: **NDA 20-625 - Labeling**

The draft annotated label submitted to the NDA has been modified below. The parts to be removed are indicated by a strike-out. Additions are indicated by bolded italics.

Draft Prescribing Information as of June 1995

ALLEGRA™
(fexofenadine hydrochloride)
60 mg capsules

DESCRIPTION

Fexofenadine hydrochloride is available as capsules for oral administration (Ref. 1). Each capsule contains 60 mg fexofenadine hydrochloride and the following inactive ingredients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide and other ingredients (Ref. 2).

Fexofenadine hydrochloride is a histamine H₁-receptor antagonist with the chemical name benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]- α,α -dimethyl-, hydrochloride, ($\pm$) (Refs. 3-9). It has the following chemical structure (Ref. 10):

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Postscript Printers Only.

The molecular weight is 538.13 (Ref. 11). The empirical formula is C₃₂H₃₉NO₄·HCl (Ref. 12). Fexofenadine hydrochloride occurs as a white to off-white crystalline powder (Ref. 13). It is freely soluble in methanol and ethanol, slightly soluble in chloroform and in water, and insoluble in hexane (Ref. 14). Fexofenadine hydrochloride is provided as a racemate and exists as a zwitterion in aqueous media at physiological pH (Ref. 15,16).

CLINICAL PHARMACOLOGY

Pharmacologic Activity

Fexofenadine hydrochloride is a nonsedating long-acting antihistamine with highly selective peripheral histamine H₁-receptor antagonist activity (Refs. 3-8). Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and inhibited histamine release from peritoneal mast cells of the rat (Refs. 17,18). In laboratory animals, no anticholinergic or alpha₁-adrenergic-receptor blocking effects were observed (Refs. 4,19,20). Moreover, no sedative or other central nervous system effects were observed (Ref. 3,21). Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier (Ref. 35).

General Human Pharmacokinetics

Fexofenadine hydrochloride was rapidly absorbed following oral administration of capsules, with mean t_{max} occurring at 1.3 to 2.6 hours postdose (Ref. 31; **Protocol PJPR0011**). The mean C_{max} value was 209 ng/mL after a single 60 mg dose was administered to healthy subjects (Ref. 32). **The mean Cmax was 286 ng/ml after 60mg BID was administered to steady state to healthy subjects (Ref. Protocol PJPR0011).** The mean elimination half-life of fexofenadine was 14.4 hours following 60 mg bid multiple-dose administration. The single- and multiple-dose pharmacokinetics of fexofenadine hydrochloride were linear from 20 mg to 120 mg doses (Refs. 32). **The absolute bioavailability of fexofenadine is unknown.** Metabolism of fexofenadine was negligible (Refs. 33,34). **From mass balance studies in humans, it was observed that approximately 5% of fexofenadine is metabolized to the de-alkylated metabolite (1.5%) and methyl ester (3.6%).** Following a single 60 mg oral dose, 80% and 11% of the total [¹⁴C]fexofenadine hydrochloride dose was recovered in the feces and urine, respectively (Refs. 33,34). The principal elimination pathways of fexofenadine were biliary and renal (Refs. 34,35). Fexofenadine was 60% to 70% bound to plasma proteins including serum albumin and alpha₂-acid glycoprotein (Refs. 36,37). The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in healthy subjects (Ref. 24).

Special Population Pharmacokinetics

Renal Impairment: Renal disease was associated with an increase in C_{max} by +93% and AUC by +133% in peak plasma levels and half-life of 54% and 19%, respectively, regardless of disease severity (Ref. 38,40).

Hepatic Impairment: Consistent with negligible approximately 5% metabolism, the pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease was similar to did not differ from that observed in healthy subjects but was more variable (Refs. 38,39).

Elderly: In the elderly (>65 years old), an increase of C_{max} and AUC was approximately twice that of normal non-weight matched volunteers. peak plasma levels and half-life were increased 68% and 15%, respectively (Ref. 38,41). Those changes were within the range of plasma levels shown to be well tolerated in adequate and well-controlled safety and efficacy trials (Refs. 7,8,24,46,47).

Pediatric Patients: In addition, Peak fexofenadine plasma concentration was similar between the small number (51) of pediatric patients 12 to 16 years of age and adult patients enrolled in clinical rhinitis studies (Ref. 24).

Effects of Gender: There did not appear to be substantial pharmacokinetic differences

between genders.

Pharmacodynamics

Wheal and Flare: Human histamine skin wheal and flare studies following single- and twice-daily doses of fexofenadine hydrochloride demonstrated the drug exhibits an antihistaminic effect within one hour, achieving maximum at 6 hours and lasting a minimum of which lasts 12 hours (Refs. 22,23). There was no evidence of tolerance to these effects after 28 days of dosing (Ref. 23).

Effects on QTc interval: In dogs and rabbits, fexofenadine did not prolong *the QTc interval* at plasma concentrations at least 28 and 63 times, respectively, the therapeutic plasma concentrations (based on 60 mg fexofenadine hydrochloride bid dose) in man (Refs. 24-26). No statistically significant increase in QTc intervals was observed in seasonal allergic rhinitis (SAR) patients given fexofenadine hydrochloride up to 240 mg twice daily for two weeks or in healthy subjects up to 400 mg twice daily for one week when compared to placebo (Refs. 28,29).

Effects on In Vitro Ion Currents and Action Potential

No effect on calcium channel current, delayed rectifier K⁺ channel current, or action potential duration in guinea pig myocytes or Na⁺ current in rat neonatal myocytes was observed at fexofenadine concentrations at least 32 times the *human* therapeutic plasma concentration in man (Refs. 24,27). Fexofenadine at concentrations 32 times the *human* therapeutic concentrations in man had no effect *in vitro* on the delayed rectifier K⁺ channel cloned from human heart (Refs. 24,30).

CLINICAL STUDIES

Controlled studies conducted during the spring and fall demonstrated 60 mg bid was superior to placebo in reducing the symptoms of seasonal allergic rhinitis (Ref. 42). Significant symptom reduction was demonstrated 60 minutes following a single dose of 60 mg ALLEGRA™ (Ref. 43). The effect observed one to three hours following dosing was maintained at the end of the 12-hour dosing interval, both in the morning and evening (Ref. 44). **Although the numbers of subjects in some of the subgroups were small**, there was no significant difference in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, and race (Ref. 45).

INDICATIONS AND USAGE

ALLEGRA™ is indicated for the relief *reduction* of symptoms associated with seasonal allergic rhinitis (Refs. 7,8,46,47).

CONTRAINDICATIONS

ALLEGRA™ is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Drug Interactions

Since fexofenadine does not undergo hepatic biotransformation, it is unlikely to interact with drugs that rely upon hepatic metabolism (Refs. 33,34).

ALLEGRA™ at twice the recommended dose (120 mg bid) has been safely coadministered with erythromycin (500 mg q8h) and ketoconazole (400 mg qd) under steady-state conditions *in small numbers of* healthy volunteers. Fexofenadine peak plasma levels following erythromycin or ketoconazole coadministration increased 80% and 130%, respectively; *and AUC increased 133% and 164%, respectively. The mechanism (i.e. reduced elimination or enhanced absorption) responsible for the drug interaction is not well understood. The potential for interaction with other azole antifungal agents and other macrolides has not been studied.* No differences in adverse events were reported whether ALLEGRA™ was administered alone or in combination *with erythromycin or ketoconazole.* Additionally, *during the coadministration of fexofenadine hydrochloride with erythromycin or ketoconazole no significant increase in mean QTc was observed in the small number of subjects studied.* resulted in no significant increase in QTc. Plasma elimination profiles were similar among treatments, suggesting erythromycin and ketoconazole increase the absorption of fexofenadine (Refs. 48,49). These changes in plasma levels were within the range of plasma levels shown to be well tolerated in adequate and well-controlled safety and efficacy trials. *Since it is desirable to maintain plasma levels not in excess of those levels observed with clinical safety and efficacy following dosing with 60mg BID, dose reduction to 60 mg QD should be considered if concomitant administration with macrolides or azole antifungal agents is necessary.* Fexofenadine hydrochloride has no effect on the pharmacokinetics of ketoconazole and erythromycin (Refs. 48,49).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Fexofenadine is an active acid metabolite of terfenadine and is an end product of terfenadine metabolism. The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were exposed to fexofenadine plasma AUC values four times human therapeutic value (based on 60 mg fexofenadine hydrochloride bid dose) for 18 and 24 months, respectively, (Refs. 50,51). In rat reproduction and fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at fexofenadine plasma AUC values greater than or equal to three times human therapeutic value (Ref. 52). These effects occurred at maternally toxic doses.

In vitro and in vivo fexofenadine hydrochloride mutagenicity tests showed no evidence of mutagenicity (Refs. 53-56).

Pregnancy

Teratogenic Effects: Category C. Teratogenic potential of fexofenadine hydrochloride was assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma AUC values). There was no evidence of teratogenicity in rats or rabbits at fexofenadine plasma AUC values four and 37 times human therapeutic value, respectively (Refs. 57-59).

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to fexofenadine plasma AUC values greater than or equal to three times human therapeutic values (Ref. 52). These effects occurred at maternally toxic doses.

Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under the age of 12 have not been established. The safety and effectiveness of fexofenadine hydrochloride have been established in pediatric patients 12 years of age and older, as supported by evidence from adequate and well-controlled studies. In a subset analysis, the safety and effectiveness of ALLEGRA™ in pediatric patients from 12 up to 18 years of age, was found to be similar to that of adults (Ref. 45). ***Across 4 well controlled clinical trials a total of 277 patients between the ages of 11-16 had evaluable efficacy results which showed reductions in symptom scores which were similar to those in older age groups (2/22/96 submission, efficacy by subgroups). With regard to safety, the frequency of adverse events were similar to those of adults with the following possible exceptions: headache - 3.4% vs 1.5% for placebo; drowsiness - 2.1% vs 0.0% for placebo; and viral infection - 3.0% vs 1.5% for placebo; comparison with the overall frequencies for these events can be made by examining the event rates in the table of adverse events below (Ref. Vol 266-p174).***

See CLINICAL PHARMACOLOGY, CLINICAL STUDIES, and DOSAGE AND ADMINISTRATION Sections.

Geriatric Use

Since the C_{max} and AUC of fexofenadine plasma levels in the elderly (>65 years) are approximately twice that of normal volunteers, dose reduction to 60mg QD should be considered for the elderly population

Renal Impairment

Since renal disease was associated with an increase in AUC by approximately 133%, a dose reduction to 60mg QD should be considered for patients with mild or more severe renal impairment.

ADVERSE REACTIONS

In four placebo-controlled trials involving seasonal allergic rhinitis (SAR) patients, adverse events were similar in ALLEGRA™- and placebo-treated patients (Ref. 60). There was no dose-related increase in adverse events, including drowsiness, for doses up to four times the recommended therapeutic dose (Ref. 60). Adverse event rates were similar among subgroups defined by age, gender, and race **with the possible exception of race since Blacks experienced headache 12.6% vs 6.4% for placebo and leukopenia 2.9% vs 0.0% for placebo; but this is difficult to assess since only 221 Blacks participated in well controlled clinical trials (Ref. 61; Volume 266, page 204).** The rate of premature withdrawal because of adverse events was 0.8% 2.1% with ALLEGRA™ vs 3.2% 0.7% with placebo (Ref. 62 V262 P196).

Incidence of All Adverse Events for Controlled Clinical Seasonal Allergic Rhinitis Studies Occurring >1% in Fexofenadine 60mg BID Group		
	Placebo BID (N=671)	Fexofenadine 60mg BID (N=679)
Headache	8.3%	7.8%
Fatigue	0.9%	1.3%
Drowsiness	0.9%	1.3%
Throat Irritation	2.2%	2.1%
Nausea	1.5%	1.6%
Dyspepsia	0.6%	1.3%
Viral Infection	1.5%	2.5%
Dysmenorrhea	0.3%	1.6%

Table 1. Percentage of Patients Reporting Adverse Events (>1%) in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials			
	<i>Placebo</i> (n=671)	<i>ALLEGRA™</i> 60 mg bid (n=679)	<i>Total ALLEGRA™</i> 20-240 mg bid (n=2319)
Headache	3.1	3.1	2.9
Nausea	1.0	1.3	0.8
Drowsiness	0.9	1.3	0.8
Fatigue	0.9	1.0	1.0

In addition to the above, the following adverse events were reported infrequently (>0.5% to <1%) in the controlled SAR studies with *the 60mg dose* doses from 20 to 240 mg bid. The rates were similar to placebo (Ref. 60).

Central and Peripheral Nervous Systems: Insomnia, dizziness

Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, flatulence, vomiting, *gastroenteritis*

Respiratory: Epistaxis, throat irritation

Metabolic and Nutritional: Thirst *hypocalcemia*

Psychiatric: Appetite increase, nervousness, agitation, nightmares

Autonomic Nervous System: Dry mouth, dryness of mucous membranes

Skin and Appendages: Pruritus, rash

Urinary: Urinary frequency *Urinary Tract Infection*

Heart Rate and Rhythm: Tachycardia, palpitation

Infectious Disease. Viral infection

Vision: Blurred vision

Musculoskeletal: Chest pain *Back Pain*

Hearing and Vestibular: Earache

White Blood Cells: *Leukopenia*

Other: *Accidental Injury*

The frequency and magnitude of laboratory abnormalities were similar with ALLEGRA™ and placebo (Ref. 63).

OVERDOSAGE

There is no clinical experience with an acute fexofenadine hydrochloride overdose. Single doses of fexofenadine hydrochloride up to 800 mg (**6 normal volunteers**) and doses up to 690 mg bid for one month (**3 normal volunteers**) were investigated without the development of clinically significant adverse events. The maximum tolerated dose of fexofenadine hydrochloride was not reached (Refs. 22,23).

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine administration (Ref. 64).

An oral LD₅₀ in rodents was not determined for fexofenadine hydrochloride as no deaths occurred, even at doses up to 5000 mg/kg (Refs. 65,66). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (Refs. 67,68).

DOSAGE AND ADMINISTRATION

The recommended dose for adults and pediatric patients 12 years of age and older is 60 mg twice daily (Refs. 7,8).

Safety and effectiveness of ALLEGRA™ in pediatric patients under the age of 12 have not been established (Refs. 7,8,46,47).

Dosage adjustment should be considered in patients who are elderly (>65 years), renally impaired, or concomitantly taking erythromycin or ketoconazole. The effects of other macrolides and azole antifungal agents on fexofenadine pharmacokinetics have not been studied (See Clinical Pharmacology and Precautions Sections).

HOW SUPPLIED

ALLEGRA™ 60 mg capsules are available in (Ref. 69): bottles of 60 (NDC 0088-1102-41); bottles of 100 (NDC 0088-1102-47); bottles of 500 (NDC 0088-1102-55); and blister packs of 100 (NDC 0088-1102-49).

Capsules have a white opaque cap and a pink opaque body. The capsules are imprinted in black ink, with "60 mg" on the cap, and "1102" on the body (Ref. 70).

Store capsules at controlled room temperature 20-25°C (68-77°F) (Ref. 71).

Draft Prescribing Information as of June 1995

Hoechst Marion Roussel, Inc.
Kansas City, MO 64114

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2. *Section 3.E.2., Components, S3-VI.2-P111.*
3. *Section 5.B.5., Ref 16, S5-VI.16-P1.*
4. *Section 5.B.5., Ref 14, S5-VI.15-P279.*
5. *Section 5.B.5., Ref 26, S5-VI.16-P244.*
6. *Protocol PJPR0004, Report K-94-0776-CDS, S6-VI.116-P1.*
7. *Protocol PJPR0023, Report K-95-0005-CDS, S8-VI.219-P1.*
8. *Protocol PJPR0024, Report K-95-0007-CDS, S8-VI.239-P1.*
9. *Section 3.A.1.a.1., Chemical Names, S3-VI.2-P8.*
10. *Section 3.A.1.b.1., Chemical Structure, S3-VI.2-P9.*
11. *Section 3.A.1.b.3., Molecular Weight, S3-VI.2-P9.*
12. *Section 3.A.1.b.2., Empirical Formula, S3-VI.2-P9.*
13. *Section 3.A.1.c.1, Description, S3-VI.2-P9.*
14. *Section 3.A.1.c.8, Solubility Profile, S3-VI.2-P11.*
15. *Section 3.A.1.c.2, Optical Activity, S3-VI.2-P9.*
16. *Section 3.A.1.c.6, Dissociation Constant, S3-VI.2-P10.*
17. *Section 5.B.5., Ref 27, S5-VI.16-P379.*
18. *Section 5.B.5., Ref 25, S5-VI.16-P220.*
19. *Section 5.B.5., Ref 10, S5-VI.15-P233.*
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23. *Protocol PJPR0003, Report K-94-0758-CDS, S6-V1.103-P1.*
24. *Report K-95-0154-DS, S6-V1.89-P15.*
25. *Section 5.B.5., Ref 6, S5-V1.15-P164.*
26. *Section 5.B.5., Ref 5, S5-V1.15-P140.*
27. *Section 5.B.5, Ref 7, S5-V1.15-P193.*
28. *Table 8-614, S8-V1.262-P277 and Table 8-615, S8-V1.262-P277.*
29. *Table 8-639, S8-V1.262-P301.*
30. *Section 5.B.5., Ref 21, S5-V1.16-P165.*
31. *Protocol PJPR0025, Report K-95-0034-DS, S6-V1.32-P1.*
32. *Protocol PJPR0011, Report K-94-0770-DS, S6-V1.55-P1.*
33. *Protocol PJPR0008, Report K-94-0833-DS, S6-V1.41-P1.*
34. *Protocol PJPR0008, Report K-94-0869-D, S6-V1.47-P1.*
35. *Section 5.D.6., Ref 46, S5-V1.19-P54.*
36. *Report K-95-0195-D, S6-V1.40-P1.*
37. *Report K-95-0208-D, S6-V1.40-P18.*
38. *Section 6.F.11., Special Population Pharmacokinetics, S6-V1.21-P100.*
39. *Protocol PJPR0021, Report K-95-0169-DS, S6-V1.80-P1.*
40. *Protocol PJPR0013, Report K-94-0772-DS, S6-V1.73-P1.*
41. *Protocol PJPR0020, Report K-95-0013-DS, S6-V1.78-P1.*
42. *Section 8.G.2.g., Primary Efficacy Results, S8-V1.261-P35.*
43. *Protocol PJPR0017, Report K-95-0041-CS, S8-V1.166-P1.*
44. *Table 8-485, S8-V1.261-P45.*
45. *Table 3-491, S8-V1.261-P53.*
46. *Protocol PJPR0009, Report K-94-0780-CDS, S8-V1.185-P12.*

47. *Protocol PJPR0010, Report K-94-0782-CDS, S8-VI.202-P1.*
48. *Protocol PJPR0018, Report K-95-0171-DS, S6-VI.82-P1.*
49. *Protocol PJPR0028, Report K-95-0128-DS, S6-VI.86-P1.*
50. *Section 5.C.5.c.i., One Month Terfenadine Toxicokinetic Biobridge to Terfenadine 18-month Carcinogenicity Studies in Mice, S5-VI.17-P32*
51. *Section 5.C.5.c.ii., One Month Terfenadine Toxicokinetic Biobridge to Terfenadine 2-year Carcinogenicity Studies in Rats, S5-VI.17-P33.*
52. *Section 5.C.6.a., Summary of Reproductive Toxicity Studies, S5-VI.17-P38.*
53. *Section 5.C.7.c.i., MDL 16,455A: Mutagenicity Test in the Salmonella-Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay, S5-VI.17-P43.*
54. *Section 5.C.7.c.ii., MDL 16,455A: Evaluation of the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, S5-VI.17-P43.*
55. *Section 5.C.7.c.iii., MDL 16,455A: Evaluation of an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, S5-VI.17-P43.*
56. *Section 5.C.7.c.iv., MDL 16,455A: Evaluation in the Mouse Bone Marrow Micronucleus Test, S5-VI.17-P44.*
57. *Section 5.C.5.c.iv., Maternal and Fetal Plasma Concentration of MDL 16,455 and Terfenadine in Sprague-Dawley Rats Given Daily 300 mg/kg Oral Doses of Terfenadine (PK-251), S5-VI.17-P35.*
58. *Section 5.C.6.a., Summary of Reproductive Toxicity Studies, S5-VI.17-P38.*
59. *Section 5.C.5.c.v., Maternal and Fetal Plasma Concentrations of MDL 16,455 and Terfenadine in Dutch-Belted Rabbits Given Daily Oral 300 mg/kg Doses of Terfenadine (PK-250), S5-VI.17-P36.*
60. *Table 8-580, S8-VI.262-P111.*
61. *Section 8.H.4.e., Analysis of Adverse Event Rates by Demographic Subgroup, S8-VI.262-P132.*
62. *Table 8-599, S8-VI.262-P216.*
63. *Table 8-607, S8-VI.262-P252.*
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A Feasibility Study to Determine if Seldane is Dialyzable.*

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66. *Section 5.C.3.c.ii., Acute Oral Toxicity in Mice and Rats, S5-V1.17-P16.*
67. *Section 5.C.3.c.iii., Acute Oral Toxicity in Beagle Dogs, S5-V1.17-P17.*
68. *Section 5.C.3.c.iv., Acute Oral Toxicity in Beagle Dogs, S5-V1.17-P17.*
69. *Section 3.B.6.c.1., Introduction, S3-V1.2-P117.*
70. *Section 3.B.7.b., Specifications and Analytical Methods for MDL 16,455A 60 mg Capsules, S3-V1.2-P127.*
71. *Section 3.D.9.a., Expiration Dating Period and Storage Requirements, S3-V1.2-P146.*

INTRODUCTION

Fexofenadine Hydrochloride is a histamine H₁-receptor antagonist that has been submitted for review as a long-acting non-sedating antihistamine for the symptomatic treatment of seasonal allergic rhinitis in patients 12 years of age and older at doses of 60mg twice a day.

Fexofenadine is not approved by any foreign government, but is currently under review in the following countries:

United Kingdom - submitted - June 19, 1995

Australia - submitted - May 25, 1995

Canada - submitted - August 3, 1995

Fexofenadine, is the synthetic molecule of the acid metabolite of terfenadine. Upon oral administration of terfenadine, terfenadine is rapidly converted to the acid metabolite which has antihistaminic activity. The acid metabolite is structurally the same as fexofenadine. It is helpful to remember as these reviews are read that it requires the administration of 80mg of fexofenadine to achieve comparable plasma concentrations that are observed following the administration of 60mg of terfenadine.

The NDA review for efficacy was conducted by individually reviewing four pivotal studies (PJPR0009, PJPR0010, PJPR0023, PJPR0024) in patients with seasonal allergic rhinitis and one study of onset of action (PJPR0017). The review for safety was conducted by examining the safety data from the clinical trials and also individually reviewing three trials designed specifically to examine cardiac safety. To further examine the safety profile, two pharmacokinetic drug interaction trials (PJPR0018 - fexofenadine and erythromycin; and PJPR0028 - fexofenadine and ketoconazole) were reviewed for their safety database, since well documented drug interactions have been observed between each of these two drugs and terfenadine. The NDA review is organized into two main sections, efficacy and safety, with reviews of individual efficacy and safety studies ordered according to their relative importance rather than ascending numerical order for that section.

In reading any of these reviews it may be of practical value to remember the following:

- 1) Prior to the naming of fexofenadine it was referred to as MDL-16,455A which is the most common designation used in the sponsor's submission.
- 2) Efficacy protocols PJPR0009 and PJPR0010 are of identical design and protocols PJPR0023 and PJPR0024 are of identical design except for the doses studied.

Pending Review Issues as of 4/23/96:

- 1) Review of final safety update, when submitted.
- 2) Review of the results of DSI Audit of the remaining investigational site, PJST0021 (Protocol PJPR0009) Dr Hampel.
- 3) Review of results from the consult to cardiorenal pharm/tox group regarding the rabbit cardiac study conducted by the Canadian HPB.
- 4) Final labeling review.
- 5) Review of pharmacology/toxicology data by pharmacology/toxicology reviewer.
- 6) Final review of chemistry data requested in letter of information request, dated April, 1996.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: NDA 20-625 - Efficacy Overview

The sponsor has provided a comprehensive table in the NDA (S2-Vol 1.1-P298) listing the completed clinical trials conducted with fexofenadine that were included in the NDA. Of these, 5 trials were selected for review and considered well-controlled in support of efficacy. Protocols PJPR0009, PJPR0010, PJPR0023 and PJPR0024 were all dose ranging trials, while Protocol PJPR0017 was conducted to define the onset of action. Protocols PJPR0009 and PJPR0010 are of identical design and tested 20mg, 40mg, 60mg and 80mg of fexofenadine versus placebo. Protocols PJPR0023 and PJPR0024 are also of identical design except for the dose levels tested. Protocol PJPR0023 tested 60mg, 120mg and 240mg versus placebo and PJPR0024 tested 40mg, 60mg and 120mg versus placebo.

Protocol PJPR0024 demonstrated the efficacy of 40mg BID, 60mg BID and 120mg BID compared to placebo with comparable magnitudes of symptom score reduction for the primary endpoint, 7PM reflective total symptom score (TSS), for the 40mg and 60mg doses and some slight additional reduction by the 120mg dose. Efficacy of all 3 doses was maintained to the end of the dosing interval and maintained for two weeks. The 40mg dose did not appear to exert an onset of action comparable to the 60mg and 120mg doses.

Protocol PJPR0023 demonstrated the efficacy of 60mg BID, 120mg BID and 240mg BID compared to placebo for symptom score reduction for the primary endpoint, 7PM reflective TSS, with little if any additional symptom reduction for the 120mg and 240mg doses compared to that of 60mg BID. Efficacy of all 3 doses was maintained to the end of the dosing interval and maintained for two weeks. All three doses demonstrated an onset of action of 1-3 hours.

The results from protocol PJPR0010 are difficult to interpret since a treatment by baseline TSS interaction was observed during data analysis making it difficult to assess the true magnitude of treatment response for the entire group. Nonetheless, these results can be viewed as supportive. Protocol PJPR0010 demonstrated the efficacy of 20mg BID, 40mg BID, 60mg BID and 80mg BID for the primary endpoint, bedtime reflective TSS, compared to placebo. The magnitude of TSS reduction was greatest with the 60mg dose with a somewhat lesser extent in symptom reduction by the 80mg dose. Based on very limited data, the 60mg dose appeared to exhibit efficacy at the end of the dosing interval.

Protocol PJPR0009 demonstrated the efficacy of 40mg BID and 80mg BID for the primary endpoint, bedtime reflective TSS, compared to placebo. Only the 40mg dose maintained efficacy for two weeks. Based on very limited data, the 40mg dose appeared to exhibit efficacy at the end of the dosing interval. It is difficult to explain the poorer response of the 60mg and 80mg dose compared to the 40mg dose.

Protocol PJPR0017 tested only the 60mg and 120mg dose in an environmental exposure unit where subjects were continuously exposed to controlled concentrations of ragweed pollen for up to 5 hours. Protocol PJPR0017 demonstrated that after the first dose, an onset of action was exhibited by 60 minutes for 60mg and by 80 minutes for 120mg. Demonstration of onset of action at these times was achieved using a relaxed definition of onset, defined as median time to clinical onset of slight/moderate/marked and complete relief of TSS rather than the pre-defined definition which was the observance of complete and marked relief of TSS. Demonstration of onset of action at these times was also demonstrated by mean change from baseline for actual TSS compared to placebo.

Dose Selection

The selection of the lowest effective dose was guided by four main efficacy criteria - overall magnitude of treatment response, durability of the response over time, onset of action, and end-of-dosing interval efficacy. The available data suggest that 40mg, 60mg, 80mg, 120mg and 240mg doses are effective, with the data from PJPR0024 suggesting a possible slight greater response with 120mg compared to 40mg or 60mg and data from PJPR0023 suggesting no additional response with either 120mg or 240mg compared to 60mg. End of dosing interval efficacy has been demonstrated for 40mg, 60mg, 120mg and 240mg with efficacy maintained for two weeks. Support for the most rapid onset of action is available for 60mg and 120mg dose based on the results from protocol PJPR0017, with a poorer onset of action observed for 40mg in protocol PJPR0024. From the data it appears that the 60mg dose is the lowest dose which appears to fulfill most closely the four main efficacy criteria.

Influence of Age, Race and Gender on Efficacy

As part of the analyses of efficacy, the sponsor provides analyses of subgroups based on age, gender and race for each of the 4 well-controlled clinical trials. Regarding age, the sponsor conducted an ANCOVA to test for interaction between age and treatment using a model with site, treatment, age category (<18; ≥18 - <40; >40 years), baseline TSS and treatment by age category interaction as factors. No interaction with age category was observed in any of the four trials (PJPR0009 - $p=0.3390$; PJPR0010 - $p=0.6149$; PJPR0023 - $p=0.2225$; PJPR0024 - $p=0.1570$). With enrollment criteria specifying an upper age limit of 65 years and a lower age limit of 12 years, very few patients greater than 60 years of age entered (PJPR0009 - 22; PJPR0010 - 22; PJPR0023 - 11; PJPR0024 - 6) and only one patient younger than 12 years of age entered.

Regarding race, the sponsor conducted an ANCOVA to test for interaction between race and treatment using a model identical to that for age but substituting race category (Caucasian vs Other) for age. These two categories seem appropriate because of the marked preponderance of Caucasians enrolled (PJPR0009 - 84%; PJPR0010 - 80%; PJPR0023 - 88%; PJPR0024 - 80%). No interaction was observed with race category in any of the four trials (PJPR0009 - $p=0.1754$; PJPR0010 - $p=0.6213$; PJPR0023 - $p=0.7302$; PJPR0024 - $p=0.5265$).

Similarly, an analogous ANCOVA for gender demonstrated no interaction with gender (PJPR0009 - $p=0.5230$; PJPR0010 - $p=0.5999$; PJPR0023 - $p=0.9027$; PJPR0024 - $p=0.4738$). Despite the observed 17% greater clearance observed in males, the results from these analyses suggest that there appears to be no impact on clinical response to treatment.

In addition to these analyses, the sponsor provided additional analyses, submitted March 4, 1996, of the spring (PJPR0009, PJPR0010) and fall (PJPR0023, PJPR0024) studies for age, gender and race by

dose for the respective primary endpoints. The results are summarized in six tables (Tables 2 through 7) reproduced below. Although some of the subgroups are small and do not demonstrate statistical significance, they do show a numerical reduction in symptoms scores for virtually every subgroup.

Table 2. Sprung SAR Studies. Intent-to-Treat Analysis of Bedtime Reflective TSS by Age Category						
Age Category (years)	Treatment (BID)	N	Baseline Mean ± SE	Double-Blind Period Mean ± SE	Change from Baseline Mean ± SE	P value†
≥11 to <16	Placebo	41	5.82 ± 0.39	4.69 ± 0.34	-1.13 ± 0.31	-
	20 mg MDL 16.455A	47	5.11 ± 0.37	4.52 ± 0.32	-0.59 ± 0.28	.5742
	40 mg MDL 16.455A	35	5.79 ± 0.50	4.46 ± 0.41	-1.33 ± 0.48	.6261
	60 mg MDL 16.455A	37	5.08 ± 0.48	4.68 ± 0.47	-0.40 ± 0.40	.3460
	80 mg MDL 16.455A	38	5.03 ± 0.41	3.98 ± 0.37	-1.05 ± 0.32	.5232
	Total MDL 16.455A	157	5.23 ± 0.22	4.41 ± 0.19	-0.82 ± 0.18	.9111
>16 to <60	Placebo	336	5.49 ± 0.16	4.78 ± 0.14	-0.71 ± 0.12	-
	20 mg MDL 16.455A	338	5.68 ± 0.15	4.41 ± 0.15	-1.27 ± 0.12	.0012
	40 mg MDL 16.455A	353	5.54 ± 0.15	4.10 ± 0.13	-1.45 ± 0.13	.0001
	60 mg MDL 16.455A	351	5.48 ± 0.14	4.13 ± 0.13	-1.36 ± 0.12	.0001
	80 mg MDL 16.455A	342	5.55 ± 0.15	4.21 ± 0.14	-1.34 ± 0.11	.0001
	Total MDL 16.455A	1384	5.56 ± 0.07	4.21 ± 0.07	-1.35 ± 0.06	.0001
≥60	Placebo	11	4.59 ± 0.66	3.74 ± 0.71	-0.85 ± 0.56	-
	20 mg MDL 16.455A	6	5.00 ± 0.97	4.25 ± 1.22	-0.75 ± 0.66	.8003
	40 mg MDL 16.455A	8	4.44 ± 0.70	2.41 ± 0.59	-2.02 ± 0.98	.1674
	60 mg MDL 16.455A	6	4.58 ± 1.08	3.10 ± 0.90	-1.48 ± 0.83	.5100
	80 mg MDL 16.455A	8	6.69 ± 1.29	4.35 ± 1.11	-2.34 ± 0.62	.4165
	Total MDL 16.455A	28	5.23 ± 0.52	3.51 ± 0.48	-1.72 ± 0.40	.3853
Treatment by Age Group Interaction* P = .4641						
† P values for comparison of each active dose and placebo are from an analyses conducted within each subgroup using an ANCOVA model containing treatment and baseline.						
• P value for treatment by age group interaction from ANCOVA model containing treatment, baseline, age group, and treatment by age group interaction						

Table 3. Fall SAR Studies. Intent-to-Treat Analysis of 7 PM Reflective TSS by Age Category						
Age Category (years)	Treatment (BID)	N	Baseline Mean $\pm$ SE	Double-Blind Period Mean $\pm$ SE	Change from Baseline Mean $\pm$ SE	P value†
≤11 to <16	Placebo	20	8.30 $\pm$ 0.29	7.81 $\pm$ 0.51	* 0.49 $\pm$ 0.47	-
	40 mg MDL 16.455A	10	8.13 $\pm$ 0.61	6.12 $\pm$ 0.82	-2.01 $\pm$ 0.85	0389
	60 mg MDL 16.455A	20	8.43 $\pm$ 0.45	7.90 $\pm$ 0.42	-0.53 $\pm$ 0.43	9735
	120 mg MDL 16.455A	17	8.23 $\pm$ 0.43	7.05 $\pm$ 0.45	-1.19 $\pm$ 0.48	2627
	240 mg MDL 16.455A	12	8.47 $\pm$ 0.49	6.32 $\pm$ 0.65	-2.15 $\pm$ 0.68	0318
	Total MDL 16.455A	59	8.33 $\pm$ 0.24	7.03 $\pm$ 0.28	-1.30 $\pm$ 0.29	0626
>16 to <60	Placebo	255	8.81 $\pm$ 0.10	7.42 $\pm$ 0.14	-1.39 $\pm$ 0.13	-
	40 mg MDL 16.455A	122	8.72 $\pm$ 0.17	7.06 $\pm$ 0.21	-1.67 $\pm$ 0.17	2064
	60 mg MDL 16.455A	253	8.78 $\pm$ 0.10	6.48 $\pm$ 0.15	-2.30 $\pm$ 0.16	.0001
	120 mg MDL 16.455A	260	8.82 $\pm$ 0.11	6.52 $\pm$ 0.16	-2.30 $\pm$ 0.16	.0001
	240 mg MDL 16.455A	129	8.89 $\pm$ 0.16	6.37 $\pm$ 0.23	-2.53 $\pm$ 0.23	.0001
	Total MDL 16.455A	764	8.80 $\pm$ 0.06	6.56 $\pm$ 0.09	-2.24 $\pm$ 0.09	.0001
≥60	Placebo	3	8.78 $\pm$ 1.09	7.50 $\pm$ 1.04	-1.28 $\pm$ 1.20	-
	40 mg MDL 16.455A	3	9.22 $\pm$ 1.06	4.41 $\pm$ 1.39	-4.81 $\pm$ 1.06	-
	60 mg MDL 16.455A	6	9.39 $\pm$ 0.84	6.66 $\pm$ 0.91	-2.73 $\pm$ 1.08	-
	120 mg MDL 16.455A	2	9.50 $\pm$ 0.50	8.54 $\pm$ 0.62	-0.96 $\pm$ 1.12	-
	240 mg MDL 16.455A	3	7.00 $\pm$ 0.58	3.66 $\pm$ 1.29	-3.34 $\pm$ 0.82	-
	Total MDL 16.455A	14	8.86 $\pm$ 0.49	5.80 $\pm$ 0.69	-3.05 $\pm$ 0.61	-
Treatment by Age Group Interaction*: P = .1141						
† P values for comparison of each active dose and placebo are from an analyses conducted within each subgroup using an ANCOVA model containing treatment and baseline.						
* P value for treatment by age group interaction from ANCOVA model containing treatment, baseline, age group, and treatment by age group interaction.						

Race	Treatment (BID)	N	Baseline Mean $\pm$ SE	Double-Blind Period Mean $\pm$ SE	Change from Baseline Mean $\pm$ SE	P value†
Caucasian	Placebo	344	5.61 $\pm$ 0.15	4.84 $\pm$ 0.14	-0.77 $\pm$ 0.11	-
	20 mg MDL 16.455A	343	5.54 $\pm$ 0.15	4.39 $\pm$ 0.15	-1.15 $\pm$ 0.11	0053
	40 mg MDL 16.455A	344	5.52 $\pm$ 0.15	4.06 $\pm$ 0.13	-1.46 $\pm$ 0.13	0001
	60 mg MDL 16.455A	339	5.58 $\pm$ 0.15	4.22 $\pm$ 0.13	-1.36 $\pm$ 0.12	0001
	80 mg MDL 16.455A	345	5.48 $\pm$ 0.15	4.14 $\pm$ 0.14	-1.34 $\pm$ 0.11	0001
	Total MDL 16.455A	1371	5.53 $\pm$ 0.07	4.20 $\pm$ 0.07	-1.33 $\pm$ 0.06	0001
Black	Placebo	28	4.20 $\pm$ 0.57	4.00 $\pm$ 0.39	-0.20 $\pm$ 0.48	-
	20 mg MDL 16.455A	33	6.30 $\pm$ 0.56	4.69 $\pm$ 0.49	-1.61 $\pm$ 0.52	.3131
	40 mg MDL 16.455A	41	5.41 $\pm$ 0.46	3.95 $\pm$ 0.39	-1.47 $\pm$ 0.35	.1239
	60 mg MDL 16.455A	27	4.57 $\pm$ 0.59	4.10 $\pm$ 0.60	-0.47 $\pm$ 0.22	.8312
	80 mg MDL 16.455A	28	5.66 $\pm$ 0.49	4.30 $\pm$ 0.49	-1.36 $\pm$ 0.42	.3104
	Total MDL 16.455A	129	5.52 $\pm$ 0.26	4.25 $\pm$ 0.24	-1.27 $\pm$ 0.20	.2486
Asian	Placebo	15	5.57 $\pm$ 0.83	3.98 $\pm$ 0.65	-1.58 $\pm$ 0.92	-
	20 mg MDL 16.455A	15	5.43 $\pm$ 0.41	4.50 $\pm$ 0.57	-0.93 $\pm$ 0.54	.4534
	40 mg MDL 16.455A	11	6.59 $\pm$ 0.61	5.55 $\pm$ 0.60	-1.04 $\pm$ 0.58	.2435
	60 mg MDL 16.455A	27	4.43 $\pm$ 0.40	3.46 $\pm$ 0.48	-0.97 $\pm$ 0.44	.8864
	80 mg MDL 16.455A	15	6.20 $\pm$ 0.77	5.12 $\pm$ 0.80	-1.08 $\pm$ 0.42	.3199
	Total MDL 16.455A	68	5.39 $\pm$ 0.28	4.39 $\pm$ 0.31	-1.00 $\pm$ 0.24	.3179
Other	Placebo	1	3.50	2.27	-1.23	-
	20 mg MDL 16.455A	0				-
	40 mg MDL 16.455A	0				-
	60 mg MDL 16.455A	1	5.50	5.21	-0.19	-
	80 mg MDL 16.455A	0				-
	Total MDL 16.455A	1	5.50	5.31	-0.19	-

Treatment by Race Interaction* P = .4908

† P values for comparison of each active dose and placebo are from analyses conducted within each subgroup using an ANCOVA model containing treatment and baseline.

* P value for treatment by race interaction from ANCOVA model containing treatment, baseline, race, and treatment by race interaction.

Race	Treatment (BID)	N	Baseline Mean $\pm$ SE	Double-Blind Period Mean $\pm$ SE	Change from Baseline Mean $\pm$ SE	P value†
Caucasian	Placebo	258	8.79 $\pm$ 0.10	7.40 $\pm$ 0.14	-1.30 $\pm$ 0.13	-
	40 mg MDL 16.455A	123	8.70 $\pm$ 0.17	6.96 $\pm$ 0.22	-1.75 $\pm$ 0.17	0480
	60 mg MDL 16.455A	251	8.76 $\pm$ 0.10	6.57 $\pm$ 0.15	-2.19 $\pm$ 0.16	0001
	120 mg MDL 16.455A	259	8.82 $\pm$ 0.11	6.54 $\pm$ 0.16	-2.28 $\pm$ 0.16	0001
	240 mg MDL 16.455A	136	8.78 $\pm$ 0.16	6.30 $\pm$ 0.23	-2.48 $\pm$ 0.22	0001
	Total MDL 16.455A	769	8.77 $\pm$ 0.06	6.57 $\pm$ 0.09	-2.20 $\pm$ 0.09	0001
Black	Placebo	19	8.49 $\pm$ 0.42	6.84 $\pm$ 0.67	-1.65 $\pm$ 0.67	-
	40 mg MDL 16.455A	9	8.30 $\pm$ 0.56	6.45 $\pm$ 0.81	-1.85 $\pm$ 0.96	7858
	60 mg MDL 16.455A	22	9.09 $\pm$ 0.45	6.64 $\pm$ 0.63	-2.45 $\pm$ 0.52	4911
	120 mg MDL 16.455A	16	8.50 $\pm$ 0.49	6.56 $\pm$ 0.59	-1.94 $\pm$ 0.57	7400
	240 mg MDL 16.455A	8	9.50 $\pm$ 0.37	6.44 $\pm$ 0.96	-3.06 $\pm$ 1.00	3524
	Total MDL 16.455A	55	8.85 $\pm$ 0.25	6.56 $\pm$ 0.35	-2.29 $\pm$ 0.33	4486
Asian	Placebo	1	8.67 $\pm$	8.33 $\pm$	-0.33 $\pm$	-
	40 mg MDL 16.455A	2	9.33 $\pm$ 0.67	5.93 $\pm$ 2.24	-3.40 $\pm$ 2.90	-
	60 mg MDL 16.455A	6	7.94 $\pm$ 0.38	7.15 $\pm$ 0.72	-0.80 $\pm$ 0.97	-
	120 mg MDL 16.455A	3	8.00 $\pm$ 0.67	7.39 $\pm$ 0.81	-0.61 $\pm$ 1.14	-
	240 mg MDL 16.455A	0				-
	Total MDL 16.455A	11	8.21 $\pm$ 0.32	6.99 $\pm$ 0.54	-1.22 $\pm$ 0.77	-
Other	Placebo	0				-
	40 mg MDL 16.455A	1	9.33	9.83	0.50	-
	60 mg MDL 16.455A	0				-
	120 mg MDL 16.455A	1	8.33	9.54	1.21	-
	240 mg MDL 16.455A	0				-
	Total MDL 16.455A	2	8.83 $\pm$ 0.50	9.69 $\pm$ 0.15	0.85 $\pm$ 0.35	-
Treatment by Race Interaction* P = 9461						
† P values for comparison of each active dose and placebo are from analyses conducted within each subgroup using an ANCOVA model containing treatment and baseline.						
* P value for treatment by race interaction from ANCOVA model containing treatment, baseline, race, and treatment by race interaction						

Table 6 Spring SAR Studies: Intent-to-Treat Analysis of Bedtime Reflective TSS by Gender

Gender	Treatment (BID)	N	Baseline Mean ± SE	Double-Blind Period Mean ± SE	Change from Baseline Mean ± SE	P value*
Male	Placebo	164	5.16 ± 0.23	4.44 ± 0.19	-0.72 ± 0.15	-
	20 mg MDL 16.455A	179	5.36 ± 0.20	4.27 ± 0.20	-1.10 ± 0.14	0.232
	40 mg MDL 16.455A	164	5.50 ± 0.22	3.95 ± 0.19	-1.55 ± 0.19	0.005
	60 mg MDL 16.455A	184	5.27 ± 0.20	4.08 ± 0.19	-1.18 ± 0.16	0.304
	80 mg MDL 16.455A	167	5.16 ± 0.20	4.03 ± 0.19	-1.13 ± 0.15	0.425
	Total MDL 16.455A	694	5.32 ± 0.10	4.09 ± 0.10	-1.23 ± 0.08	0.038
Female	Placebo	224	5.75 ± 0.18	4.95 ± 0.18	-0.79 ± 0.16	-
	20 mg MDL 16.455A	212	5.81 ± 0.19	4.55 ± 0.19	-1.26 ± 0.16	0.229
	40 mg MDL 16.455A	232	5.57 ± 0.18	4.20 ± 0.16	-1.38 ± 0.16	0.005
	60 mg MDL 16.455A	210	5.58 ± 0.19	4.23 ± 0.17	-1.34 ± 0.16	0.014
	80 mg MDL 16.455A	221	5.80 ± 0.19	4.31 ± 0.18	-1.49 ± 0.14	0.004
	Total MDL 16.455A	875	5.69 ± 0.09	4.32 ± 0.09	-1.37 ± 0.08	0.001

Treatment by Gender Interaction* P = 7811

* P values for comparison of each active dose and placebo are from an analyses conducted within each subgroup using an ANCOVA model containing treatment and baseline

* P value for treatment by gender interaction from ANCOVA model containing treatment, baseline, gender, and treatment by gender

Table 7 Fall SAR Studies: Intent-to-Treat Analysis of 7 PM Reflective TSS by Gender

Gender	Treatment (BID)	N	Baseline Mean ± SE	Double-Blind Period Mean ± SE	Change from Baseline Mean ± SE	P value*
Male	Placebo	111	8.65 ± 0.15	7.37 ± 0.21	-1.28 ± 0.19	-
	40 mg MDL 16.455A	62	8.62 ± 0.26	6.68 ± 0.30	-1.95 ± 0.24	0.497
	60 mg MDL 16.455A	105	8.76 ± 0.16	6.44 ± 0.24	-2.32 ± 0.24	0.009
	120 mg MDL 16.455A	108	8.53 ± 0.17	6.26 ± 0.22	-2.26 ± 0.23	0.004
	240 mg MDL 16.455A	65	8.75 ± 0.25	6.22 ± 0.32	-2.53 ± 0.35	0.004
	Total MDL 16.455A	340	8.56 ± 0.10	6.38 ± 0.13	-2.28 ± 0.13	0.001
Female	Placebo	167	8.85 ± 0.12	7.49 ± 0.17	-1.35 ± 0.17	-
	40 mg MDL 16.455A	73	8.74 ± 0.21	7.14 ± 0.28	-1.60 ± 0.24	0.331
	60 mg MDL 16.455A	174	8.77 ± 0.13	6.67 ± 0.18	-2.10 ± 0.20	0.018
	120 mg MDL 16.455A	171	8.95 ± 0.14	6.75 ± 0.20	-2.19 ± 0.20	0.015
	240 mg MDL 16.455A	79	8.88 ± 0.19	6.38 ± 0.30	-2.50 ± 0.28	0.003
	Total MDL 16.455A	497	8.85 ± 0.08	6.72 ± 0.11	-2.12 ± 0.11	0.004

Treatment by Gender Interaction* P = 9291

* P values for comparison of each active dose and placebo are from an analyses conducted within each subgroup using an ANCOVA model containing treatment and baseline

* P value for treatment by gender interaction from ANCOVA model containing treatment, baseline, gender, and treatment by gender interaction

Patients Enrolled in More Than One Trial

It was noted on pages 50-53 of Volume 262 of the NDA, that the sponsor reported that 209 subjects participated in more than one clinical trial. Of these, 8 subjects participated in more than one trial during the same season in the same year, without the knowledge of the investigators. Of these 8 subjects only 2 participated in more than one trial (1 in the Fall trials and the other in the Spring trials) with overlapping enrollment dates, with each subject receiving exactly the same treatment in both trials. It is doubtful that these few subjects would have substantially biased the efficacy or safety outcomes of the four well controlled clinical trials of efficacy and safety.

Final Determination:

Available data support the assertion that compared to placebo fexofenadine 60mg BID is efficacious for the mitigation of the symptoms associated with seasonal allergic rhinitis in patients 12 years of age and older. Onset of action occurs at approximately 1 hour, is sustained throughout the dosing interval and is maintained over two weeks. There appears to be no indication that treatment response is influenced by gender, race or age including those between 12 and 18 years of age or those greater than 60 years of age.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: NDA 20-625 - Safety Overview

The sponsor has provided a comprehensive table in the NDA (S2 Vol 1.1-P298) of all completed clinical protocols, which lists 20 clinical pharmacology studies, 4 well controlled studies in patients with seasonal allergic rhinitis (SAR) and 1 controlled trial in healthy subjects. From these completed trials the sponsor has compiled the safety database. In the integrated summary of safety the sponsor also provides (S8-V1.262-P16) a table of all investigations pertinent to safety. From this table it is noted that 7 clinical trials (3-US; 4-Europe) were ongoing at the time of NDA submission, from which safety data was not available for inclusion in the NDA at the time of submission. Of the clinical pharmacology studies, PJPR0003, PJPR0004, PJPR0007, PJPR0018 and PJPR0028 were viewed as providing important safety data and were reviewed separately.

Overall Exposure to Drug

The sponsor provides tables, reproduced below, to summarize exposure data by number of patients/subjects (from all completed clinical studies and from controlled clinical trials), by duration of exposure, by exposure by dose, by exposure by multidose trials and exposure by population. The sponsor explains that the number of exposures is not the same as the number of subjects or patients since 220 participants were exposed in more than one study (clinical pharmacology - 11; controlled SAR - 209). Since subjects were not excluded from the Fall SAR studies if they had participated in the Spring SAR studies, 201 of the 209 patients in SAR studies participated in studies for both seasons, while the remaining 8 patients participated in more than one study during the same season without the investigator's or sponsor's knowledge.

From these tables it can be seen that the majority of exposures to fexofenadine were in patients enrolled in controlled SAR trials (2326 exposures in 2127 patients) vs clinical pharmacology trials (522) vs controlled trial in healthy subjects (27). With regard to duration of exposure, the largest exposure group was to SAR patients (2299 multidose exposures) for less than 30 days. Duration of exposure for the SAR trials was not collected on the case report forms but rather estimated by counting the number of days with at least one total symptom score (TSS) recorded. With regard to exposure by dose (BID dosing), the majority of exposures were to SAR patients at 40mg (540), 60mg (680), 80mg (395), 120mg (290) and 240mg (145).

Table 8-562. Number of Patient/Subject Exposures						
Study Type/Protocol Number	Population	Dose Regimen	Number of Subjects/Patients			
			Placebo	Terfenadine	MDL 16,455A	Total*
Clinical Pharmacology						
PJPR0001	Healthy Subjects	Single Dose	0	0	24	24
PJPR0002	Healthy Subjects	Single Dose	21	0	66	87
PJPR0003	Healthy Subjects	Q12h	8	0	24	32
PJPR0004	Healthy Subjects	Q12h	0	23	24	24
PJPR0005	Healthy Subjects	Single Dose	0	0	24	24
PJPR0007	Healthy Subjects	Q12h	40	0	40	40
PJPR0008	Healthy Subjects	Q12h	0	0	6	6
PJPR0011	Healthy Subjects	Q12h	0	0	24	24
PJPR0012	Healthy Subjects	Single Dose	0	0	24	24
PJPR0013	Renally Impaired	Single Dose	0	0	29	29
PJPR0015	Healthy Subjects	Single Dose	0	0	30	30
PJPR0017	SAR Patients	Single Dose	33	0	66	99
PJPR0018	Healthy Subjects	Q12h	0	0	20	22†
PJPR0020	Healthy Elderly Subjects	Single Dose	0	0	20	20
PJPR0021	Hepatically Impaired	Single Dose	0	0	14	14
PJPR0025	Healthy Subjects	Single Dose	0	0	24	24
PJPR0026	Healthy Subjects	Single Dose	0	0	25	25
PJPR0028	Healthy Subjects	Q12h	0	0	24	24
PJPR0029	Healthy Subjects	Single Dose	0	0	24	24
SEPR0045	Healthy Subjects	Q12h	0	6	0	6
TOTAL*			102	29	522	591
Controlled SAR						
PJPR0009	SAR Patients	BID	193	0	782	975
PJPR0010	SAR Patients	BID	202	0	809	1011
PJPR0023	SAR Patients	BID	142	0	430	572
PJPR0024	SAR Patients	BID	148	0	440	588
TOTAL*			674	0	2325	2932
Controlled Healthy Subjects						
PJPR0014	Healthy Subjects	BID	14	0	27	41
All Controlled*			688	0	2353	2973
TOTAL*			790	29	2875	3564
* Note: Patient/subject counts cannot be summed to obtain total counts since patients/subjects may have participated in more than one study or may have participated in a crossover study. † Two subjects in PJPR0018 discontinued prior to receiving MDL 16,455A.						
Supporting Data						
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Appendix A1. Summary 1: Number of Exposures in All MDL 16,455A Studies					S8-VI.263-P15	
Appendix A2. Listing 3: Study Medication Exposure for Clinical Pharmacology Studies					S8-VI.263-P232	
Appendix A2. Listing 6: Study Medication Exposure for Controlled Clinical Studies by Protocol and Patient/Subject					S8-VI.264-P134	
Appendix A2. Listing 8: Subjects Participating in More Than One Clinical Pharmacology Study by Master Patient Number					S8-VI.265-P156	
Appendix A2. Listing 9: Patients Participating in More Than One Controlled Clinical SAR Study by Master Patient Number					S8-VI.265-P159	

Treatment (BID)	Patients in One Protocol (N=2723)	Patients in Two Protocols (N=205)		Patients in More Than Two Protocols (N=4)				Total Patients (N=2932)
		1st Protocol	2nd Protocol	1st Protocol	2nd Protocol	3rd Protocol	4th Protocol	
Placebo	596	35	50	--	1	2	0	674
20 mg MDL 16 455A	355	38	1	--	--	0	0	394
40 mg MDL 16 455A	479	35	27	1	1	1	0	540
60 mg MDL 16 455A	602	38	50	1	0	0	0	680
80 mg MDL 16 455A	336	57	--	2	1	0	0	395
120 mg MDL 16 455A	235	--	54	--	1	1	0	290
240 mg MDL 16 455A	120	1	23	--	0	0	0	145
Total MDL 16 455A	2127	169	155	4	3	3	0	2326

Supporting Data

Appendix A1. Summary 2. Number of Exposures in Controlled Clinical SAR Studies by Dose Group	Page SB-V1 263-P29
Appendix A2. Listing 6. Study Medication Exposure for Controlled Clinical Studies by Protocol and Patient/Subject	SB-V1 264-P134
Appendix A2. Listing 9. Patients Participating in More Than One Controlled Clinical SAR Study by Master Patient Number	SB-V1 265-P159

Duration of Exposure MDL 16 455A	Clinical Pharmacology Studies (N=522)	Controlled Studies		All Studies (N=2875)
		Healthy Subjects (N=27)	SAR Patients (N=2326)	
Single Dose	N=361	N=0	N=0	N=361
Multiple Dose < 30 Days	N=160	N=0	N=2299	N=2459
Multiple Dose ≥ 30 Days	N=1	N=27	N=12	N=40
Unknown	N=0	N=0	N=15	N=15
N	522	27	2311	2860
Mean (Days)±SD	6.7±9.4	89.1±3.1	14.4±7.8	13.7±9.5
Range (Days)	1-33	84-94	1-41	1-94

Supporting Data

Appendix A1. Summary 3. Duration of Exposure to MDL 16 455A	Page SB-V1 263-P44
Appendix A2. Listing 3. Study Medication Exposure for Clinical Pharmacology Studies	SB-V1 263-P232
Appendix A2. Listing 6. Study Medication Exposure for Controlled Clinical Studies by Protocol and Patient/Subject	SB-V1 264-P134

MDL 16 455A Dose (BID)	Clinical Pharmacology Studies (N=169)	Controlled Studies		Total (N=3142)
		SAR Patients (N=2932)	Healthy Subjects (N=41)	
Placebo	48	674	14	736
20 mg	27	394	0	421
40 mg	43	540	0	583
60 mg	53	680	0	733
80 mg	3	395	27	425
120 mg	68	290	0	358
160 mg	3	0	0	3
180 mg	23	0	0	23
200 mg	40	0	0	40
240 mg	23	145	0	168
260 mg	3	0	0	3
390 mg	3	0	0	3
400 mg	40	0	0	40
520 mg	3	0	0	3
690 mg	3	0	0	3
Total MDL 16 455A	161	2326	27	2514

Note: Patient/subject counts cannot be summed to obtain total counts since patients/subjects may have participated in more than one protocol

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Appendix A1, Summary 5: Exposure by Dose in Multiple Dose Studies	S8-V1.263-P59
Appendix A2, Listing 3: Study Medication Exposure for Clinical Pharmacology Studies	S8-V1.263-P232
Appendix A2, Listing 8: Subjects Participating in More Than One Clinical Pharmacology Study by Master Patient Number	S8-V1.265-P156

Demographics

Baseline demographics for individual SAR trials is presented in the medical officer's overview of efficacy. The sponsor reports that the overall demographic characteristics of study populations that the majority of subjects exposed to fexofenadine in the SAR trials were Caucasian (89%), 18- < 40 years of age (64%), weighing 60- < 90 kilograms (59%) with a slight preponderance of females (57%). For clinical pharmacology studies the characteristics were Caucasian (92%), 18- < 40 years of age (76%), weighing 60- < 90 kilograms (82%) with a preponderance of males (83%).

Adverse Events in Clinical Trials

The sponsor indicates that adverse events were reported using the Merrell Dow version of the World Health Organization Reaction Terminology Dictionary which was the same as was used for collecting historical terfenadine data. For the 4 major controlled SAR trials, in adverse event data were examined for each individual trial and the reader is referred to the individual trial reviews for those results.

With regard to patient accounting for safety, the sponsor provides a table reproduced below which shows 2319 patient exposures were safety evaluable out of 2326 exposures during the SAR trials. The sponsor indicates that 10 subjects from trials PJPR0009 and PJPR0010 were exposed but had no post baseline adverse event assessments because these patients failed to return for follow-up visits and were therefore not safety-evaluable.

Treatment (BID)	Clinical Pharmacology (MDL 16,455A Only)		Controlled Studies (MDL 16,455A and Placebo)						All Studies (MDL 16,455A Only)	
			SAR Patients		Healthy Subjects		All Controlled			
	Exposed (N=522)	Safety Evaluable (N=522)	Exposed (N=2932)	Safety Evaluable (N=2922)	Exposed (N=41)	Safety Evaluable (N=41)	Exposed (N=2973)	Safety Evaluable (N=2963)	Exposed (N=2875)	Safety Evaluable (N=2868)
Placebo	-	-	674	671	14	14	688	685	-	-
20 mg	-	-	394	393	-	-	394	393	-	-
40 mg	-	-	540	538	-	-	540	538	-	-
60 mg	-	-	680	679	-	-	680	679	-	-
80 mg	-	-	395	392	27	27	422	419	-	-
120 mg	-	-	290	290	-	-	290	290	-	-
240 mg	-	-	145	145	-	-	145	145	-	-
Total MDL 16,455A*	522	522	2326	2319	27	27	2353	2346	2875	2868
* Patient/subject counts can not be summed to obtain total counts since patients/subjects may have participated in more than one study.										
Supporting Data									Page	
Table 8-562. Number of Patient/Subject Exposures									S8-V1.262-P48	
Table 8-564. Number of Exposures in Patients for the Controlled Clinical SAR Studies by Dose									S8-V1.262-P53	
Appendix A1 Summary B. Demographic Characteristics of the Safety Evaluable Study Population									S8-V1.263-P109	

For controlled clinical trials the sponsor provides a table of the incidence of all adverse events in tabular format in Table 8-578. Overall, the sponsor reports that the total number of patients with 1 or more adverse event for the SAR trials was: Placebo 37.9% (254/671) and fexofenadine 32.5% (754/2319). From Table 8-578 only those events which occurred at a rate of at least 0.5% in the fexofenadine group in the SAR trials were extracted and placed in an abbreviated version of Table 8-578 reproduced below. Of the events in this table only diarrhea, viral infection, back pain and chest pain appear to occur at a frequency margin of 0.5% or more frequently in the fexofenadine group than placebo.

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence of All Adverse Events for Controlled Clinical Studies: P.JPR0009, P.JPR0010, P.JPR0023, P.JPR0024, P.JPR0014					
	SAR Patients		Healthy Subjects		Total	
	Placebo (N=671) N(%)	MDL 16.455A (N=2319) N(%)	Placebo (N=14) N(%)	MDL 16.455A (N=27) N(%)	Placebo (N=685) N(%)	MDL 16.455A (N=2346) N(%)
Total Occurrence Rate: Patients with 1 or more Adverse Event(s):	254 (37.6)	754 (32.5)	7 (50.0)	15 (55.6)	261 (38.1)	769 (32.8)
HEADACHE	56 (8.3)	172 (7.4)	1 (7.1)	1 (3.7)	57 (8.3)	173 (7.4)
DRIZZINESS	9 (1.3)	15 (0.6)	0 (0.0)	0 (0.0)	9 (1.3)	15 (0.6)
INSOMNIA	7 (1.0)	14 (0.6)	0 (0.0)	0 (0.0)	7 (1.0)	14 (0.6)
DROWSINESS	6 (0.9)	24 (1.0)	0 (0.0)	0 (0.0)	6 (0.9)	24 (1.0)
FATIGUE	6 (0.9)	26 (1.2)	0 (0.0)	0 (0.0)	6 (0.9)	28 (1.2)
PAIN	2 (0.3)	14 (0.6)	0 (0.0)	0 (0.0)	2 (0.3)	14 (0.6)
THROAT IRRITATION	15 (2.2)	48 (2.1)	1 (7.1)	0 (0.0)	16 (2.3)	48 (2.0)
SINUSITIS	9 (1.3)	14 (0.6)	0 (0.0)	1 (3.7)	9 (1.3)	15 (0.6)
UPPER RESPIRATORY TRACT INFECTION	9 (1.3)	22 (0.9)	0 (0.0)	2 (7.4)	9 (1.3)	24 (1.0)
EPISTAXIS	4 (0.6)	19 (0.8)	1 (7.1)	0 (0.0)	5 (0.7)	19 (0.8)
NAUSEA	10 (1.5)	27 (1.2)	1 (7.1)	1 (3.7)	11 (1.6)	28 (1.2)
ABDOMINAL PAIN	5 (0.7)	17 (0.7)	1 (7.1)	1 (3.7)	6 (0.9)	18 (0.8)
DYSPEPSIA	4 (0.6)	1A (0.8)	0 (0.0)	0 (0.0)	4 (0.6)	18 (0.8)
DIARRHEA	1 (0.1)	20 (0.9)	1 (7.1)	1 (3.7)	2 (0.3)	21 (0.9)
INFECTION VIRAL	10 (1.5)	53 (2.3)	4 (28.6)	5 (18.5)	14 (2.0)	58 (2.5)
OTITIS MEDIA	3 (0.4)	12 (0.5)	0 (0.0)	0 (0.0)	3 (0.4)	12 (0.5)
MYALGIA	6 (0.9)	20 (0.9)	0 (0.0)	1 (3.7)	6 (0.9)	21 (0.9)
BACK PAIN	2 (0.3)	20 (0.9)	2 (14.3)	2 (7.4)	4 (0.6)	22 (0.9)
CHEST PAIN	0 (0.0)	11 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.5)
HYPERLIPEMIA	5 (0.7)	15 (0.6)	0 (0.0)	0 (0.0)	5 (0.7)	15 (0.6)
HYPOCALCEMIA	2 (0.3)	12 (0.5)	0 (0.0)	0 (0.0)	2 (0.3)	12 (0.5)
LEUKOPENIA	6 (0.9)	19 (0.8)	0 (0.0)	0 (0.0)	6 (0.9)	19 (0.8)
URINARY TRACT INFECTION	5 (0.7)	13 (0.6)	0 (0.0)	0 (0.0)	5 (0.7)	13 (0.6)
SGPT INCREASED	4 (0.6)	16 (0.7)	0 (0.0)	0 (0.0)	4 (0.6)	16 (0.7)
DYSMENORRHEA	2 (0.3)	17 (0.7)	0 (0.0)	1 (3.7)	2 (0.3)	18 (0.8)
DRY MOUTH	6 (0.9)	16 (0.7)	0 (0.0)	0 (0.0)	6 (0.9)	16 (0.7)
Note	A patient may have experienced more than one adverse event, therefore, patient counts for preferred terms may not equal the sum of patient/subject counts for System Organ Classes or the Total Occurrence Rate					
Supporting Data						Page
Appendix B1. Summary 7. All Adverse Events for Controlled Studies						S8-V1 266-P45
Appendix B2. Listing 8. All Adverse Events for Controlled Studies						S8-V1 267-P162

The table below presents another abbreviation of Table 8-578 showing the adverse events reported at a rate of $\geq 1\%$ in the total fexofenadine group in controlled clinical trials. None of these events occurred substantially more frequently in the fexofenadine treated patients than placebo treated.

All Adverse Events Most Frequently Reported From Controlled Clinical Trials ($\geq 1\%$ in total fexofenadine group)		
Preferred Term	Placebo (n=685) (%)	Fexofenadine (n=2346) (%)
Headache	57 (8.3)	173 (7.4)
Drowsiness	6 (0.9)	24 (1.0)
Fatigue	6 (0.9)	28 (1.2)
Throat Irritation	16 (2.3)	48 (2.0)
Upper Resp. Tract Infection	9 (1.3)	24 (1.0)
Nausea	11 (1.6)	28 (1.2)
Viral Infection	14 (2.0)	58 (2.5)

The sponsor was asked to provide a table (See Attachment A for a photocopy) of all adverse events by dose from the four well controlled clinical trials. The sponsor provided that table on April 22, 1996 by teletax. Examination of that table revealed no obvious dose response for any of the listed adverse events. From that table a smaller table was constructed listing all adverse events which occurred at a rate greater than 1% in the 60mg fexofenadine group. That table is listed below and is suggested for inclusion in the product labeling.

Incidence of All Adverse Events for Controlled Clinical Seasonal Allergic Rhinitis Studies Occurring $> 1\%$ in Fexofenadine 60mg Dose Group		
	Placebo BID (N=671)	Fexofenadine 60mg BID (N=679)
Headache	8.3%	7.8%
Fatigue	0.9%	1.3%
Drowsiness	0.9%	1.3%
Throat Irritation	2.2%	2.1%
Nausea	1.5%	1.6%
Dyspepsia	0.6%	1.3%
Viral Infection	1.5%	2.5%
Dysmenorrhea	0.3%	1.6%

For the controlled clinical trials in SAR patients, the sponsor reports that in general adverse event rates did not appear to differ significantly for treatment-related events by age, gender or race. Possible exceptions may be age less than 18 years and race. For age less than 18 years, with the following are possible exceptions: headache - 3.4% vs 1.5% for placebo; drowsiness - 2.1% vs 0.0% for placebo; and viral infection - 3.0% vs 1.5% for placebo; comparison with the overall frequencies for these events can be made by examining the event rates in the tables of adverse events above. For Blacks, the possible exceptions are: headache 12.6% vs 6.4% for placebo and leukopenia 2.9% vs 0.0% for placebo; but this is difficult to assess since only 221 Blacks participated in well controlled clinical trials.

Deaths, Dropouts and Other Serious Adverse Events

The sponsor reports that no deaths occurred during any of the clinical trials. However one subject (54 year old Black male - PJST0180-0019) was hospitalized and discontinued the study after suffering a cerebrovascular accident after 14 days of treatment with placebo.

For controlled clinical trials the sponsor reports that discontinuation due to an adverse event occurred more frequently in the placebo group (3.2% - 22/685) than the total fexofenadine group (2.0% - 48/2346). The sponsor also reports that the drop out rate was not dose related as noted from the sponsor's Table 8-596, reproduced below.

Table 8-596. Reasons for Early Discontinuation in Safety Evaluable Patients in the Controlled Clinical Studies: PJPR0009, PJPR0010, PJPR0023, PJPR0024, and PJPR0014

Reason	MDL 16,455A (BID)							Total (N=2346)
	Placebo (N=685)	20 mg (N=393)	40 mg (N=538)	60 mg (N=679)	80 mg (N=419)	120 mg (N=290)	240 mg (N=145)	
Patient Elected to Discontinue % (N)	5.3% (36)	3.8% (15)	3.2% (17)	3.5% (24)	3.3% (14)	4.1% (12)	1.4% (2)	3.6% (84)
Adverse Event % (N)	3.2% (22)	2.8% (11)	1.7% (9)	2.2% (15)	2.1% (9)	0.3% (1)	2.1% (3)	2.0% (48)
Lack of Effect/Treatment Failure % (N)	2.2% (15)	2.0% (8)	1.5% (8)	1.0% (7)	1.9% (8)	1.0% (3)	1.4% (2)	1.5% (36)
Other % (N) †	2.5% (17)	2.5% (10)	1.1% (6)	1.2% (8)	1.4% (6)	1.7% (5)	1.4% (2)	1.6% (37)
Total % (N) *	7.3% (50)	5.9% (23)	4.8% (26)	5.4% (37)	6.0% (25)	5.5% (16)	4.1% (6)	5.7% (133)

* A patient may have more than one reason for discontinuation, therefore, patient counts for individual reasons may not equal the patient total. This table does not include 10 patients who were randomized and exposed to double-blind study medication but had no post baseline adverse event assessments (not safety evaluable)

† Includes family emergency, patient noncompliance, prohibited medication taken, visit date on holiday, and patient out-of-town on visit date

Supporting Data

Appendix B1, Summary 32. Reasons for Early Discontinuation in Patients in Controlled Clinical Studies SB V1 266.P280

Appendix B2, Listing 34. Reasons for Early Discontinuation in Patients/Subjects in Controlled Clinical Studies and Clinical Pharmacology and Pharmacokinetic Studies SB V1 271.P301

For other serious adverse events, in controlled clinical trials, the sponsor reports that only 2 subjects were hospitalized due to an adverse event - a 44 year old female because of a fractured tibia and an 18 year old male because of a fractured right arm. The incidence of serious adverse events from controlled clinical trials was summarized by the sponsor in Table 8-599, reproduced below. Serious adverse events did not appear to occur with substantially greater frequency in the total fexofenadine group compared to placebo. In clinical pharmacology studies one subject was hospitalized - 55 year old male because of pyloric stenosis.

Serious Event Criteria	Placebo (N=685)			MDL 16,455A (N=2348)		
	Not Related n(%)	Related n(%)	Total n(%)	Not Related n(%)	Related n(%)	Total n(%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Life Threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hospitalization	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)	0 (0%)	2 (0.1%)
Disability	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Congenital Anomaly	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cancer	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Overdose	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dropped from Study Due to Adverse Event*	17 (2.5%)	5 (0.7%)	22 (3.2%)	30 (1.3%)	18 (0.8%)	48 (2.1%)
Therapy Interrupted	1 (0.2%)	1 (0.2%)	2 (0.3%)	5 (0.2%)	0 (0%)	6 (0.3%)
Dose Reduced	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treated with Counter- Active Medication*	99 (14.5%)	24 (3.5%)	121 (17.7%)	295 (12.6%)	73 (3.1%)	361 (15.4%)
Overall Total	103 (15.0%)	29 (4.2%)	130 (19.0%)	309 (13.2%)	87 (3.7%)	387 (16.5%)
Note: A patient may have experienced more than one type of serious adverse event; therefore, patient counts for serious adverse event criteria may not equal the patient total. * For incidence of serious adverse events by dose group for patients who dropped from study due to an adverse event and patients who were treated with counteractive medication, see Table 8-600, S8-V1.262-P217.						
Supporting Data:						
Appendix B1, Summary 35: Incidence of Serious Adverse Events in Patients Who Received MDL 16,455A or Placebo in Controlled Clinical Studies					Page S8-V1.266-P306	
Appendix B2, Listing 38: Serious Adverse Events in Patients Who Received MDL 16,455A or Placebo in Controlled Clinical Studies					Page S8-V1.271-P323	

Clinical Laboratory Evaluations

Mean Changes

Examination of Table 8-604, which displays mean change from baseline for lab values from controlled clinical trials by dose, shows no obvious mean change from baseline or dose response mean change from baseline for any analyte except triglyceride.

The sponsor reports mean changes in 4 analytes. The sponsor reports an increase in SGPT of 2.7 ± 0.60 U/L over baseline in the 240 mg fexofenadine group with the range of -18 to 34 in change from baseline for the 240 mg dose group. The correlation coefficient (0.06318) in change from baseline in SGPT and increasing MDL 16,455A dose was small but statistically significant ($P = .0004$); but mean postbaseline values remained within normal reference ranges.

Albumin ($P = .0003$) and A/G ratio ($P = .0041$) were also noted to have statistically significant dose-related changes with a small correlation coefficient -0.0642 and -0.0511, respectively between change from baseline and fexofenadine dose. The sponsor attributes the p value to be due to the large sample size. Mean change from baseline for albumin for placebo and for fexofenadine (40mg to 120mg) was -0.1 ± 0.01 g/dL and for 240mg -0.1 ± 0.02 g/dL. A similar magnitude for change from

baseline was reported for A/G ratio: -0.0 ± 0.01 for placebo and fexofenadine doses, 40mg to 240mg.

Triglyceride was noted to have increases in mean change from baseline in 4 dose groups: 60 mg (1.8 ± 2.19 mg/dL), 80 mg (4.9 ± 2.53 mg/dL), 120 mg (6.5 ± 5.28 mg/dL), and 240 mg (5.1 ± 5.84 mg/dL); but the mean change was similar for total fexofenadine and placebo (1.4 ± 1.28 mg/dL and -0.4 ± 3.36 mg/dL, respectively). The sponsor attributes the finding to unreliable fasting by patients.

Shift Tables

The sponsor reports that the results with fexofenadine and placebo were similar with no obvious dose-related trends in the incidence of patients with laboratory shifts. Examination of these tables does not reveal any obvious clinically significant trends or dose-related trends in shifts.

Outliers

The sponsor reports that there were no obvious dose-related trends in the incidence of patients having outlier laboratory values. The largest number of outliers reported is for decreased WBCs - fexofenadine-2.5% and placebo 3.2% but that the incidence of outliers for leukocytes and neutrophils compared to placebo could be considered to be within normal lab variations for the conduct of a study. Examination of the outlier tables does not reveal any obvious clinically significant trends or dose-related trends in numbers of outliers. Although several patients were observed to have SGPT elevations during the clinical trials, the sponsor reports in the outlier tables that the incidence of SGPT high outliers for total fexofenadine (0.4%) was similar to placebo (0.6%) with no increasing trend with increasing doses.

Pharmacokinetics in Special Populations

Protocols PJPR0013 (Renal Impairment) and PJPR0021 (Hepatic Impairment) are two open-label single dose (80mg) pharmacokinetic studies in patients with renal or hepatic impairment. Pharmacokinetic data from a limited number of patients - renal-29, hepatic-14, indicate there were no substantial pharmacokinetic differences observed in hepatically impaired subjects compared to healthy volunteers; but that C_{max} was increased by 93% and AUC increased by 133% compared to non-age/weight matched normal volunteers. Limited machine-read ECG information is available from these subjects. The ECG collection was at 0hr, 2hr, 6hr, 12hr, 24hr, and 72hr after dosing. Only one baseline ECG was obtained. The sponsor reports that there were no appreciable changes in mean QTc intervals; but it is difficult to draw conclusions based on these limited data. The sponsor will be encouraged to re-examine this issue more accurately during Phase IV trials.

Cardiac Effects

The sponsor presents data from 9 trials (PJPR0002/ 03/ 04/ 07/ 14/ 18/ 28/ 23/ 24) which were either specifically designed to examine fexofenadine's effect on ECG parameters or were clinical or drug interaction trials which collected important cardiac conductance data. Of these, 7 were reviewed individually during the NDA review. The results of these 7 trials are summarized below. The cardiac results from the remaining 2 studies - PJPR0002 and PJPR0014 will be only mentioned below because PJPR0002 was a single-dose, dose-escalating trial which yields less information than from the multidose trials of longer duration, some of which included doses of comparable size or greater and

PJPR0014 enrolled only 41 subjects because it was terminated early when results from trials PJPR0009/10 suggested 80mg may not be the appropriate dose. Most of these trials had ECG readings conducted both by ECG machine and by a cardiologist, Dr Joel Morganroth. The definition of an outlier value is a value for QTc >440msec which also shows an increase of 10 msec above baseline.

Protocol PJPR0003 was placebo controlled, parallel, dose escalating (8 dose levels) trial in 32 healthy males (4 per dose level) who took fexofenadine for 28.5 days. Serial ECGs (8 over 12 hours) were obtained on Days 1, 2, 8, 15, 22 and 30. An additional 18 hour ECG was obtained on Days 1 and 30; and an additional ECG was obtained on Days 31, 32, and 33. Day 1 was the placebo baseline. Since there were only 4 subjects per dose (1-placebo; 3-fexofenadine) only descriptive statistics were performed. Nonetheless an examination of the data tables and graphic display shows no obvious increase or trend in increase in QTc interval duration over a broad range of doses, from 20mg BID to 690mg BID.

Protocol PJPR0004 was a four way complete crossover trial which compared fexofenadine 60mg, fexofenadine 180mg, terfenadine 60mg and terfenadine 180mg with each treatment administered Q12H for 6.5 days to 24 male subjects. Serial ECGs (5 over 12 hours) were obtained on Days 1 (no drug baseline) and Days 2 and 8. The results for QTc intervals are summarized below. Comparison between terfenadine 60mg and fexofenadine 60mg was not provided by the sponsor in the original NDA submission but was later provided by submission dated April 1, 1996 at the Agency's request and included in the tables below. The comparisons provided demonstrate the greater potential of terfenadine to prolong QTc intervals relative to baseline and to fexofenadine at the same nominal dose. The frequency of outliers was: fexofenadine-60mg-12.5%; fexofenadine 180mg-4.4%; terfenadine 60mg-13%; terfenadine 180mg-17.4%.

PJPR0004	Day 8 minus Day 1 (baseline) Comparison Fitted Mean $\pm$ Std Error			
	Daily Mean QTc (msec)		Daily Mean QTc Maxima (msec)	
	organroth	Machine	Morganroth	Machine
Treatment Q12H				
Ter 60mg	9.3 $\pm$ 2.9 P=0.001	9.8 $\pm$ 2.1 P<0.001	12.2 $\pm$ 3.9 P=0.002	5.7 $\pm$ 3.2 P=0.001
Ter 180mg	23.2 $\pm$ 2.9 P<0.001	22.9 $\pm$ 2.1 P<0.001	26.0 $\pm$ 3.9 P<0.001	24.4 $\pm$ 3.2 P<0.001
Fex 60mg	0.5 $\pm$ 2.9 P=0.868	2.2 $\pm$ 2.1 P=0.302	-2.3 $\pm$ 3.8 P=0.544	-0.6 $\pm$ 3.2 P=0.848
Fex 180mg	3.3 $\pm$ 2.9 P=0.255	4.3 $\pm$ 2.1 P=0.047	4.2 $\pm$ 3.9 P=0.281	6.3 $\pm$ 3.2 P=0.050

PIPR0004	Day 8 minus Day 1 (baseline) Difference Between Treatments Fitted Mean ± Std Error			
	Daily Mean QTc (msec)		Daily Mean QTc Maxima (msec)	
	Comparison	Morganroth	Machine	Morganroth
Fex 60mg vs Fex 180mg	2.8 ± 4.1 p=0.490	2.1 ± 3.0 p=0.492	6.5 ± 5.5 p=0.234	6.9 ± 4.5 p=0.127
Ter 60mg vs Ter 180mg	13.9 ± 4.1 p=0.001	13.1 ± 3.0 p<0.001	13.8 ± 5.5 p=0.012	18.7 ± 4.5 p<0.001
Fex 60mg vs Ter 60mg	8.8 ± 4.1 p=0.032	7.6 ± 3.0 p=0.012	14.5 ± 5.5 p=0.008	6.3 ± 4.5 p=0.158
Fex 180mg vs Ter 180mg	19.9 ± 4.1 p<0.001	18.7 ± 3.0 p<0.001	21.9 ± 5.5 p<0.001	18.1 ± 4.5 p<0.001

Protocol PIPR0007 was a four period, complete crossover trial which compared placebo to fexofenadine 40mg, 200mg and 400mg BID for 6 days in 20 males and 20 females. Serial ECGs (8 over 12 hours) were obtained on Days 1 (placebo baseline) and on Days 2 and 8. The ECGs for this trial were read twice by Dr Morganroth (Morganroth - first and Morganroth - final) at the request of the sponsor because of the observance of a carryover effect which the sponsor noted was present in the first readings of the ECGs but not in the machine read ECGs. Only the Morganroth final data are presented below which are devoid of carryover effects. No statistically significant difference was observed for any comparison of fexofenadine and placebo.

PIPR0007	Difference Between Treatments in Change from Baseline to Day 8 Fitted Mean ± Std Error			
	Daily Mean QTc (msec)		Daily Mean QTc Maxima (msec)	
	Comparison	Morganroth	Machine	Morganroth
Fex 40mg vs Placebo	-2.5 ± 2.2 p=0.251	0.2 ± 2.1 p=0.919	-1.3 ± 3.3 p=0.688	9.0 ± 4.6 p=0.052
Fex 200mg vs Placebo	-0.8 ± 2.2 p=0.717	0.5 ± 2.1 p=0.795	-3.0 ± 3.3 p=0.361	6.0 ± 4.6 p=0.193
Fex 400mg vs Placebo	0.7 ± 2.2 p=0.731	1.2 ± 2.1 p=0.571	1.2 ± 3.3 p=0.703	4.8 ± 4.6 p=0.299

Protocols PJPR0018 and PJPR0028 were three way complete crossover drug interaction trials (erythromycin and ketoconazole, respectively) of similar design. Each drug was administered individually and then in combination for 6.5 days to 24 subjects in each trial. Fexofenadine 120mg Q12H was administered in both trials. Serial ECGs (Eryth-5 over 8 hours; Keto-8 over 12 hours) were obtained at baseline with no drug administered and on the first day and last day of drug administration. Significant pharmacokinetic drug interactions were observed showing marked elevation of fexofenadine plasma concentrations but no effect on erythromycin or ketoconazole plasma concentrations. There was no significant pharmacodynamic interaction for changes in QTc interval duration although the combination of ketoconazole and fexofenadine did cause a mean change from baseline in QTc prolongation of 8.0msec which approached statistical significance at the 0.0597 level. The frequency of outliers were higher on fexofenadine (26%) and on fexofenadine with ketoconazole (26%) than on ketoconazole alone (0%). For erythromycin, the outlier frequencies were: fexofenadine-5.6%; fexofenadine plus erythromycin-26.3%; erythromycin-20%.

Ketoconazole and Fexofenadine: Change from Baseline in Mean and Maximum QTc - Morganroth-Read (Day 0 to Day 7)		
Treatments	Mean QTc ± SE msec	Maxima QTc ± SE msec
Fexo alone	-4.7 ± 2.2 P=0.0465	-3.3 ± 4.4 P=0.4661
Keto alone	-2.0 ± 2.3 P=0.3960	-2.8 ± 4.2 P=0.5194
Fexo plus Keto	3.1 ± 2.3 P=0.1812	8.0 ± 4.0 P=0.0597

Erythromycin and Fexofenadine: Change from Baseline in Mean and Maximum QTc - Morganroth-Read (Day 0 to Day 7)		
Treatments	Mean QTc ± SE msec	Maxima QTc ± SE msec
Fexo alone	-4.6 ± 3.3 P=0.1793	-5.6 ± 4.1 P=0.1849
Erythro alone	2.2 ± 2.4 P=0.3839	2.5 ± 4.4 P=0.5776
Fexo plus Erythro	1.6 ± 2.5 P=0.5285	-2.3 ± 4.1 P=0.5810

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Protocols PJPR0023 and PJPR0024 were large clinical trials in patients with seasonal allergic rhinitis which tested different doses from 20mg BID to 240mg BID for 2 weeks. ECGs were obtained at baseline and at the last visit approximately 1-3 hours after the final dose at the final visit. The sponsor reports that no statistically significant differences were observed for mean change from baseline to final visit compared to placebo for PR, QT, QRS, QTc, or RR intervals.

Protocol PJPR0002 was a double-blind (but sponsor unblinded), parallel, randomized, placebo controlled dose escalating single dose (6 subjects per 11 dose levels- 20mg-800mg and 21 subjects on placebo) study with ECGs collected for 12 hours at baseline and for 72 hours after fexofenadine treatment. Mean QTc change from baseline was negative at all dose levels except 200mg (0.0 ± 4.0 msec), 280mg (1.4 ± 3.9 msec), 360mg (0.1 ± 4.2 msec).

Protocol PJPR0014 was a double-blind, placebo controlled, parallel, safety/tolerance study in normals given placebo or 80mg BID for 3 months. Only 41 subjects enrolled. ECGs were obtained from 2 -14 days predose and 1-3 hours after final dose. Mean QTc change from baseline was -8.8 ± 5.0 msec for placebo and -2.3 ± 3.9 msec for fexofenadine.

ECG Handling Techniques

With concern expressed by the sponsor that ECGs for protocol PJPR0007 may not have been optimal, resulting in bias in reading during the first ECG readings by Dr Morganroth, the Agency asked the sponsor and the ECG reading contractor, RDW, to examine the ECG handling techniques for the major cardiac trials (PJPR0003/ 04/ 07/ 18/ 28/23 /24), particularly PJPR0003 and PJPR0004 which were conducted prior to PJPR0007. The sponsor responded by submission on April 1, 1996, indicating that their audit showed that for protocols PJPR0023/ 24/ 18/ 28, all printed information on the ECGs was covered and that the ECG measurement was performed by the same technician of all ECGs collected for a given patient. Audit for protocols PJPR0003/ 04, were also well blinded since ECG parameters were not printed on the ECG tracing provided to RDW. Additionally, the sponsor points out that machine generated QTc data provided an internal check of the data from RDW which were consistent with the analysis of the machine read data for protocols PJPR0003/ 04/ 07/ 18/ 28, except for the first reading of PJPR0007. Results from the audit of RDW by the Division of Scientific Investigations will need to be examined when available to further support adequacy of ECG handling.

Telemetry Handling

The sponsor was asked on March 6, 1996 to provide how data from telemetry monitoring was handled for protocols PJPR0003/ 04/ 07/ 18/ 28. The sponsor responded by submission dated April 1, 1996 indicating that telemetry data was not explicitly collected on the case report forms (CRFs) since it was used to monitor subjects. If an abnormality was noted to be a treatment emergent event, then this information would have been recorded as an adverse event in the CRF. The sponsor indicates that no ECG related adverse events were reported in PJPR0003/ 04/ 07; and that protocols PJPR0018/ 28 did not require telemetric monitoring.

ECG Compliance

The sponsor was asked on March 6, 1996 to provide compliance with obtaining ECG assessments for the major cardiac trials. The sponsor responded by submission dated April 1, 1996 indicating that compliance was extremely high with the majority of missing ECGs in comparison to the expected number of ECGs per trial accounted for by patients discontinuing study participation early. For

protocols PJPR0003/ 04/ 07/ 18/ 28. eighteen patients were missing ECGs but that their compliance for the number of expected ECGs for the duration of study participation was no less than 97% for any one patient. For protocols PJPR0023/ 24, 99% (1143/1160) of patients had ECGs collected at baseline and postbaseline, with only 17 patients missing either a baseline or postbaseline ECG.

Information From Other Sources

Discussion of Results from the Canadian Health Protection Branch Arrhythmia Study in Rabbits

Introduction

On March 28, 1996 the FDA received a draft copy of a study conducted under the auspices of the Canadian Health Protection Branch, by Dr Gregory Beatch, which examined the proarrhythmic potential of several antihistamines in an animal model. The findings are summarized below. Comments have been requested from the pharmacology/toxicology reviewers from the Division of Cardiorrenal Drug Products and will be included when available.

Methods

Following induction of anesthesia using methohexital, alpha-chloralose and isoflurane, the animals were intubated, artificially ventilated, and surgically prepared by cannulation of the right carotid artery and jugular vein for blood pressure recording and drug infusion, respectively. ECG monitoring was conducted using needle electrodes placed on the limbs for recording standard surface ECGs which were recorded along with blood pressure on a PC-based data acquisition system and stored for off-line analysis. After surgical preparation, the animals were allowed to stabilize, a continuous infusion of methoxamine (20ug/kg/min), an alpha₁-agonist, was initiated 10 minutes before test drug infusions were started. For each test drug, two studies (low and high doses) were conducted using 2 test doses in each study. Test drugs were infused starting with the smaller dose and infused over 30 minutes with ECGs recorded every 5 minutes. Measurements were averaged from at least 3 beats at each time point and QTc calculated according to the Bazett formula. ECGs were monitored for ventricular tachycardia (VT) defined as 5 or more consecutive ventricular premature beats. If VT was detected, blood samples for drug level were obtained and the animal sacrificed. If VT was not noted after 30 minutes, the second infusion of higher drug dose was started and data collection repeated. Diphenhydramine treated rabbits also received a third infusion of the higher dose.

Results

The results of arrhythmia frequency and drug blood level measurements are summarized in the table below. The author reports that high dose fexofenadine induced arrhythmia in 3/10 animals while terfenadine high dose induced only 1/10; but the $\mu\text{mol/kg}$ dose for fexofenadine high dose was 10 fold that of terfenadine. Further, the plasma concentrations measured at the end of the infusions of high dose fexofenadine, $1.3 \pm 0.4 \mu\text{g/ml}$ (1300 ng/ml), are in excess of the concentrations ($C_{\text{max}} = 299\text{ng/ml}$) observed in human subjects taking fexofenadine 60mg BID for one week in Protocol PJPR0004; and comparable to those observed ($C_{\text{max}} = 1518\text{ng/ml}$) in human subjects taking 200mg BID for one week in Protocol PJPR0007 where QTc prolongation was not observed. It is not clear why the author states that the blood levels observed in this study in rabbits were within the range of plasma concentrations encountered during clinical subchronic dose tolerance studies.

Note: BLQ = Below Limit of Quantitation	Arrhythmia Incidence	Infusion Dose	Drug Plasma Levels at Infusion End	Drug Plasma Levels at Time of Arrhythmia (respective dose)
Vehicle	1/7	1-10% DMSO in PEG 200		
Low Terfenadine		4 nmol/kg	BLQ (5ng/ml)	
		40 nmol/kg		
High Terfenadine	1/10	0.1 μ mol/kg	9.3 $\pm$ 0.9 ng/ml	160ng/ml (0.9 μ mol/kg)
		1 μ mol/kg	120 $\pm$ 16 ng/ml	
Low Fexofenadine	1/7	40 nmol/kg	BLQ (100ng/ml)	
		400 nmol/kg		
High Fexofenadine	3/10	1 μ mol/kg	1.3 $\pm$ 0.4 μ g/ml	0.8, 3.2, 2.3 μ g/ml (0.7, 5.2, 1.8 μ mol/kg)
		10 μ mol/kg	12.8 $\pm$ 1.5 μ g/ml	
Low Diphenhydramine	1/7	40 nmol/kg		
		400 nmol/kg		
High Diphenhydramine	1/10	0.1 μ mol/kg 10 μ mol/kg		
Dofetilide	7/10	0.02 μ mol/kg 0.2 μ mol/kg		

With regard to ECG changes the investigator reports that changes at the lower doses for terfenadine, fexofenadine and diphenhydramine generally showed the same pattern as vehicle. QT intervals were prolonged with the infusion of dofetilide and high dose groups but high dose fexofenadine failed to show a significant QTc prolongation compared to baseline. The time course of the effects of the high dose groups on QTc interval were presented in graphic form, reproduced in Attachment B, which shows the effects of fexofenadine at the end of the second infusion remained flat relative to the effects of terfenadine and considerably less than that of dofetilide or diphenhydramine.

Comment

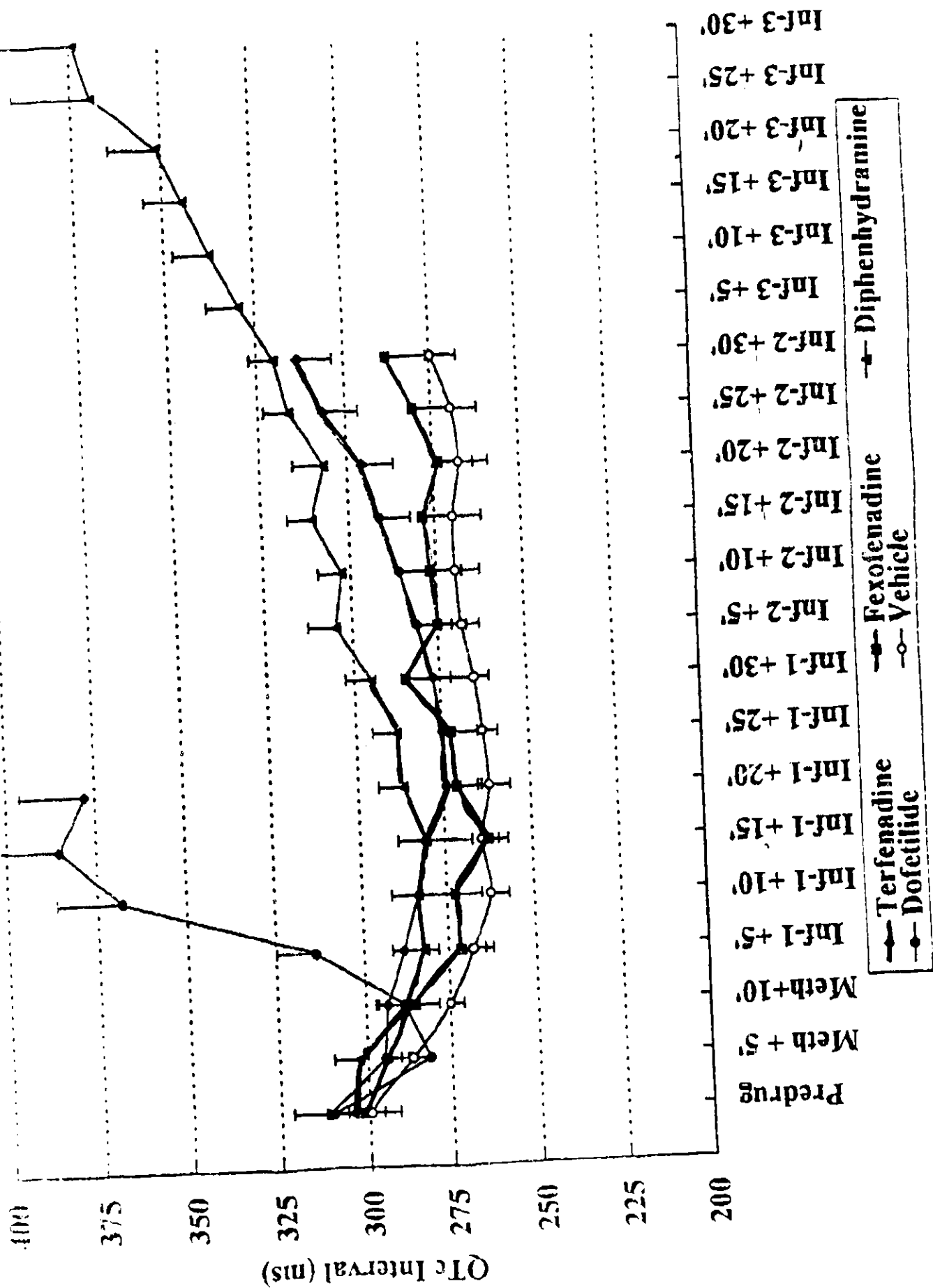
The proarrhythmic potential of terfenadine, fexofenadine, diphenhydramine and dofetilide (a class III antiarrhythmic) was examined in this methoxamine rabbit model of drug induced arrhythmia. The author points out that while the results of this study are not conclusive or directly applicable to clinical situations, they do suggest that fexofenadine may not be completely free of risk. He also points out that this rabbit model has been used to demonstrate that class III antiarrhythmics reproducibly induce polymorphic ventricular tachycardia when infused in combination with methoxamine. He points also that while the model may provide a useful indicator of a drug's proarrhythmic potential, a direct extrapolation to clinical practice should be made with caution. Given limitations of this animal model and the difficulty of correlating clearly an observed effect to the clinical situation, it is difficult to ascribe direct clinical significance to this animal trial, which does not concur with lack of observed QTc prolongation in clinical trials with fexofenadine in doses well above the proposed clinically effective dose.

Determinations

- 1) Of the concerns regarding the safety profile for fexofenadine, paramount is any potential for QTc prolongation and any potential for the induction of torsades de pointes or other ventricular arrhythmias. Available data suggests that at doses administered to humans to 690mg BID for 28 days (PJPR0003) and 400mg BID for 1 week (protocol PJPR0007) it would not be expected to exhibit this phenomenon at the doses necessary for efficacy. The direct comparisons to terfenadine in protocol PJPR0004 support the assertion that fexofenadine would have considerably less propensity.
- 2) The available data support the assertion that fexofenadine in doses of 60mg BID is reasonably safe for administration to patients greater than 12 years of age.
- 3) The pharmacokinetic interactions with ketoconazole and erythromycin will need to be addressed in the labeling; and potential for interactions with other macrolides and antifungal agents will also need to be addressed in the labeling..
- 4) Limited pharmacokinetic and pharmacodynamic data in patients with hepatic impairment has not established fexofenadine's safety profile in this patient population.

ATTACHMENT A

Effects on QTc Interval



ATTACHMENT B

Reference NDA 20-625
fexofenadine hydrochloride capsule

Table 1 Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJPR0009, PJPR0010, PJPR0023, PJPR0024

SYSTEM ORGAN CLASS PREFERRED TERM	MDL 16,455A (BID)							
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=538) N(%)	60 mg (N=673) N(%)	80 mg (N=392) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)	Total (N=2319) N(%)
Total Occurrence Rate: Patients with 1 or more Adverse Event(s)	254 (37.9)	121 (30.8)	177 (32.9)	235 (34.6)	102 (26.0)	88 (30.3)	45 (31.0)	754 (32.5)
CENTR & PERIPH NERVOUS SYSTEM	89 (13.3)	42 (10.7)	58 (10.8)	79 (11.6)	45 (11.5)	26 (9.0)	11 (7.6)	258 (11.0)
HEADACHE	56 (8.3)	29 (7.4)	39 (7.2)	53 (7.8)	26 (6.6)	22 (7.6)	6 (4.1)	172 (7.4)
FATIGUE	6 (0.9)	2 (0.5)	4 (0.7)	9 (1.3)	6 (1.5)	2 (0.7)	5 (3.4)	28 (1.2)
DROWSINESS	6 (0.9)	4 (1.0)	6 (1.1)	9 (1.3)	5 (1.3)	0 (0.0)	0 (0.0)	24 (1.0)
DIZZINESS	9 (1.3)	2 (0.5)	3 (0.6)	4 (0.6)	3 (0.8)	3 (1.0)	0 (0.0)	15 (0.6)
INDOMEN	7 (1.0)	2 (0.5)	2 (0.4)	4 (0.6)	4 (1.0)	2 (0.7)	0 (0.0)	14 (0.6)
PAIN	2 (0.3)	3 (0.8)	2 (0.4)	7 (1.0)	2 (0.5)	0 (0.0)	0 (0.0)	14 (0.6)
DYSPHONIA	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.1)
HYPERKINESIA	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
HYPERTONIA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
HYPOESTHESIA	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)
MIGRAINE	4 (0.6)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
HEADACHE	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.1)
VERTIGO	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
CONCENTRATION IMPAIRED	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
CONFUSION	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
NYCTOPHORIA	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
COORDINATION ABNORMAL	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PAROSMIA	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reference NDA 20-625
 fexofenadine hydrochloride capsule

MDL 16,455A (BID)

SYSTEM OR ORGAN CLASS PREFERRED TERM	Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJPR0009, PJPR0010, PJPR0023, PJPR0024									
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=598) N(%)	60 mg (N=679) N(%)	80 mg (N=392) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)	Total (N=2319) N(%)		
RESPIRATORY SYSTEM	52 (7.7)	26 (6.6)	30 (5.6)	43 (6.3)	16 (4.1)	19 (6.6)	10 (6.9)	144 (6.2)		
THROAT IRRITATION	15 (2.2)	9 (2.3)	10 (1.9)	14 (2.1)	5 (1.3)	6 (2.1)	4 (2.8)	48 (2.1)		
UPPER RESPIRATORY TRACT INFECTION	9 (1.3)	5 (1.3)	7 (1.3)	3 (0.4)	4 (1.0)	3 (1.0)	0 (0.0)	22 (0.9)		
EPISTAXIS	4 (0.6)	2 (0.5)	5 (0.9)	7 (1.0)	2 (0.5)	2 (0.7)	1 (0.7)	19 (0.8)		
SINUSITIS	9 (1.3)	2 (0.5)	0 (0.0)	7 (1.0)	1 (0.3)	1 (0.3)	3 (2.1)	14 (0.6)		
COUGHING	2 (0.3)	3 (0.8)	2 (0.4)	3 (0.4)	1 (0.3)	1 (0.3)	0 (0.0)	10 (0.4)		
BRONCHITIS	3 (0.4)	2 (0.5)	2 (0.4)	2 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	8 (0.3)		
BRONCHOSPASM AGGRAVATED	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.4)	2 (0.5)	2 (0.7)	0 (0.0)	8 (0.3)		
DYSPNEA	2 (0.3)	3 (0.8)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.3)		
BRONCHOSPASM	2 (0.3)	1 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)	1 (0.7)	5 (0.2)		
NASAL IRRITATION	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.1)		
NASAL POLYP	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.1)		
COUGH NON-PRODUCTIVE	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.1)		
WHEEZING	2 (0.3)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)		
UPPER RESPIRATORY CONGESTION	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.1)		
RESPIRATORY DISORDER	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)		
RHINITIS	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		
RHINORRHEA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		

Reference NDA 20-625
 fexofenadine hydrochloride capsule

SYSTEM ORGAN CLASS PREFERRED TERM	MDL 16,455A (BID)										Total (N=2319) N(%)
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=538) N(%)	60 mg (N=679) N(%)	80 mg (N=392) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)				
YAWNING	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
LARYNGITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SNEEZING	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ABNORMAL BREATH SOUNDS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GASTRO- INTESTINAL SYSTEM	37 (5.5)	13 (3.3)	28 (5.2)	38 (5.5)	14 (3.6)	6 (2.1)	4 (2.8)	103 (4.4)			
NAUSEA	10 (1.5)	3 (0.8)	6 (1.5)	11 (1.6)	3 (0.8)	1 (0.3)	1 (0.7)	27 (1.2)			
ERUCTA	1 (0.1)	7 (1.8)	5 (0.9)	4 (0.6)	2 (0.5)	1 (0.3)	1 (0.7)	20 (0.9)			
LETTIPESIA	4 (0.6)	2 (0.5)	3 (0.6)	9 (1.3)	3 (0.8)	1 (0.3)	0 (0.0)	18 (0.8)			
ABDOMINAL PAIN	5 (0.7)	3 (0.8)	6 (1.1)	2 (0.3)	3 (0.8)	2 (0.7)	1 (0.7)	17 (0.7)			
VOMITUS	2 (0.3)	0 (0.0)	4 (0.7)	4 (0.6)	1 (0.3)	1 (0.3)	0 (0.0)	10 (0.4)			
GASTROENTERITIS	3 (0.4)	1 (0.3)	3 (0.6)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.3)			
FLATULENCE	1 (0.1)	0 (0.0)	1 (0.2)	3 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	5 (0.2)			
ANDREXIA	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.1)			
CONSTIPATION	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)			
TOOTH DISORDER	6 (0.9)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)			
ENANTHEMA	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
ENTERITIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
FFCES	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.0)			
DIPCOLORED											
RECTAL DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
STOMATITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.0)			
GASTROESOPHA- GICAL REFLUX	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
GLOSSITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
STOMATITIS ATROPHIC	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			

Reference NDA 20-625
 fexofenadine hydrochloride capsule

MDL 16,455A (BID)

SYSTEM ORGAN CLASS PREFERRED TERM	Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJPR0006, PJPR0010, PJPR0023, PJPR0024									
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=538) N(%)	60 mg (N=679) N(%)	80 mg (N=392) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)	Total (N=2319) N(%)		
INFECTIOUS DISEASE	16 (2.4)	13 (3.3)	17 (3.2)	24 (3.5)	9 (2.3)	9 (3.1)	9 (6.2)	78 (3.4)		
INFECTION VIRAL	10 (1.5)	9 (2.3)	9 (1.7)	17 (2.5)	6 (1.5)	5 (1.7)	7 (4.9)	53 (2.3)		
OTITIS MEDIA	3 (0.4)	2 (0.5)	5 (0.9)	2 (0.3)	2 (0.5)	1 (0.3)	0 (0.0)	12 (0.5)		
INFLUENZA LIKE SYMPTOMS	1 (0.1)	1 (0.3)	1 (0.2)	3 (0.4)	0 (0.0)	2 (0.7)	2 (1.4)	9 (0.4)		
HERPES SIMPLEX	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	5 (0.2)		
CANDIDIASIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)		
HERPES ZOSTER	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		
INFECTIO	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.0)		
INFECTIO FUNGAL	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		
INFECTIO BACTERIAL	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
MUSCULO-SKELETAL SYSTEM	17 (2.5)	17 (4.3)	16 (3.0)	20 (2.9)	6 (1.5)	10 (3.4)	6 (3.4)	73 (3.1)		
BACK PAIN	2 (0.3)	7 (1.8)	4 (0.7)	5 (0.7)	1 (0.3)	1 (0.3)	2 (1.4)	20 (0.9)		
MYALGIA	6 (0.9)	4 (1.0)	3 (0.6)	7 (1.0)	1 (0.3)	3 (1.0)	2 (1.4)	20 (0.9)		
CHEST PAIN	0 (0.0)	1 (0.3)	2 (0.4)	7 (1.0)	0 (0.0)	1 (0.3)	0 (0.0)	11 (0.5)		
ARTHRALGIA	6 (0.9)	5 (1.3)	1 (0.2)	0 (0.0)	2 (0.5)	2 (0.7)	0 (0.0)	10 (0.4)		
ARTHRITIS	2 (0.3)	0 (0.0)	2 (0.4)	1 (0.1)	0 (0.0)	2 (0.7)	0 (0.0)	5 (0.2)		
BONE DISORDER	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.7)	5 (0.2)		
TENDINITIS	1 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)		
ARTRITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)		

Reference NDA 20-625
 fexofenadine hydrochloride capsule

SYSTEM ORGAN CLASS PREFERRED TERM	MDL 16,458A (BID)										Total (N=2319) N(%)
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=538) N(%)	50 mg (N=679) N(%)	80 mg (N=982) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)				
WHITE BLOOD CELLS & RES	12 (1.8)	1 (0.3)	9 (1.7)	13 (1.9)	0 (0.0)	12 (4.1)	7 (4.8)	42 (11.8)			
LEUKOPENIA	6 (0.9)	0 (0.0)	5 (0.9)	6 (0.9)	0 (0.0)	6 (2.1)	2 (1.4)	19 (0.8)			
GRANULOCYTO- PENIA	1 (0.1)	0 (0.0)	1 (0.2)	3 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)	6 (0.3)			
THROMBOCYTOSIS	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.7)	2 (1.4)	6 (0.3)			
LYMPHADENOP- ATHY	2 (0.3)	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)	1 (0.3)	2 (1.4)	6 (0.3)			
LYMPHO- PENIA	1 (0.1)	0 (0.0)	2 (0.4)	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	6 (0.3)			
EOSINOPHILIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.7)	3 (0.1)			
LEUKOCYTOSIS	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.1)			
LYMPHADENOP- ATHY CERVICAL	2 (0.3)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)			
SKIN & APPENDAGES	15 (2.2)	5 (1.3)	6 (1.1)	7 (1.0)	3 (0.8)	6 (2.1)	2 (1.4)	29 (1.3)			
RASH	4 (0.6)	1 (0.3)	2 (0.4)	2 (0.3)	0 (0.0)	2 (0.7)	2 (1.4)	9 (0.4)			
ERYTHRITIS	4 (0.6)	1 (0.3)	2 (0.4)	1 (0.1)	1 (0.3)	1 (0.3)	0 (0.0)	6 (0.3)			
ACNE	3 (0.4)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.7)	0 (0.0)	4 (0.2)			
ALOPECIA	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)			
ECZEMA	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)			
DRY SKIN	4 (0.6)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
ERYTHEMA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)			
HAIR DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)			
ERYTHRITIS GENITAL	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
RASH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.0)			
ERYTHEMATOUS SKIN DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			

Reference NDA 20-825
 ferofenadine hydrochloride capsule

Table 1 Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJP00008, PJP00010, PJP00023, PJP00024

SYSTEM ORGAN CLASS PREFERRED TERM	MDL 16455A (BID)								Total (N=2319) N(%)
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=538) N(%)	60 mg (N=675) N(%)	80 mg (N=593) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)		
URINARY SYSTEM	8 (1.2)	5 (1.3)	4 (0.7)	0 (1.2)	6 (1.5)	3 (1.0)	1 (0.7)	27 (1.2)	
URINARY TRACT INFECTION	5 (0.7)	1 (0.3)	2 (0.4)	6 (0.7)	6 (1.3)	0 (0.0)	0 (0.0)	13 (0.5)	
URINARY FREQUENCY	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	
CYSTITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.7)	3 (0.1)	
ALBUMINURIA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	
NOCTURIA	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)	
HEMATURIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
HEMURIA	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
URINAL TURBIDITY ABNORMAL	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
POLYURIA	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
PSYCHIATRIC	10 (1.5)	4 (1.0)	8 (1.7)	7 (1.0)	4 (1.0)	1 (0.3)	1 (0.7)	26 (1.1)	
AGITATION	3 (0.4)	0 (0.0)	2 (0.4)	1 (0.1)	3 (0.8)	0 (0.0)	0 (0.0)	6 (0.3)	
ALLEGEDLY INCREASED	4 (0.6)	2 (0.5)	2 (0.4)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.3)	
NERVOUSNESS	2 (0.3)	1 (0.3)	3 (0.6)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)	
INSOMNIA	0 (0.0)	1 (0.3)	2 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	
APATHY	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.7)	2 (0.1)	
DEPRESSION	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.1)	
EMOTIONAL LABILITY	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)	
AGGRESSIVE REACTION	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
DREAMING ABNORMAL	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
THINKING ABNORMAL	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	

Reference NDA 20-625
 fexofenadine hydrochloride capsule

Table 1. Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJPR0009, PJPR0010, PJPR0023, PJPR0024

SYSTEM ORGAN CLASS PREFERRED TERM	MDL 16455A (BID)										Total (N=2319) N(%)
	Placebo (N=671) N(%)	20 mg (N=393) N(%)	40 mg (N=538) N(%)	60 mg (N=379) N(%)	80 mg (N=382) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)				
REPRODUCTIVE, FEMALE	6 (0.9)	1 (0.3)	5 (0.9)	12 (1.8)	4 (1.0)	2 (0.7)	1 (0.7)	25 (1.1)			
DYSMENORRHEA	2 (0.3)	0 (0.0)	1 (0.2)	10 (1.5)	4 (1.0)	2 (0.7)	0 (0.0)	17 (0.7)			
MENORRHAGIA	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)			
MENSTRUAL DISORDER	1 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	3 (0.1)			
IRREGULAR MENSTRUAL BLEEDING	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
PREMENSTRUAL SYMPTOMS	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)			
PREGNANCY ECTOPIC	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
VAGINITIS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
LIVER & BILIARY SYSTEM	8 (1.2)	3 (0.6)	3 (0.6)	10 (1.5)	4 (1.0)	1 (0.3)	2 (1.4)	23 (1.0)			
SGPT INCREASED	4 (0.6)	1 (0.3)	2 (0.4)	7 (1.0)	4 (1.0)	1 (0.3)	1 (0.7)	16 (0.7)			
SGOT INCREASED	2 (0.3)	2 (0.5)	2 (0.4)	2 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	8 (0.3)			
BILIRUBINEMIA	3 (0.4)	1 (0.3)	0 (0.0)	2 (0.3)	1 (0.3)	0 (0.0)	1 (0.7)	5 (0.2)			
AUTONOMIC NERVOUS SYSTEM	6 (0.9)	4 (1.0)	7 (1.3)	6 (0.9)	3 (0.8)	1 (0.3)	0 (0.0)	21 (0.9)			
DRY MOUTH	6 (0.9)	3 (0.8)	5 (0.9)	5 (0.7)	2 (0.5)	1 (0.3)	0 (0.0)	16 (0.7)			
DRYNESS OF MUCOUS MEMBRANES	0 (0.0)	1 (0.3)	2 (0.4)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	5 (0.2)			
VISION	2 (0.3)	3 (0.8)	1 (0.2)	5 (0.7)	4 (1.0)	3 (1.0)	0 (0.0)	16 (0.7)			
CONJUNCTIVITIS	2 (0.3)	1 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	4 (0.2)			
VISION ABNORMAL	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.2)			
EYE PAIN	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.5)	0 (0.0)	0 (0.0)	3 (0.1)			
EYE ABNORMALITY	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)			

Reference NDA 20-625
 lexofenadine hydrochloride capsule

Table 1 Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJPR0009, PajPR0023, PJPR0024

SYSTEM ORGAN CLASS PREFERRED TERM	MDL 16,455A (BID)									
	Placebo (N=671) N(%)	20 mg (N=993) N(%)	40 mg (N=538) N(%)	60 mg (N=679) N(%)	80 mg (N=392) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)	Total (N=2319) N(%)		
CONJUNCTIVAL HEMORRHAGE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.0)		
DRY EYES	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		
SCLERITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.0)		
HEARING & VESTIBULAR	6 (0.9)	0 (0.0)	5 (0.9)	8 (0.9)	0 (0.0)	0 (0.0)	2 (1.4)	13 (0.6)		
EARACHE	3 (0.4)	0 (0.0)	2 (0.4)	5 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	8 (0.3)		
EAR DISORDER NOS	1 (0.1)	0 (0.0)	2 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.7)	4 (0.2)		
TINNITUS	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		
HEART RATE & RHYTHM	1 (0.1)	0 (0.0)	5 (0.9)	3 (0.4)	2 (0.5)	1 (0.3)	0 (0.0)	11 (0.5)		
TACHYCARDIA	1 (0.1)	0 (0.0)	4 (0.7)	2 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	7 (0.3)		
PALPITATION	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.1)		
BRADYCARDIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)		
EXTRASYSTOLES	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		
OTHER	5 (0.7)	1 (0.3)	1 (0.2)	6 (0.9)	0 (0.0)	2 (0.7)	0 (0.0)	10 (0.4)		
INJURY ACCIDENTAL	5 (0.7)	1 (0.3)	1 (0.2)	6 (0.9)	0 (0.0)	2 (0.7)	0 (0.0)	10 (0.4)		
BODY AS A WHOLE	1 (0.1)	3 (0.8)	1 (0.2)	2 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	8 (0.3)		
EDEMA GENERALIZED	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)		
EDEMA PERIPHERAL	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)		
MAlaise	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)		
EDEMA DEPENDENT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.0)		
EDEMA FACE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		

Reference NDA 20-625
 dexofenadine hydrochloride capsule

Table 1 Incidence of All Adverse Events by Dose for Controlled Clinical SAR Studies: PJPR0008, PJPR0010, PJPR0023, PJPR0024

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=671) N(%)	MDL 16,456A (BID)							Total (N=2319) N(%)
		20 mg (N=395) N(%)	40 mg (N=538) N(%)	60 mg (N=679) N(%)	80 mg (N=392) N(%)	120 mg (N=290) N(%)	240 mg (N=145) N(%)		
RED BLOOD CELL	4 (0.6)	1 (0.3)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	6 (0.3)	
ANEMIA	3 (0.4)	1 (0.3)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	5 (0.2)	
POLYCYTHEMIA	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.0)	
ALLERGY & IMMUNOLOGY	3 (0.4)	1 (0.3)	2 (0.4)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	5 (0.2)	
URTICARIA	3 (0.4)	1 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	
ALLERGIC REACTION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)	
ANGIOEDEMA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)	
NEOPLASMS	0 (0.0)	1 (0.3)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	
NEOPLASM NOS	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	
LIPOMA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
PLATELET, BLEEDING & CLOTTING	1 (0.1)	0 (0.0)	2 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	
THROMBOCYTOSIS	1 (0.1)	0 (0.0)	2 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	
THROMBOCYTO- PENIA	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
SPECIAL SENSES, OTHER	2 (0.3)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.1)	
TASTE PERVERSION	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	
PAROSMIA	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
TASTE LOSS	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
CARDIOVASCULAR, GENERAL	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	
HYPERTENSION	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	
ECG ABNORMAL SPECIFIC	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Reviewed: **Protocol PJPR0010** - conducted from March 17 to July 19, 1994

Title: "Placebo-Controlled, Double-Blind, Randomized, Parallel Study, Comparing the Safety and Efficacy of Four Dosage Strengths of MDL-16,455A in the Treatment of Spring Allergies--II."

Objectives: "The primary objective of this trial was to determine the safety and efficacy profile of MDL-16,455A at 20 mg BID, 40 mg BID, 60 mg BID, and 80 mg BID as compared to placebo in the treatment of seasonal allergic rhinitis (SAR)."

Study Design: The study was a multi-center (16 centers), placebo-controlled, double-blind, randomized, parallel design trial in patients (ages 12 -65 years) with spring SAR. It consisted of a 2-day single-blind placebo lead-in period, followed by a 2-week double-blind treatment period. There were 3 or 4 Visits - Screening (which could be combined with Entry), Entry, Interim, Final or Early Discontinuation. It was estimated by the sponsor that 960 procedurally correct patients would be needed to achieve the study objectives.

Following screening, patients meeting the entry criteria were randomized to study treatment. To be randomized subjects were required to have two individual allergy symptoms except nasal congestion as rated by the investigator as moderate or severe but not very severe. Study treatments were to be taken at approximately 7PM and 7AM. An Interim Visit was scheduled 8-10 days after the Entry Visit and the Final Visit was scheduled 6-7 days after the Interim Visit.

The efficacy assessments were 1) patient evaluations of individual allergy symptoms recorded reflectively for the previous 12 hours in daily diaries twice daily (noon and bedtime) throughout the study including the final visit; 2) patient evaluation of individual symptoms recorded reflectively for the previous 12 hours in predose diaries on the morning of days of the Interim and Final Visits; 3) physician evaluations of individual allergy symptoms at the Entry Visit and Final Visit, 4) physician evaluation of the overall effectiveness of study medication made at the Final Visit, and 5) the patient's willingness to take the study medication again, asked at the Final Visit. The period of time over which assessments were to be conducted by the investigator at Entry and Final Visits, and by the patient at the Final Visit was not defined in the protocol; but the sponsor states that at the investigator meeting it was agreed that it would be acceptable to assess symptom severity from the time the patient awakened on the day of the visit in question until the time of assessment.

The severity of the following individual allergy symptoms were rated - 1) nasal congestion, 2) sneezing, 3) rhinorrhea, 4) itchy nose, palate, and/or throat, 5) itchy, watery, red eyes, according to the following 5-point scale:

0 = Absent - Symptom not present

1 = Mild - Symptom is present but is not annoying or troublesome

2 = Moderate - Symptom is frequently troublesome but does not interfere with either normal daily activity or sleep

3 = Severe - Symptom is sufficiently troublesome to interfere with normal daily activity or sleep

4 = Very Severe:

---when evaluated by the physician, the definition was: Symptom is so severe as to warrant the use of agents other than antihistamines (eg, corticosteroids);

---when evaluated by the patient, the definition was: Symptom is so severe as to warrant an immediate visit to a physician.

At the Final Visit, the physician's overall effectiveness rating was performed using the following scale:

0 = Complete Relief - Symptoms not present

1 = Marked Relief - Symptoms are vastly improved and, although still present, are scarcely troublesome

2 = Moderate Relief - Symptoms are noticeably improved but are still present and may be troublesome

3 = Slight Relief - Symptoms are present and only minimal improvement has been obtained

4 = No Relief/Worse - Patient's symptoms are unchanged or worse.

Study Treatments:

Treatment	Dose
A) Placebo Lead-In	4-20 mg placebo capsules
B) Double-Blind:	
Placebo	4-20 mg placebo capsules
MDL 16,455A 20 mg BID	1-20 mg MDL 16,455A capsule 3-20 mg placebo capsules
MDL 16,455A 40 mg BID	2-20 mg MDL 16,455A capsules 2-20 mg placebo capsules
MDL 16,455A 60 mg BID	3-20 mg MDL 16,455A capsules 1-20 mg placebo capsule
MDL 16,455A 80 mg BID	4-20 mg MDL 16,455A capsules

At study entry qualifying subjects were randomized to double-blind study treatment. At entry each subject was dispensed single-blind placebo treatment (screw cap bottle) and the first week of double-blind treatment (blister pack cards). At entry each subject was administered the first dose of placebo by the investigator and instructed to take the next placebo dose at 7PM that night and the two additional placebo doses at 7AM and 7PM the following day. Although both single-blind and double-blind treatments were dispensed at the entry visit, the subjects were also instructed to begin double-blind treatment after completing the placebo treatment.

The lot numbers of the study medication are presented below.

<i>Study Medication</i>	<i>Lot Numbers</i>
MDL 16.455A 20 mg capsule	RA 9404 RN 9323
Placebo 20 mg capsule	RN 9321

Protocol Amendments

Four amendments were written during the course of the study. These amendments basically provided for a) the addition of symptom assessments prior to the AM dose on the days of the Interim Visit and the Final Visit, "trough symptom assessments" b) removal of the study objective to "ascertain the minimal effective dose", c) changing the date of the interim analysis, d) modification of statistical methods for secondary parameters using Mantel-Haenzel statistics with modified ridit scores, e) redefining the Protocol Correct subjects at time of disposition, and f) adding the collection of blood samples at selected sites for pharmacokinetic measurements.

Subject Inclusion Criteria

- Patients were to be between 12 and 65 years of age, inclusive.
 - Females, who were not pregnant, not lactating, nor likely to become pregnant, and males could participate.
 - History of seasonal allergic rhinitis during the spring season for the previous 2 years. Trees and/or grasses must have been the allergens associated with the patient's history of seasonal allergic rhinitis. The trees and/or grasses which produced a positive epicutaneous skin test for the patient must have been common to the geographic area in which the patient was studied.
 - Positive epicutaneous skin test wheal to trees and/or grasses with a diameter at least 5 mm greater than diluent within 15 minutes, at the Screen Visit or during the previous 15-month period. The skin test must have been performed at the participating investigative site and results reported in the patient's medical record.
 - History of positive response to antihistamines for symptoms of seasonal allergic rhinitis.
 - Two or more of the following symptoms rated as moderate or severe at the Entry Visit:
 - sneezing
 - rhinorrhea
 - itchy nose, palate and/or throat
 - itchy, watery, red eyes.
- (Nasal congestion was not one of the symptoms that qualified a patient for the study, but no symptom, including nasal congestion, could be rated very severe.)
- At the Screen Visit written informed consent was obtained from each patient and a parent or legal guardian of each minor patient admitted into the study.

Subject Exclusion Criteria

- Patients with any symptom rated "very severe" (ie, so severe as to warrant the use of agents other than antihistamines, eg, corticosteroids) on the day of the Entry Visit.
- Females who were pregnant, lactating, or were likely to become pregnant during the study period. Females of child-bearing potential were expected to use an acceptable contraceptive regimen throughout the study.
Females in certain categories (eg, adolescent, celibacy, husband vasectomy, etc) were allowed to be admitted to the study at the discretion of the investigator and sponsor on a case-by-case basis which was to be documented in a waiver letter from the sponsor.
- Upper respiratory tract infection within 30 days prior to the Entry Visit.
- Evidence of sinusitis within 30 days prior to the Entry Visit.
- Any of the following underlying conditions known or suspected to be present:
 - malnutrition
 - blood dyscrasia
 - renal or hepatic insufficiency
 - chronic infection
 - drug abuse or alcoholism
 - malignancy
 - malabsorption.
- Clinically significant hepatic, neurologic, endocrine, or other major systemic disease making implementation/interpretation of the protocol results difficult.
- Chronic hypokalemia or potassium less than 3.4 mEq/L or chronic hypomagnesemia or magnesium less than 1.2 mEq/L.
- Any disease state or surgery known to affect the gastrointestinal absorption of drugs.
- Mental capacity limited to the extent that the patient could not provide legal consent or information regarding side effects/tolerance of drug.
- Desensitization therapy (immunotherapy) in changing doses within 60 days prior to the Entry Visit. (Patients on maintenance immunotherapy were acceptable.)
- Antihistamines (including all H₁ and H₂-antagonists), oral decongestants, or decongestant nasal sprays or drops used within 48 hours prior to the Entry Visit (including all OTC preparations).
- Hypersensitivity to terfenadine.
- Systemic oral corticosteroids used within 30 days prior to the Entry Visit.

- Systemic injectable corticosteroids used within 90 days prior to the Entry Visit.
- Systemic antibiotics for respiratory infections within 30 days prior to the Entry Visit.
- Topical/inhaled corticosteroids, nedocromil or topical cromolyn sodium used within 14 days prior to the Entry Visit.
- Use of hydroxyzine within 72 hours prior to the Entry Visit.
- Use of systemic ketoconazole, fluconazole or itraconazole within 90 days prior to the Entry Visit.
- Use of loratadine (Claritin®) within 7 days prior to the Entry Visit.
- Use of systemic macrolide antibiotics including, but not limited to, erythromycin, troleandomycin, azithromycin, and clarithromycin within 7 days prior to the Entry Visit.
- Use of astemizole within 90 days prior to the Entry Visit.
- Use of an investigational drug within 30 days prior to the Entry Visit.

Concomitant Medications

Patients could not be entered into this trial if they were unable to discontinue use (whether topical or systemic) of the following medications. Any other medications considered important for the patient's welfare could be continued.

- Corticosteroids.
- Antihistamines other than study medication (H₁-antagonists).
- All H₂-antagonists (cimetidine, ranitidine, etc).
- Any substance having antihistaminic properties (eg, phenothiazines, tricyclic antidepressants, benzodiazepines, etc).
- Prozac® or other antidepressants.
- Anticholinergic agents, sedatives, or hypnotics.
- Alpha adrenergic drugs (eg, decongestants or drugs which produce adrenergic activity).
- Reserpine and reserpine combined products (eg, Ser-Ap-Es®, Hydropres®, etc).
- Antibiotics (systemic) used for respiratory infections.
- Cromolyn sodium or nedocromil.
- Systemic ketoconazole, fluconazole, or itraconazole.
- Systemic macrolide antibiotics such as erythromycin, troleandomycin, azithromycin, or clarithromycin.

Efficacy Parameters**Primary Parameter**

The primary efficacy analysis variable was change from baseline in the Bedtime Total Symptom Score (TSS). The Bedtime TSS was computed by summing the Bedtime individual symptom scores (excluding nasal congestion) as recorded on the patient's symptom diary card. If a patient was missing any of the Bedtime individual symptoms used in calculating Bedtime TSS, then that patient's Bedtime TSS evaluation was also treated as missing.

Secondary Parameters

1. **Secondary Evaluations of Bedtime TSS**
 - a. Changes in Daily Bedtime TSS (average of the two Bedtime TSS observations during the placebo lead-in period vs Bedtime TSS each day during the double-blind period)
 - b. Changes in Bedtime Individual Symptom Assessments (average of Bedtime evaluations for the double-blind dosing period vs average of the two Bedtime evaluations during the placebo lead-in). Individual symptoms are nasal congestion; sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes.
2. **Additional Secondary Evaluations**
 - a. Change in Noon TSS (average of Noon TSS during the double-blind dosing period) from baseline Noon TSS (Noon TSS observation during the placebo lead-in period)
 - b. Change in Average Morning Predose TSS (average of the Interim Visit TSS and the Final Visit predose TSS) from baseline TSS (Noon TSS during the placebo lead-in period)
 - c. Changes in Physician's Assessment of Individual Symptoms and TSS (Entry Visit vs Final Visit)
 - d. Physician's Evaluation of Overall Effectiveness (Final Visit assessment)
 - e. Patient's willingness to take study medication again.

Safety Parameters

Safety was evaluated by adverse event reporting, physical examinations, and clinical laboratory tests.

Tree and Grass Pollen Counts

During the study, pollen counts for tree and/or grass allergen(s) were recorded on a Follen Count Form.

Statistical Methods

The sponsor indicates that the primary efficacy variable was analyzed by an analysis of covariance (ANCOVA) model which contains baseline TSS as a covariate and terms for investigative site, treatment, investigative site by treatment interaction, and baseline TSS by treatment interaction. This model was also used to evaluate the physician's assessment of TSS and individual symptoms and the patient's bedtime individual symptom assessment. Physician's overall evaluation of effectiveness and the patient's willingness to take study medication again were analyzed using Mantel-Haenzel statistics with modified ridit scores and investigative site by treatment interaction. Methods similar to those proposed for the primary efficacy variable were used to analyze remaining secondary assessments of patients symptoms.

The investigative site by treatment and baseline TSS by treatment interactions were included in the model since these terms were noted to be statistically significant $p=0.0884$ and $p=0.0369$, respectively. The sponsor also reports that because a site by treatment interaction was noted, a "by site" analysis of the effect of fexofenadine was conducted and that a greater effect of fexofenadine was noted in 13 of the investigative sites showing that the results were not driven by only a few sites. Sites 31, 37, and 40 had a greater placebo effect.

The sponsor indicates that missing values were handled as follows. With the exception of daily bedtime TSS, all variables used the average of the available data. If a patient had no available baseline and/or postbaseline data for an analysis (primary or secondary), then that patient was excluded from the Intent-to-Treat analysis for that variable.

For change in daily bedtime, the analysis was conducted without treatment by baseline and treatment by site interaction because dropouts reduced the sample size to estimate all interaction terms. For daily TSS, missing data was handled in two ways. Patients were excluded from all daily analyses for which they had missing daily evaluations or, as an additional analysis, missing daily evaluations were filled with the most previously observed daily evaluation (ie, data was imputed forward for missing daily evaluations).

RESULTS

Results - Patient Accounting

The sponsor reports the following patient tally:

Screened ----- 1203
 Screening failures ----- 182
 Randomized ----- 1021
 Placebo Lead-in Discontinuation - 9
 Exposed To Double-Blind Med--- 1012
 Double-Blind Discontinuation ---- 70
 Completed ----- 942

The sponsor prepared the 4 tables reproduced below to summarize patient disposition and distribution of patients exposed to double-blind study medication a) across treatment groups and investigative sites, b) who had major protocol violations, and c) who discontinued early. Eight patients were lost to follow-up after the Entry Visit and were not safety evaluable (had no postbaseline adverse event information) and 995 were identified as Intent-to-Treat (patients with baseline and postbaseline bedtime symptom assessments).

Table 8-297. Summary of Patient Disposition					
<i>Treatment (BID)</i>	<i>Randomized N(%)</i>	<i>Exposed N(%)</i>	<i>Safety Evaluable N(%)</i>	<i>Intent-to-Treat N(%)</i>	<i>Protocol Correct N(%)</i>
Placebo	204 (20%)	202 (20%)	200 (20%)	198 (20%)	191 (20%)
20 mg MDL 16.455A	203 (20%)	199 (20%)	198 (20%)	197 (20%)	185 (19%)
40 mg MDL 16.455A	204 (20%)	203 (20%)	201 (20%)	201 (20%)	196 (21%)
60 mg MDL 16.455A	205 (20%)	205 (20%)	205 (20%)	203 (20%)	190 (20%)
80 mg MDL 16.455A	205 (20%)	203 (20%)	200 (20%)	196 (20%)	187 (20%)
Total	1021	1012	1004	995	949
<i>Supporting Data:</i>					<i>Page</i>
<i>Appendix F1. Summary 2: Summary of Patient Disposition by Treatment</i>					<i>S8-V1.205-P40</i>
<i>Appendix F2. Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group</i>					<i>S8-V1.205-P59</i>

Table 8-296. Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group						
<i>Investigative Site</i>	<i>Placebo BID</i>	<i>MDL 16.455A (BID)</i>				<i>Total</i>
		<i>20 mg</i>	<i>40 mg</i>	<i>60 mg</i>	<i>80 mg</i>	
030	12	12	12	12	12	60
031	12	12	12	12	12	60
032	12	12	12	12	12	60
033	12	12	12	12	12	60
034	13	12	14	14	14	67
035	12	11	12	12	12	59
036	13	13	13	13	13	65
037	12	12	11	12	12	59
038	14	14	14	14	14	70
039	14	14	14	14	14	70
040	15	16	15	16	15	77
041	14	14	14	14	14	70
042	11	10	12	12	12	57
043	12	12	12	12	12	60
044	12	11	12	12	12	59
045	12	12	12	12	11	59
Total	202	199	203	205	203	1012
<i>Supporting Data:</i>						<i>Page</i>
<i>Appendix F1, Summary 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group</i>						<i>S8-V1.205-P36</i>
<i>Appendix F2, Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group</i>						<i>S0-V1.205-P59</i>

Table 8-298. Summary of Major Protocol Violations in Patients Exposed to Double-Blind Study Medication

Major Protocol Violation	Placebo BID (N=202)	MDL 16,455A (BID)					Total (N=1012)
		20 mg (N=199)	40 mg (N=203)	60 mg (N=205)	80 mg (N=203)	Total Active (N=810)	
Failure to Meet Entrance Criteria	2 (1%)	6 (3%)	2 (1%)	2 (1%)	2 (1%)	12 (1%)	14 (1%)
Use of Prohibited Medications Prior to or During Study	6 (3%)	6 (3%)	2 (1%)	5 (2%)	4 (2%)	17 (2%)	23 (2%)
Missing Efficacy Data (Primary Measure)	4 (2%)	2 (1%)	3 (1%)	3 (1%)	7 (3%)	15 (2%)	19 (2%)
Non-Compliance with Study Medication	6 (3%)	4 (2%)	4 (2%)	5 (2%)	8 (4%)	21 (3%)	27 (3%)
Study Medication not Taken in the Proper Order	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	2 (0%)	2 (0%)
Total Patients	11 (5%)	14 (7%)	7 (3%)	15 (7%)	16 (8%)	52 (6%)	63 (6%)

Patients may have had more than one major protocol violation, therefore, patient counts for Major Violations may not equal the total number of patients having major protocol violations (Total Patients)

Supporting Data Page

Appendix F1, Summary 3 Summary of Major Protocol Violations So-V1.205-P43

Appendix F1, Summary 7 Disposition Criteria So-V1.205-P53

Appendix F2, Listing 2 Major Protocol Violations So-V1.205-P81

Table 8-299. Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication

Primary Reason	Placebo (N=202)	MDL 16,455A (BID)					Total (N=1012)
		20 mg (N=199)	40 mg (N=203)	60 mg (N=205)	80 mg (N=203)	Total Active (N=810)	
Adverse Event	8 (4%)	5 (3%)	2 (1%)	7 (3%)	5 (2%)	19 (2%)	27 (3%)
Elected to Discontinue	0 (0%)	1 (1%)	1 (0%)	1 (0%)	2 (1%)	5 (1%)	5 (0%)
Failed to Return to Study Site for a Scheduled Visit	3 (1%)	2 (1%)	2 (1%)	2 (1%)	5 (2%)	11 (1%)	14 (1%)
Abnormal Baseline Laboratory Value	1 (0%)	2 (1%)	1 (0%)	1 (0%)	1 (0%)	5 (1%)	6 (1%)
Treatment Failure	6 (3%)	2 (1%)	2 (1%)	1 (0%)	3 (1%)	8 (1%)	14 (1%)
Other	0 (0%)	1 (1%)	1 (0%)	1 (0%)	1 (0%)	4 (0%)	4 (0%)
Total Patients	18 (9%)	13 (7%)	9 (4%)	13 (6%)	17 (8%)	52 (6%)	70 (7%)

Patients may have had more than one reason for discontinuing the study, however, only the primary reason is summarized

Supporting Data Page

Appendix F1, Summary 4 Summary of Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication So-V1.205-P46

Appendix F2, Listing 4 Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication So-V1.205-P135

Reviewer Comments Regarding Patient Accounting

The distribution of patients exposed to double-blind treatments appears similar across treatments and across treatments within investigative sites. The frequency of major protocol violations and early discontinuations appears similar across treatment groups. Inspection of the randomization schedule does not reveal any obvious lack of randomization.

its - Subject Demographics

Below is the sponsor's table of baseline demographic characteristics for the Intent-to-Treat dataset.

Baseline Characteristics	Placebo BID (n=198)	MDL 16,455A (BID)				Total (n=995)	P value*
		20 mg (n=197)	40 mg (n=201)	60 mg (n=203)	80 mg (n=196)		
Gender							
Male % (N)	45(90)	48(94)	47(94)	46(93)	41(81)	45(452)	.7536
Female % (N)	55(108)	52(103)	53(107)	54(110)	59(115)	55(543)	
Age (years)							
Mean ± SD	34±12	33±12	32±12	33±12	34±12	33±12	.3566
Range	12-68	12-67	12-63	12-65	12-63	12-68	
Race							
Caucasian % (N)	82(162)	77(151)	80(161)	79(160)	83(162)	80(796)	.9197
Black % (N)	6(12)	9(17)	8(17)	7(14)	7(13)	7(73)	
Asian % (N)	4(8)	6(11)	3(7)	6(13)	5(10)	5(49)	
Other % (N)	8(16)	9(18)	8(16)	8(16)	6(11)	8(77)	
Weight (kg)							
Mean ± SD	72±16	73±16	73±16	73±17	72±17	73±17	.9206
Range	38-130	35-151	36-114	44-133	37-144	35-151	
Height (cm)							
Mean ± SD	169±10	170±10	171±10	170±10	169±10	170±10	.6065
Range	127-196	150-201	145-194	146-196	145-198	127-201	
Years Since First Episode Occurred							
Mean ± SD	17±12	18±11	18±12	18±11	18±11	18±11	.9504
Range	3-62	2-58	2-62	2-56	2-50	2-62	
Successive Years of Spring Allergy							
Mean ± SD	17±11	17±11	17±12	17±11	17±11	17±11	.9575
Range	2-62	2-58	2-62	2-56	2-46	2-62	
* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.							
Supporting Data:						Page	
Appendix G2, Listing 1: Patient Demographics and Medical History						So-V1.205-P380	

Reviewer Comments Regarding Demographics

Although there are no statistically significant differences for any of the baseline demographic variables displayed in the sponsor's table above, there is a slight preponderance of female subjects and a marked preponderance of Caucasians; but there is no apparent imbalance across study treatments.

In addition to this examination of baseline demographics, we requested the sponsor to submit an analysis of baseline demographics by investigational site. The sponsor provide this information by a submission to the NDA dated December 13, 1995. Below is a table displaying the ranges across study sites for baseline demographics. Although it is difficult from this information to conclude what influence any one center or group of centers may have contributed to the overall study results it is helpful to observe that extreme differences in baseline demographics other than race are not apparent. However it is interesting to note that site 31 which had the highest baseline total symptom scores also had the highest proportion of Asian subjects and also is one of the 3 sites which did not show a response to active study treatment.

Range of Baseline Demographics Across Study Sites - Intent-To-Treat						
PJPR0010	Age	Gender %Male	Race			Total Symptom Scores
			Asian	Black	Caucasian	
High (site)	39 ± 14 (45)	56.9% (45)	33.3% (31)	20.0% (43)	97.1% (38,41)	6.88 ± 2.73 (31)
Low (site)	27 ± 12 (30)	28.1% (35)	0.0% (30,35,40, 43,44)	0.0% (31,34)	62.3% (42)	4.31 ± 2.67 (45)

Results - Baseline Symptom Assessments

Below are the sponsor's tables of baseline symptom assessments.

Table 5-301 Baseline Bedtime Symptom Assessments (Intent-to-Treat)							
Baseline Symptoms	Placebo BID (n=198)	MDL 16-455A (BID)				Total (n=995)	P value*
		20 mg (n=197)	40 mg (n=201)	60 mg (n=203)	80 mg (n=196)		
Nasal Congestion							
Mean ±SD	1.7±0.8	1.8±0.8	1.7±0.9	1.7±0.9	1.8±0.9	1.8±0.9	4864
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-3.5	0.0-4.0	
Sneezing							
Mean ±SD	1.2±0.9	1.3±0.8	1.2±0.9	1.3±0.9	1.2±0.9	1.3±0.9	5966
Range	0.0-3.5	0.0-3.5	0.0-3.5	0.0-3.0	0.0-3.0	0.0-3.5	
Rhinorrhea							
Mean ±SD	1.5±0.9	1.5±0.9	1.5±0.9	1.4±0.9	1.5±1.0	1.5±0.9	9176
Range	0.0-4.0	0.0-3.5	0.0-3.5	0.0-3.5	0.0-3.0	0.0-4.0	
Itchy Nose/Palate and/or Throat							
Mean ±SD	1.4±0.9	1.5±0.9	1.4±0.9	1.5±0.9	1.5±0.8	1.5±0.9	5885
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-3.5	0.0-4.0	
Itchy/Watery Red Eyes							
Mean ±SD	1.4±0.9	1.6±0.9	1.4±1.0	1.5±1.0	1.5±1.0	1.5±1.0	2790
Range	0.0-4.0	0.0-4.0	0.0-3.5	0.0-4.0	0.0-3.5	0.0-4.0	
TSS at Bedtime (Excluding Nasal Congestion)							
Mean ±SD	5.5±2.8	5.9±2.8	5.6±3.0	5.7±2.7	5.7±2.8	5.7±2.9	6255
Range	0.0-15	0.0-15	0.0-15	0.5-14	0.0-14	0.0-15	
* P value from Kruskal-Wallis test							
Supporting Data						Page	
Appendix E3, Listing 1 Kruskal-Wallis Test for Baseline Bedtime Symptom Assessments (ITT)						So-V1 204-P47	
Appendix 12, Listing 4 Average PM Diary Listing						So-V1 208-P241	

Table 5-302 Baseline Noon Symptom Assessments (Intent-to-Treat)							
Baseline Symptoms	Placebo BID (n=198)	MDL 16-455A (BID)				Total (n=995)	P value*
		20 mg (n=197)	40 mg (n=201)	60 mg (n=203)	80 mg (n=196)		
Nasal Congestion							
Mean ±SD	1.8±1.0	1.8±0.9	1.7±1.0	1.8±1.0	1.8±0.9	1.8±1.0	6273
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	
Sneezing							
Mean ±SD	1.3±1.1	1.5±1.0	1.3±1.0	1.4±1.0	1.3±1.0	1.4±1.0	3626
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	
Rhinorrhea							
Mean ±SD	1.5±1.0	1.5±1.0	1.6±1.0	1.5±1.0	1.5±1.1	1.5±1.0	8990
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	
Itchy Nose/Palate and/or Throat							
Mean ±SD	1.4±1.0	1.5±1.0	1.4±1.0	1.6±1.0	1.5±0.9	1.5±1.0	4336
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	
Itchy/Watery Red Eyes							
Mean ±SD	1.5±1.0	1.5±1.0	1.4±1.1	1.5±1.0	1.5±1.0	1.5±1.0	7932
Range	0.0-4.0	0.0-3.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	
TSS at Noon (Excluding Nasal Congestion)							
Mean ±SD	5.7±3.3	6.0±3.2	5.7±3.1	6.0±3.0	5.8±3.2	5.9±3.1	4815
Range	0.0-16.0	0.0-14.0	0.0-14.0	0.0-13.0	0.0-15.0	0.0-16.0	
* P value from Kruskal-Wallis test							
Supporting Data						Page	
Appendix E3, Listing 2 Kruskal-Wallis Test for Baseline Noon Assessments (ITT)						So-V1 204-P65	
Appendix 12, Listing 3 Average AM Diary Listing						So-V1 208-P169	

Table 8-303 Baseline Physician's Rating of Symptoms (Intent-to-Treat)							
Baseline Symptoms	Placebo BID (n=198)	MOL 16 455A (BID)				Total Active (n=995)	P value*
		20 mg (n=197)	40 mg (n=201)	60 mg (n=203)	80 mg (n=196)		
Nasal Congestion							
Mean ±SD	2.0±0.8	2.1±0.8	2.0±0.8	2.0±0.8	2.1±0.8	2.1±0.8	5038
Range	0.0-3.0	0.0-4.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-4.0	
Sneezing							
Mean ±SD	1.8±0.8	1.8±0.7	1.9±0.8	1.9±0.8	1.8±0.7	1.8±0.8	8272
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea							
Mean ±SD	2.1±0.7	2.0±0.7	2.1±0.8	2.1±0.8	2.2±0.7	2.1±0.7	1715
Range	0.0-3.0	0.0-3.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-4.0	
Itchy Nose, Palate and/or Throat							
Mean ±SD	1.9±0.9	2.0±0.8	1.9±0.8	2.0±0.8	2.0±0.8	2.0±0.8	7895
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery Red Eyes							
Mean ±SD	2.0±0.8	1.9±0.8	1.9±0.8	2.0±0.9	1.9±0.9	2.0±0.8	5489
Range	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-4.0	
TSS (Excluding Nasal Congestion)							
Mean ±SD	7.8±2.0	7.7±1.7	7.8±1.9	8.0±1.9	7.9±1.8	7.9±1.9	6002
Range	4.0-12.0	4.0-12.0	4.0-12.0	4.0-12.0	4.0-12.0	4.0-12.0	
* P value from Kruskal-Wallis test							
Supporting Data						Page	
Appendix E3 Listing 3 Kruskal-Wallis Test for Baseline Physician's Rating of Symptoms (ITT)						So-V1 204-P82	
Appendix I2 Listing 5 Physician's Rating of Individual Symptoms						So-V1 208-P313	

Reviewer Comments Regarding Baseline Symptom Assessments

There are no statistically significant differences for any of the baseline symptom assessments displayed in the sponsor's tables above. There is no apparent imbalance across study treatments. For information regarding baseline symptom assessments by study sites please refer to the section above regarding baseline demographics.

Results - Patient Compliance With Study Procedures

The sponsor summarizes duration of exposure to double-blind treatment which was estimated using the first and last date of symptom assessments during the double-blind period. The sponsor reports that the mean duration of exposure was 14±2 days with a range of 1 to 16 days.

The sponsor's table indicates that compliance with double-blind treatment was 99-100% for each treatment with the broadest range for placebo (50%-150%). The sponsor reports that 12 patients had compliance below 80% or above 120%. Compliance was computed by dividing the total number of doses taken during the double-blind dosing period by the total number of doses that should have been taken based on the number of days the patient was exposed to double-blind study medication.

We requested that the sponsor provide a summary of patient's compliance with diary symptom assessments. On December 13, 1995 the sponsor reported that compliance in completing diary symptom assessments for Protocol # PJPR0010 was 99.7±1.3%. Compliance was calculated by comparing the number of complete symptom assessments performed versus the number of symptom assessments that should have been performed.

For major protocol violations based on concomitant medications, the sponsor reports that 17 patients (17/810 - 2%) receiving fexfenadine and 6 (6/202 - 3%) receiving placebo had such violations - Placebo-6; 20mg-6; 40mg-2; 60mg-5; 80mg-4.

Results - Efficacy

Results - Primary Efficacy Parameter (Average Bedtime TSS) - Intent-to-Treat Analysis

The pre-defined primary assessment of efficacy was the patient's change in bedtime TSS from baseline in the Intent-To-Treat (ITT) population compared to placebo. The change from baseline was computed by subtracting the average Bedtime TSS during the placebo run-in period from the average bedtime TSS during the double-blind period. These results were summarized by the sponsor in Table 8-307 and Figure 8-127 reproduced below. All active treatments were statistically significant over placebo with the 60mg dose exhibiting a larger numerical reduction in scores compared to the other active treatments including the 80mg dose.

The sponsor also reports:

A) that the three additional factors, baseline bedtime TSS, treatment by baseline bedtime TSS interaction and treatment by investigative site interaction were statistically significant factors and were therefore included in the primary analysis model.

B) that a "by site" analysis to examine the significance of the treatment by site interaction indicated that the results are not driven by only a few sites since 13 of 16 sites showed a greater reduction in TSS with increasing dose and a greater placebo effect was observed on average at the remaining 3 sites.

Table 8-307. Intent-to-Treat Analysis of Bedtime TSS (N=995)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean ± SE</i>		
		<i>Baseline</i>	<i>Double-Blind Period</i>	<i>Change from Baseline*</i>
Placebo	198	5.52±0.20	4.73±0.18	-0.85±0.14
20 mg MDL 16.455A	197	5.90±0.20	4.56±0.21	-1.26±0.14
40 mg MDL 16.455A	201	5.56±0.21	4.20±0.18	-1.44±0.14
60 mg MDL 16.455A	203	5.71±0.19	4.10±0.18	-1.58±0.14
80 mg MDL 16.455A	196	5.73±0.21	4.38±0.19	-1.36±0.14
<i>Treatment Comparison</i>		<i>Mean ± SE* (Active-Placebo)</i>		<i>P value *</i>
Overall Treatment Differences				.0034
Dose Response (Linear Trend)				.0022
20 mg MDL 16.455A vs Placebo		-0.40±0.20		.0415
40 mg MDL 16.455A vs Placebo		-0.58±0.20		.0030
60 mg MDL 16.455A vs Placebo		-0.73±0.20		.0002
80 mg MDL 16.455A vs Placebo		-0.51±0.20		.0095
* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction.				
<i>Supporting Data</i>				<i>Page</i>
Appendix E3, Listing 4: Intent-to-Treat Analysis of Bedtime TSS				So-V1.204-P98
Appendix 12, Listing 4: Average PM Diary Listing				So-V1.208-P241

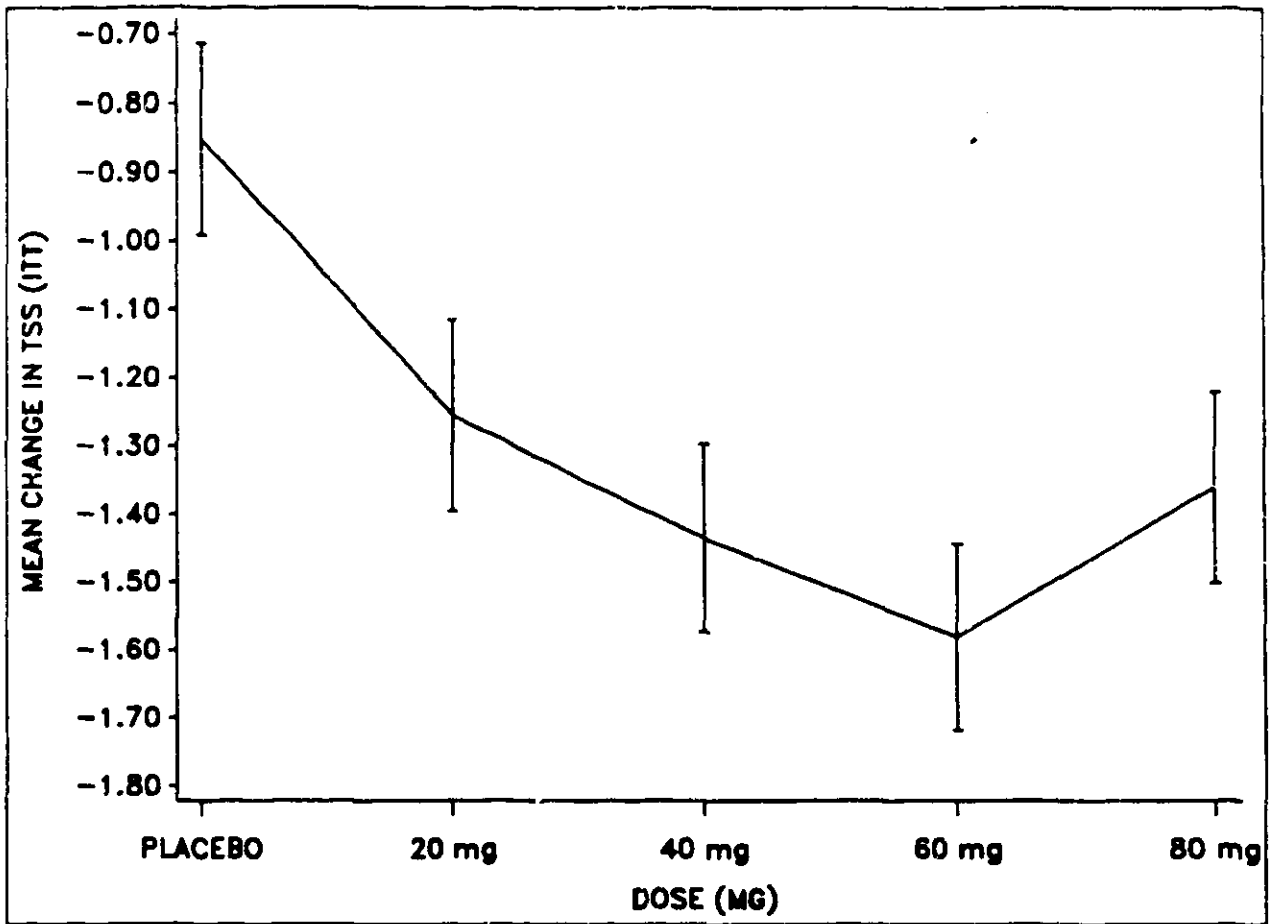


Figure 8-127. Change from Baseline in TSS. Mean±SE (Intent-to-Treat)

Supporting Data:	Page
Appendix E3, Listing 4: Intreat-to-Treat Analysis of Bedtime TSS	So-V1.204-P98
Appendix I2, Listing 4: Average PM Diary Listing	So-V1.208-P241

Results - Primary Efficacy Parameter (Average Bedtime TSS) - Protocol Correct Analysis

The sponsor performed a secondary analysis using 949 patients with no major protocol violations (Protocol Correct Patients) and summarized the results in Table 8-308 and Figure 8-128, reproduced below. Although all doses produced greater reduction in TSS than placebo, the magnitude of the difference is smaller than in the ITT population. The 20mg dose is no longer statistically significant treatment group.

Table 8-308. Protocol Correct Analysis of Bedtime TSS (N=949)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean ± SE</i>		
		<i>Baseline</i>	<i>Double -Blind Period</i>	<i>Change from Baseline*</i>
Placebo	191	5.52±0.20	4.68±0.18	-0.90±0.14
20 mg MDL 16.455A	185	5.92±0.20	4.60±0.21	-1.24±0.14
40 mg MDL 16.455A	196	5.57±0.21	4.24±0.18	-1.40±0.14
60 mg MDL 16.455A	190	5.65±0.19	4.06±0.18	-1.56±0.14
80 mg MDL 16.455A	187	5.76±0.21	4.42±0.20	-1.36±0.14
<i>Treatment Comparison</i>		<i>Mean ± SE*</i> <i>(Active-Placebo)</i>		<i>P value*</i>
Overall Treatment Differences				.0160
Dose Response (Linear Trend)				.0063
20 mg MDL 16.455A vs Placebo		-0.34±0.20		.0883
40 mg MDL 16.455A vs Placebo		-0.50±0.20		.0118
60 mg MDL 16.455A vs Placebo		-0.66±0.20		.0010
80 mg MDL 16.455A vs Placebo		-0.46±0.20		.0228
* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction.				
<i>Supporting Data:</i>				<i>Page</i>
Appendix E3, Listing 5: Protocol Correct Analysis of Bedtime TSS				So-V1.204-P103
Appendix I2, Listing 4: Average PM Diary Listing				So-V1.208-P241

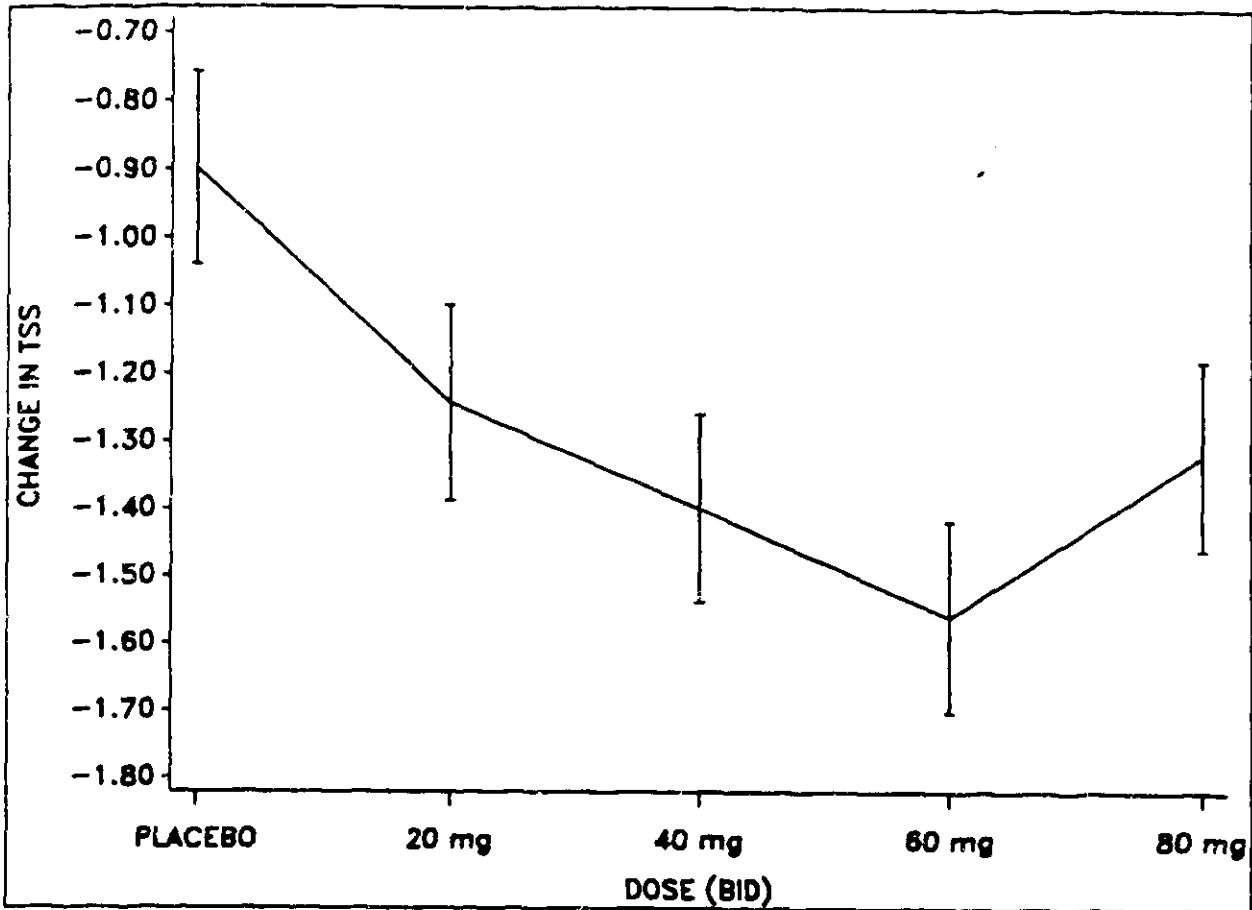


Figure 8-128. Change from Baseline in TSS. Mean ± SE (Protocol Correct)

Supporting Data:	Page
Appendix E3, Listing 5: Protocol Correct Analysis of Bedtime TSS	So-V1.204-P103
Appendix I2, Listing 4: Average PM Diary Listing	So-V1.208-P241

Reviewer Comment Regarding Results of Primary Efficacy Parameter

The results from the primary pre-planned efficacy parameter in the ITT population support the assertion that fexofenadine at all the doses tested can mitigate the symptoms of seasonal allergic rhinitis. The response to the 60mg dose was the largest. Failure to see any additional response with the increased dose at the 80mg dose level suggests that little additional symptom control is conferred by that dose level. It is difficult to understand why the 80mg dose response is less than that of the 60mg dose.

The results from the analysis of the protocol correct analysis are in general agreement with those from the ITT analysis. However the 20mg dose is no longer statistically significant.

The sponsor also indicates that the test for dose response (linear trend) was statistically significant ($p=0.0022$). The question regarding the inclusion of zero in the statistical computation and the appropriateness of this test for linear response will need examination by the statistical reviewer.

Results - Analysis of Secondary Efficacy Parameters -Alternative Analysis of Efficacy

For bedtime TSS using the ITT population the sponsor calculated the number and percentage of subjects with greater than 20% reduction in bedtime TSS. They are: Placebo = 43%; 20mg = 54%; 40mg = 49%; 60mg = 60%; and 80mg = 54%.

Reviewer Comment Regarding Alternative Analysis

Although the percentage of patients who exhibited a greater than 20% reduction in TSS is larger in the active treatment groups compared to the placebo group, with the largest percentage at the 60mg level, a 20% reduction seems modest. At our request the sponsor provided additional calculations for larger reductions in bedtime TSS on December 22, 1995. The table below displays the sponsors calculations for the percentage of subjects with greater than 20% and 50% reduction in bedtime TSS. The magnitude of percentages at the 50% level of response is approximately half that of the 20% level but approximately the same across all active treatments. At the 50% level the response in all active treatment groups is still greater than placebo.

		Symptom Improvement Above A Fixed Level	
PJPR0010	N	≥20%	≥50%
Placebo	198	0.43	0.15
20mg	197	0.54 p=0.031	0.25 p=0.015
40mg	201	0.49 p=0.178	0.27 p=0.003
60mg	203	0.60 p=0.001	0.25 p=0.015
80mg	196	0.54 p=0.031	0.22 p=0.069

Additionally the sponsor provided the results for an alternative definition of response - improvement greater than the average improvement for placebo patients. The table below summarizes the results for this alternative definition. The magnitude of response at the 50% level is only slightly less than that at the 20% level.

		Symptom Improvement Above Placebo	
PJPR0010	N	≥20%	≥50%
Placebo	198	0.45	0.38
20mg	197	0.54 p=0.064	0.49 p=0.031
40mg	201	0.50 p=0.273	0.47 p=0.052
60mg	203	0.60 p=0.002	0.55 p=0.001
80mg	196	0.57 p=0.018	0.50 p=0.017

The response rates observed in the examination of these data suggest that all active treatments are more effective than placebo.

Results - Analysis of Secondary Efficacy Parameters - Daily Bedtime TSS

The sponsor provided an analysis of response for each day for change from baseline in daily bedtime TSS using the ITT population. The sponsor's table of the results are displayed below.

All active treatments achieve statistical significance by Day 2 but only the 60mg dose sustains significance to the fourteenth day, with statistical significance on 12 out of the 14 days. The 40mg and 80mg dose levels were able to sustain statistical significance only on Days 2 through 6. The 20mg dose level achieved statistical significance only on Days 2 and 5.

Table 8-310		Intent-to-Treat Analysis of Daily Bedtime TSS					Dose Response P value*
		Mean Change from Baseline					
		Placebo (N=192)	MDL 16 455A (B/D)				
Day			20 mg (N=197)	40 mg (N=201)	60 mg (N=203)	80 mg (N=196)	
1	n	198	197	200	203	195	1459
	Mean±SE	-0.90±0.16	-0.84±0.16	-1.25±0.16	-1.13±0.16	-1.12±0.16	
	P value*		7905	1228	3091	3237	
2	n	196	195	201	203	195	0260
	Mean±SE	-0.65±0.18	-1.21±0.18	-1.54±0.18	-1.23±0.18	-1.29±0.18	
	P value*		0285	0004	0217	0146	
3	n	195	195	199	201	195	0183
	Mean±SE	-0.82±0.18	-1.11±0.18	-1.35±0.18	-1.39±0.18	-1.35±0.18	
	P value*		2602	0373	0250	0370	
4	n	193	193	198	199	194	0063
	Mean±SE	-0.68±0.19	-1.17±0.19	-1.30±0.19	-1.26±0.19	-1.42±0.19	
	P value*		0650	0202	0296	0053	
5	n	194	193	197	200	195	0042
	Mean±SE	-0.65±0.19	-1.39±0.19	-1.26±0.19	-1.64±0.18	-1.37±0.19	
	P value*		0050	0189	0002	0063	
6	n	181	188	196	195	193	0044
	Mean±SE	-0.86±0.19	-1.16±0.20	-1.50±0.19	-1.65±0.19	-1.49±0.19	
	P value*		2799	0190	0039	0220	
7	n	179	183	188	190	183	3300
	Mean±SE	-1.11±0.20	-1.45±0.20	-1.20±0.20	-1.57±0.20	-1.36±0.20	
	P value*		2298	7431	0996	3842	
8	n	182	182	189	188	182	0601
	Mean±SE	-0.95±0.20	-1.28±0.20	-1.22±0.19	-1.56±0.20	-1.40±0.20	
	P value*		2282	3321	0275	1080	
9	n	185	185	195	193	188	1361
	Mean±SE	-1.05±0.19	-1.55±0.19	-1.44±0.18	-1.79±0.18	-1.37±0.19	
	P value*		0571	1335	0052	2191	
10	n	186	185	194	193	187	0719
	Mean±SE	-1.19±0.20	-1.48±0.20	-1.34±0.20	-1.99±0.20	-1.50±0.20	
	P value*		2971	5764	0043	2660	
11	n	186	186	195	193	186	0468
	Mean±SE	-0.99±0.21	-1.42±0.21	-1.42±0.20	-1.78±0.20	-1.46±0.21	
	P value*		1431	1375	0061	1115	
12	n	183	185	194	192	184	1084
	Mean±SE	-1.09±0.20	-1.48±0.20	-1.44±0.19	-1.87±0.19	-1.30±0.20	
	P value*		1660	2066	0055	4534	
13	n	143	144	151	159	149	1729
	Mean±SE	-1.02±0.22	-1.55±0.22	-1.49±0.22	-2.22±0.21	-1.15±0.22	
	P value*		0931	1311	0001	6707	
14	n	91	79	88	94	87	0175
	Mean±SE	-1.13±0.31	-1.33±0.35	-1.65±0.33	-2.68±0.32	-1.61±0.32	
	P value*		6633	2338	0003	2672	

* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, and treatment

Supporting Data	Page
Appendix E3 Listing 6 Intent-to-Treat Analysis of Daily Bedtime TSS	So-V1 204-P106
Appendix I2 Listing 1 PM Diary Listing	So-V1 206-P110

Reviewer Comment Regarding Daily Bedtime TSS

These data suggest that the durable dose is 60mg. It is difficult to understand the failure of the 80mg dose to mimic the response of the 60mg dose.

Results - Analysis of Secondary Efficacy Parameters - Bedtime Individual Symptom Assessments

The sponsor provides an analysis of change from baseline in bedtime individual symptom assessments using the ITT population. No dose level produced significant improvement over placebo for nasal congestion. The 60 mg dose produced significant improvement over placebo for all other symptoms. The 40 mg and 80 mg dose groups showed statistically significant improvement over placebo only for sneezing and itchy eyes. The 20 mg group showed statistically significant improvement over placebo for sneezing only symptom.

Symptoms		Mean Change from Baseline					Dose Response P Value*
		Placebo (N=198)	MDL 16.455A (BID)				
			20 mg (N=197)	40 mg (N=201)	60 mg (N=203)	80 mg (N=196)	
Nasal Congestion	n	198	197	201	203	196	.0380
	Mean ± SE	-0.13 ± 0.04	-0.18 ± 0.04	-0.19 ± 0.04	-0.24 ± 0.04	-0.24 ± 0.04	
	P value*		0.3464	0.2939	0.0581	0.0642	
Sneezing	n	198	197	201	203	196	0032
	Mean ± SE	-0.12 ± 0.04	-0.27 ± 0.04	-0.33 ± 0.04	-0.36 ± 0.04	-0.26 ± 0.04	
	P value*		0.0107	0.0002	0.0001	0.0150	
Rhinitis	n	198	197	201	203	196	.0269
	Mean ± SE	-0.21 ± 0.04	-0.25 ± 0.04	-0.31 ± 0.04	-0.36 ± 0.04	-0.30 ± 0.04	
	P value*		0.4401	0.0851	0.0112	0.1092	
Itchy Nose, Palate and/or Throat	n	198	197	201	203	196	.0191
	Mean ± SE	-0.27 ± 0.04	-0.34 ± 0.04	-0.37 ± 0.04	-0.44 ± 0.04	-0.38 ± 0.04	
	P value*		0.2817	0.0871	0.0062	0.0718	
Itchy, Watery, Red Eyes	n	198	197	201	203	196	.0151
	Mean ± SE	-0.27 ± 0.04	-0.39 ± 0.04	-0.41 ± 0.04	-0.42 ± 0.04	-0.42 ± 0.04	
	P value*		0.0509	0.0170	0.0122	0.0142	
TSS (Excluding Nasal Congestion)	n	198	197	201	203	196	0022
	Mean ± SE	-0.85 ± 0.14	-1.26 ± 0.14	-1.44 ± 0.14	-1.58 ± 0.14	-1.37 ± 0.14	
	P value*		0.0415	0.0030	0.0002	0.0095	

* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction.

Supporting Data	Page
Appendix E3, Listing 7 Intent-to-Treat Analysis of Bedtime Individual Symptoms and TSS	So-V1 204-F151
Appendix I2, Listing 4 Average PM Diary Listing	So-V1 208-P241

Results - Analysis of Secondary Efficacy Parameters - Noon TSS

The sponsor also provides an analysis of change from baseline for Noon TSS using the ITT population. Only the 60mg and 40mg dose levels attained statistical significance while the 20mg and 80mg dose levels approached statistical significance.

Table 8-312. Intent-to-Treat Analysis of Noon TSS (N=994)				
Treatment (BID)	N	Mean ±SE		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	198	5.71±0.23	4.87±0.18	-0.92±0.14
20 mg MDL 16 455A	197	6.03±0.23	4.64±0.19	-1.27±0.14
40 mg MDL 16 455A	201	5.66±0.22	4.40±0.18	-1.39±0.14
60 mg MDL 16 455A	202	6.01±0.21	4.27±0.18	-1.65±0.14
80 mg MDL 16 455A	196	5.84±0.23	4.59±0.19	-1.29±0.14
Treatment Comparison		Mean ±SE (Active-Placebo)		P value *
Overall Treatment Differences				0076
Dose Response (Linear Trend)				0117
20 mg MDL 16 455A vs Placebo		-0.35±0.20		0812
40 mg MDL 16 455A vs Placebo		-0.47±0.20		0197
60 mg MDL 16 455A vs Placebo		-0.74±0.20		0002
80 mg MDL 16 455A vs Placebo		-0.38±0.20		0621
* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction.				
Supporting Data				Page
Appendix E3. Listing 8. Intent-to-Treat Analysis of Noon TSS				So-V1 204-P176
Appendix I2. Listing 3. Average AM Diary Listing				So-V1 208-P169

Reviewer Comment Regarding Individual Symptom Scores and Noon Symptom Scores

The results of these analyses suggest that the 60mg dose is superior to the other doses in controlling all the symptoms of SAR except nasal congestion. The noon TSS continue to support the efficacy of the active treatments.

Results - Analysis of Secondary Efficacy Parameters - Average Morning Predose TSS

The sponsor provides an analysis of change from baseline for average morning predose TSS using the ITT population. This analysis was included in the protocol to represent trough levels (i.e. end-of-dosing efficacy). Only the 60mg dose reached statistical significance (p=0.0004) with 40mg the nearest other dose level (p=0.1968). The sponsor also conducted a supportive analysis excluding subjects with the minor protocol violation of less than 8 hours or more than 16 hours from the time of the last dose to the morning predose symptom assessment. With this enriched population only the 60mg dose attained statistical significance (p=0.0004) with the 40mg dose approaching significance (p=0.0758).

Reviewer Comment Regarding Morning Predose TSS

Although the 60mg dose level reaches statistical significance it is difficult to rely on these results in support of end-of-dosing interval efficacy since the data consist of so few time points (i.e. two morning predose assessments over a two week period) which are compared to the noon TSS as a baseline.

Results - Analysis of Secondary Efficacy Parameters -**Physician's Assessment of Individual Symptoms and TSS**

The sponsor provides an analysis of change from baseline for physician's assessment of individual symptoms and TSS using the ITT population. For TSS only the 60 mg dose group achieved statistical significance ($P = .0044$) compared to placebo. For individual symptoms only the 60mg dose group achieved statistical significance (sneezing, $P = .0377$; rhinorrhea, $P = .0361$; itchy nose, palate and/or throat, $P = .0006$). No dose group including 60mg achieved statistical significance for itchy watery eyes.

Results - Analysis of Secondary Efficacy Parameters**-Physician's Evaluation of Overall Effectiveness**

Responders were defined as patients having moderate, marked, or complete relief of symptoms. Only the 60 mg dose group achieved statistical significance ($P = .029$). The reported responder rates were: Placebo- 48.7%; 20mg-48.5%; 40mg-54.2%; 60mg-59.6%; 80mg-57.4%.

Results - Analysis of Secondary Efficacy Parameters**- Patient's Willingness to Take Study Medication Again**

All active dose groups had a greater percentage of patients willing to take study medication again for the symptoms of seasonal allergic rhinitis than placebo (Yes - Placebo-56.9%; 20mg-57.1%; 40mg-57.7%; 60mg-64.4%; 80mg-61.5%); but no statistically significant difference from placebo was achieved by any dose level.

Results - Subgroup Analyses for Efficacy

The sponsor provides also the results of additional analyses using the ITT population for interaction using subgroup factors and bedtime TSS. The sponsor reports that analyses were not statistically significant for interaction between treatment and age ($p = 0.6149$); gender ($p = 0.5999$); race ($p = 0.6213$); and weight ($p = 0.3055$).

Results - By-Weekly Symptom Analysis for Efficacy

On December 8, 1995, at our request, the sponsor submitted analyses of individual symptoms and TSS over each week of the trial. After examining each individual symptom score and TSS for statistical significance ($P \leq 0.05$) and trend in statistical significance (i.e. $p \leq 0.1$), the following general patterns were observed. These data are presented in tabular form below.

Interestingly, 40mg, 60mg and 80mg achieved efficacy for nasal congestion for week 1 but not week 2.

For bedtime symptom assessments, 60mg appeared efficacious for the 4 remaining symptoms for both weeks except rhinorrhea during week 1. The 40mg and 80mg doses also appeared effective for the 4 remaining symptoms for week 1 but not week 2.

For noon symptom assessments, 60mg efficacious for the remaining 4 symptoms except itchy eye during both weeks. The 80mg dose appeared effective for the 4 remaining symptoms for week 1 but not week 2. The 40mg dose appeared effective for most symptoms during week 1 but not week 2.

For morning predose symptom assessment, only the 60mg dose appeared to demonstrate any efficacy for most symptoms for either week 1 or week 2 compared to all other doses.

++ = Statistically Significant i.e. ≤ 0.05
 + = Trend i.e. > 0.05 and < 0.10
 - = Statistically Insignificant i.e. ≥ 0.10

Bedtime Individual Symptoms and TSS for PJPR0010

Symptoms Week 1	20mg	40mg	60mg	80mg
Nasal Congestion	-	+	++	++
Sneezing	++	++	++	++
Rhinorrhea	-	+	-	+
Itchy Nose	-	++	+	+
Itchy Eyes	+	++	++	++
TSS	+	++	++	++
Symptoms Week 2	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	++	-
Rhinorrhea	-	-	++	-
Itchy Nose	-	-	++	-
Itchy Eyes	-	-	++	-
TSS	+	+	++	-

Noon Individual Symptoms and TSS for PJPR0010

Symptoms Week 1	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	+	++	++	+
Rhinorrhea	++	++	++	+
Itchy Nose	-	++	++	+
Itchy Eyes	-	-	-	+
TSS	-	++	++	++
Symptoms Week 2	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	++	-
Rhinorrhea	-	-	+	-
Itchy Nose	-	-	++	-
Itchy Eyes	-	-	-	-
TSS	-	-	++	-

Morning Predose Individual Symptoms and TSS for PJPR0010

Symptoms Week 1	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	-	-	++	-
Rhinorrhea	-	-	++	-
Itchy Nose	-	-	++	+
Itchy Eyes	-	-	-	-
TSS	-	-	++	+
Symptoms Week 2	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	-	-	-	-
Rhinorrhea	-	-	++	-
Itchy Nose	-	-	++	-
Itchy Eyes	-	-	-	-
TSS	-	-	++	-

Safety Results - Adverse Events:

Overall the sponsor reports that the total number of patients with 1 or more adverse event was: Placebo 67-(33.5%); 20mg-58(29.3%); 40mg-58(28.9%); 60mg-72(35.1%); 80mg-46(23.0%).

The table below condenses the sponsor's table of the incidence of all adverse events to show those events which occurred at a rate of 1% or greater in the total active group.

Table 8-324. Incidence of All Adverse Events

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (<i>BID</i>) (<i>N</i> =200) <i>N</i> (%)	MDL 16.455A (<i>BID</i>)				Total Active (<i>N</i> =804) <i>N</i> (%)
		20 mg (<i>N</i> =198) <i>N</i> (%)	40 mg (<i>N</i> =201) <i>N</i> (%)	60 mg (<i>N</i> =205) <i>N</i> (%)	80 mg (<i>N</i> =200) <i>N</i> (%)	
HEADACHE	13 (6.5)	7 (3.5)	15 (7.5)	14 (6.8)	12 (6.0)	48 (6.0)
FATIGUE	5 (2.5)	2 (1.0)	3 (1.5)	5 (2.4)	4 (2.0)	14 (1.7)
DROWSINESS	3 (1.5)	1 (0.5)	2 (1.0)	3 (1.5)	2 (1.0)	8 (1.0)
THROAT IRRITATION	5 (2.5)	3 (1.5)	3 (1.5)	7 (3.4)	2 (1.0)	15 (1.9)
UPPER RESPIRATORY TRACT INFECTION	1 (0.5)	4 (2.0)	1 (0.5)	1 (0.5)	2 (1.0)	8 (1.0)
NAUSEA	3 (1.5)	2 (1.0)	3 (1.5)	5 (2.4)	3 (1.5)	13 (1.6)
DYSPEPSIA	2 (1.0)	1 (0.5)	2 (1.0)	4 (2.0)	1 (0.5)	8 (1.0)
INFECTION VIRAL	2 (1.0)	5 (2.5)	4 (2.0)	3 (1.5)	2 (1.0)	14 (1.7)
THIRST	0 0	1 (0.5)	3 (1.5)	2 (1.0)	2 (1.0)	8 (1.0)
DRY MOUTH	1 (0.5)	2 (1.0)	4 (2.0)	1 (0.5)	1 (0.5)	8 (1.0)

Reviewer Comment On Adverse Events

From the table above the following events appear to have occurred very slightly more frequently in the active treatment groups than in the placebo group: infection viral and thirst with no dose response.

Deaths and Discontinuations Due to Adverse Events

The sponsor reports that no deaths or hospitalizations occurred during this trial; and the sponsor summarizes information regarding subjects who had discontinued medication due to adverse events in the table reproduced below.

Table 8-328. Summary of Patients Who Discontinued Study Medication Due to Adverse Events								
Patient	Age	Sex	Treatment (BID)	Adverse Event (Preferred Term)	Duration of Double-Blind Treatment Prior to Discontinuation (days)	Severity	Study Drug Reason	Outcome
043-052								
043-054								
044-010								
044-048								
045-003								
045-007								
045-042								
045-051								
Supporting Data								
Appendix J3. Listing 8 Adverse Events Meeting the Serious Criteria								So-V1 208-P457

Reviewer Comment on Discontinuations Due to Adverse Events

In reviewing the narratives for these subjects it is difficult to ascribe causality of the event to active treatment or placebo treatment.

Clinical Laboratory Evaluation

The sponsor reports that there were 5 laboratory parameters with a statistically significant change from baseline: WBCs ($p=0.0288$; $r=-0.0693$) - slight decreases in the 40mg, 60mg and 80mg groups ranging from -0.2 ± 0.05 to $-0.3 \pm 0.11 \times 10^6 / \mu\text{L}$; Lymphocytes ($p=0.0164$; $r=-0.0760$); Monocytes ($p=0.0109$; $r=-0.0806$); Basophiles ($p=0.0016$; $r=-0.0996$); and Blood Glucose ($p=0.0314$; $r=0.0314$) with the largest change of 2.8 ± 0.84 mg/dL in the 60mg group.

Vital Signs

The sponsor reports no statistically significant change in SBP, DBP or HR from baseline to the final visit in the patients treated with fexofenadine compared to placebo.

Pharmacokinetic Results

At 5 of the investigative sites two plasma samples were collected for assay of MDL 16,455A on the day of the final visit one at 1-3 hours and one 5-9 hours after the last dose.

<i>Treatment (BID)</i>	<i>1-3 Hours Postdose</i>		<i>5-9 Hours Postdose</i>	
	<i>N</i>	<i>Mean (% CV)</i>	<i>N</i>	<i>Mean (% CV)</i>
20 mg MDL 16,455A	9	87.31 (47)	7	45.06 (35)
40 mg MDL 16,455A	11	93.34 (75)	10	58.37 (56)
60 mg MDL 16,455A	7	129.78 (81)	5	91.80 (104)
80 mg MDL 16,455A	7	284.24 (60)	5	108.34 (27)

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Appendix M2 Pharmacokinetic Listings S8-V1 218-P278

Reviewer Comment Regarding Pharmacokinetic Results

Plasma concentrations appear to increase as dose level increases. It is difficult to explain the poorer efficacy response of the 80mg dose when its plasma concentrations exceeded that of the 60mg dose.

Final Reviewer Comments Regarding Protocol #PJPR0010: Protocol #PJPR0010 fulfills the criteria for a well controlled clinical trial in support of safety and efficacy.

Reviewer's Determinations

- 1) The results of the primary pre-defined endpoint of this study support the assertion that compared to placebo treatment fexofenadine is efficacious for the mitigation of the symptoms associated with seasonal allergic rhinitis in doses of 20mg BID, 40mg BID, 60mg BID, and 80mg BID in patients greater than 12 years of age.
- 2) The magnitude of symptom reduction is not comparable across the doses studied, with the 60mg dose level demonstrating the largest symptom reduction and no additional symptom reduction by increasing to the 80mg dose level. It is difficult to explain the inability of the 80mg dose level to achieve a statistical significance at least comparable to that of the 60mg dose for many of the secondary assessments of efficacy.
- 3) Based on daily bedtime symptom scores and by-weekly analyses of all symptom scores including individual symptoms, the effect on individual symptom scores or TSS is not sustained for the second week of treatment by any dose other than the 60mg dose.
- 4) The onset of action before 24 hours can not be supported by this trial since assessment of daily symptom scores were analyzed only for the bedtime TSS scores and noon TSS were not analyzed on a daily basis.
- 5) Based on the limited morning predose symptom assessments, the end-of-dosing interval can not be supported by this trial despite the observation of statistical significance achieved by the 60mg dose.
- 6) The examination of the safety profile of fexofenadine compared to placebo does not reveal any obvious significant toxicities with doses up to 80mg BID after two weeks administration. EKGs were not measured during this trial.
- 7) There does not appear to be an interaction between fexofenadine and age, gender, race or weight.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Reviewed: **Protocol #PJPR0009** - conducted from March 2, 1994 to July 15, 1994.

Title

"A Placebo-Controlled, Double-Blind, Randomized Parallel Study Comparing the Safety and Efficacy of Four Dosage Strengths of MDL-16,455A in the Treatment of Spring Allergies--I."

Objectives

"To determine the safety and efficacy profile of MDL-16,455A at 20 mg BID, 40 mg BID, 60 mg BID, and 80 mg BID compared to placebo in the treatment of seasonal allergic rhinitis (SAR)."

Study Design

The study design plans for this protocol, including protocol amendments, is identical to that for protocol #PJPR0010. The reader is referred to the Medical Officer review for protocol #PJPR0010 for details regarding study design and plans for analysis. The only identified difference between the two trials is in the statistical model used in the analysis of data.

Statistical Methods

The statistical model used for data analysis in this study is different from that used in protocol #PJPR0010. An analysis of covariance (ANCOVA) model with baseline bedtime TSS as a covariate and investigative site and treatment as predictor variables was used to analyze the primary efficacy variable, change in bedtime TSS from baseline compared to placebo using the Intent-to-Treat (ITT) population. Protocol PJPR0010 included treatment by investigative site term in the ANOVA. The evaluations of Physician's Assessment of Individual Symptoms and TSS and patient's bedtime individual symptom assessments was conducted in the same manner as the primary efficacy parameter. For this protocol, evaluations of other secondary parameters were conducted in the same way as for protocol #PJPR0010.

Study Treatments

The treatments utilized in this trial consisted of the following:

<u>Treatment</u>	<u>Dose</u>
A) Placebo Lead-In BID	4-20 mg placebo capsules
B) Double-Blind:	
Placebo	4-20 mg placebo capsules
MDL 16,455A 20 mg BID	1-20 mg MDL 16,455A capsule 3-20 mg placebo capsules
MDL 16,455A 40 mg BID	2-20 mg MDL 16,455A capsules 2-20 mg placebo capsules
MDL 16,455A 60 mg BID	3-20 mg MDL 16,455A capsules 1-20 mg placebo capsule
MDL 16,455A 80 mg BID	4-20 mg MDL 16,455A capsules

<i>Study Medication</i>	<i>Lot Numbers</i>
MDL 16,455A 20 mg capsule	PA 9404 RN 9323
Placebo 20 mg capsule	RN 9321

Efficacy Parameters - The efficacy parameters are reproduced for reference, if needed.

Primary Parameter

The primary efficacy analysis variable was change from baseline in the Bedtime Total Symptom Score (TSS). The Bedtime TSS was computed by summing the Bedtime individual symptom scores (excluding nasal congestion) as recorded on the patient's symptom diary card. If a patient was missing any of the Bedtime individual symptoms used in calculating Bedtime TSS, then that patient's Bedtime TSS evaluation was also treated as missing. Further, the change in Bedtime TSS assessment is defined as follows:

Average Double Blind Bedtime TSS - Average Baseline Bedtime TSS

Secondary Parameters

1. Secondary Evaluations of Bedtime TSS
 - a. Changes in Daily Bedtime TSS (average of the two Bedtime TSS observations during the placebo lead-in period vs Bedtime TSS each day during the double-blind period)
 - b. Changes in Bedtime Individual Symptom Assessments (average of bedtime evaluations for the double-blind dosing period vs average of the two bedtime evaluations during the placebo lead-in). Individual symptoms are nasal congestion; sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes
2. Additional Secondary Evaluations
 - a. Change in noon TSS (average of noon TSS during the double-blind dosing period) from baseline noon TSS (noon TSS observation during the placebo lead-in period)
 - b. Change in Average Morning Predose TSS (average of the Interim Visit predose TSS and the Final Visit predose TSS) from baseline TSS (noon TSS during the placebo lead-in period)
 - c. Changes in Physician's Assessment of Individual Symptoms and TSS (Entry Visit vs Final Visit)
 - d. Physician's Evaluation of Overall Effectiveness: (Final Visit assessment)
 - e. Patient's willingness to take study medication again.

RESULTS

Results - Patient Accounting

The sponsor reports the following patient tally:

Screened ----- 1194
 Screening Failures ----- 212
 Randomized ----- 982
 Placebo Lead-in Discontinuation -7
 Exposed To Double-Blind Med -- 975
 Double-Blind Discontinuation ---- 56
 Completed ----- 919

The sponsor prepared the 4 tables reproduced below to summarize patient disposition and distribution of patients exposed to double-blind study medication a) across treatment groups and investigative sites, b) who had major protocol violations, and c) who discontinued early. Three patients were lost to follow-up after the Entry Visit and 962 patients were identified as Intent-To-Treat (ITT).

Table 8-247. Summary of Patient Disposition					
Treatment (BID)	Randomized N(%)	Exposed N(%)	Safety Evaluable N(%)	Intent-to-Treat N(%)	Protocol Correct N(%)
Placebo	196 (20%)	193 (20%)	192 (20%)	190 (20%)	181 (20%)
20 mg MDL 16.455A	197 (20%)	195 (20%)	195 (20%)	194 (20%)	186 (20%)
40 mg MDL 16.455A	196 (20%)	196 (20%)	196 (20%)	195 (20%)	185 (20%)
60 mg MDL 16.455A	198 (20%)	197 (20%)	196 (20%)	191 (20%)	181 (20%)
80 mg MDL 16.455A	195 (20%)	194 (20%)	193 (20%)	192 (20%)	182 (20%)
Total	982	975	972	962	915
<i>Supporting Data:</i>					<i>Page</i>
<i>Appendix F1, Summary 2: Summary of Patient Disposition by Treatment</i>					<i>S8-VI.188-P7</i>
<i>Appendix F2, Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group</i>					<i>S8-VI.188-P27</i>

Table 8-246 Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group

Investigative Site	Placebo BID	MDL 16 455A (BID)				Total
		20 mg	40 mg	60 mg	80 mg	
014	14	14	14	14	14	70
015	11	11	11	12	10	55
016	12	11	12	12	12	59
017	12	12	12	12	11	59
018	12	12	12	12	12	60
019	14	14	14	14	14	70
020	12	12	12	12	12	60
021	14	14	14	14	14	70
022	11	12	12	12	12	59
023	10	12	12	12	12	58
024	14	14	14	14	14	70
025	14	14	14	14	13	69
026	12	11	12	12	12	59
027	13	14	14	14	14	69
028	12	12	12	12	12	60
029	6	6	5	5	6	28
TOTAL	193	195	196	197	194	975

Supporting Data *Page*
Appendix F1, Summary 1 Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group S8-V1 188-P3
Appendix F2, Listing 1 Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group S8-V1 188-P27

Table 8-248. Summary of Major Protocol Violations (Patients Exposed to Double-Blind Study Medication)

Major Protocol Violation	Placebo BID (N=193)	MDL 16.455A (BID)				Total Active (N=782)	Total (N= 975)
		20 mg (N=195)	40 mg (N=196)	60 mg (N=197)	80 mg (N=194)		
Failure to meet entrance criteria	0 (0%)	0 (0%)	1 (1%)	4 (2%)	2 (1%)	7 (1%)	7 (1%)
Use of prohibited medications prior to or during study	8 (4%)	7 (4%)	6 (3%)	8 (4%)	3 (2%)	24 (3%)	32 (3%)
Missing efficacy data (primary measure)	3 (2%)	1 (1%)	1 (1%)	6 (3%)	2 (1%)	10 (1%)	13 (1%)
Non-compliance with study medication	3 (2%)	2 (1%)	2 (1%)	4 (2%)	6 (3%)	14 (2%)	17 (2%)
Study medication not taken in the proper order	0 (0%)	0 (0%)	2 (1%)	0 (0%)	1 (1%)	3 (0%)	3 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0%)	2 (0%)
TOTAL PATIENTS	12 (6%)	9 (5%)	11 (6%)	16 (8%)	12 (6%)	48 (6%)	60 (6%)

Patients have had more than one major protocol violation, therefore, patient counts for Major Violations may not equal the total number of patients having major protocol violations (Total Patients)

Supporting Data *Page*
Appendix F1, Summary 3 Summary of Major Protocol Violations S8-V1 188-P10
Appendix F1, Summary 7 Disposition Criteria S8-V1 188-P21
Appendix F2, Listing 2 Major Protocol Violations S8-V1 188-P49

Table 8-249 Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication							
Primary Reason	Placebo BID (N=193)	MDL 16 455A (BID)				Total Active (N=782)	Total (N= 975)
		20 mg (N=195)	40 mg (N=196)	60 mg (N=197)	80 mg (N=194)		
Adverse Event	5 (3%)	6 (3%)	4 (2%)	3 (2%)	4 (2%)	17 (2%)	22 (2%)
Use of prohibited medication	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Failed to return to study site for a scheduled visit	2 (1%)	1 (1%)	2 (1%)	1 (1%)	3 (2%)	7 (1%)	9 (1%)
Abnormal baseline laboratory value	0 (0%)	0 (0%)	0 (0%)	3 (2%)	2 (1%)	5 (1%)	5 (1%)
Treatment failure	3 (2%)	4 (2%)	3 (2%)	3 (2%)	3 (2%)	13 (2%)	16 (2%)
Other	2 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	3 (0%)
TOTAL PATIENTS	13 (7%)	11 (6%)	10 (5%)	10 (5%)	12 (6%)	43 (5%)	56 (6%)
Patients may have had more than one reason for discontinuing the study; however only the primary reason is summarized							
<i>Supporting Data</i>							<i>Page</i>
Appendix F1, Summary 4, Summary of Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication							S8-V1 188-P13
Appendix F2, Listing 4, Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication							S8-V1 188-P101

Reviewer Comments Regarding Patient Accounting

The distribution of patients exposed to double-blind treatments, major protocol violations and early discontinuations appears similar across treatments and across treatments within investigative sites. The majority of sites enrolled between 55 to 70 patients per site with the exception of site #029 which enrolled only 28 subjects. Examination of the randomization schedule for this study does not reveal any repetitive patterns in treatment assignment that would suggest a lack of randomization.

Results - Subject Demographics

Below is the sponsor's table of baseline demographic characteristics for the Intent-To-Treat dataset.

Table 8.250 Demographics: Intent-to-Treat Patients							
Baseline Characteristics	Placebo BID (n=190)	MDL 16 455A (BID)				Total (n=962)	P value*
		20 mg (n=194)	40 mg (n=195)	60 mg (n=191)	80 mg (n=192)		
Gender							
Male % (N)	39(74)	44(85)	36(70)	48(91)	45(86)	42(406)	0.1329
Female % (N)	61(116)	56(109)	64(125)	52(100)	55(106)	56(556)	
Age (years)							
Mean ± SD	33±12	30±11	32±11	32±12	31±11	32±11	0.1656
Range	11-65	12-63	12-61	12-65	12-64	11-65	
Race							
Caucasian % (N)	84(160)	87(169)	81(157)	82(157)	88(168)	84(811)	0.3582
Black % (N)	8(16)	8(16)	12(24)	7(13)	6(15)	8(84)	
Asian % (N)	2(4)	2(3)	2(3)	4(7)	1(2)	2(19)	
Other % (N)	5(10)	3(6)	6(11)	7(14)	4(7)	5(46)	
Weight (kg)							
Mean ± SD	73±16	72±19	73±21	74±20	72±18	73±18	0.8503
Range	33-113	32-150	30-178	38-182	31-135	30-178	
Height (cm)							
Mean ± SD	169±10	169±10	169±10	170±10	169±10	169±10	0.7380
Range	140-203	142-193	132-193	145-196	142-191	132-203	
Years Since First Episode Occurred							
Mean ± SD	19±12	17±10	18±11	18±10	16±11	18±11	0.1330
Range	2-58	2-58	2-45	2-44	2-54	2-58	
Successive Years of Spring Allergy							
Mean ± SD	17±11	16±10	17±11	16±10	15±10	16±11	0.2232
Range	2-50	2-58	2-45	2-44	2-54	2-58	

* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors

Sponsor's Date: _____ Page: _____

Appendix G1: Summary 1: Demographics: Intent-to-Treat Patients SB-V1 188-P178

Appendix G2: Listing 1: Patient Demographics and Medical History SB-V1 189-P2

Reviewer Comments Regarding Demographics

Although there are no statistically significant differences for any of the baseline demographic variables displayed in the table above, there is a slight preponderance of females and a marked preponderance of Caucasians; but there is no apparent imbalance across study treatments.

We asked the sponsor to submit an analysis of baseline demographics by investigational site. The sponsor provided this information by submission to the NDA dated December 13, 1995. Below is a table displaying the ranges across study sites for the range of baseline demographics. Although it is difficult from this information to conclude what influence any one center or group of centers may have contributed to the overall study results it is helpful to observe that extreme differences in baseline demographics other than race are not apparent.

Range of Baseline Demographics Across Study Sites - Intent-To-Treat						
PJPR0009	Age	Gender % Male	Race			Total Symptom Scores
			Asian	Black	Caucasian	
High (site)	36 ± 13 (26)	63.8% (16)	18.5% (29)	48.1% (29)	98.6% (19)	7.42 ± 2.29 (21)
Low (site)	28 ± 11 (22) 28 ± 12 (23)	30.0% (18)	0.0% (14, 15, 18, 19, 21, 23, 25)	0.0% (16, 19, 26, 28)	29.6% (29)	3.61 ± 2.23 (29)

Results - Baseline Symptom Assessments

Below are the sponsor's tables of baseline symptom assessments.

Baseline Symptoms	Placebo BID (n=190)	MDL 16.455A (SID)				Total (n=962)	P value*
		20 mg (n=194)	40 mg (n=195)	60 mg (n=191)	80 mg (n=192)		
Nasal Congestion							
Mean ±SD	1.6±0.9	1.6±0.8	1.7±0.9	1.6±0.8	1.8±0.9	1.7±0.8	0.4311
Range	0-3.0	0-4.0	0-4.0	0-3.0	0-4.0	0-4.0	
Sneezing							
Mean ±SD	1.2±0.8	1.1±0.8	1.1±0.8	1.2±0.8	1.1±0.8	1.1±0.8	0.5646
Range	0-3.5	0-3.0	0-3.0	0-3.0	0-4.0	0-4.0	
Rhinorrhea							
Mean ±SD	1.5±0.9	1.4±0.9	1.5±0.9	1.3±0.9	1.4±0.9	1.4±0.9	0.1359
Range	0-3.0	0-3.5	0-3.5	0-3.0	0-3.0	0-3.5	
Itchy Nose, Palate and/or Throat							
Mean ±SD	1.4±0.9	1.4±0.9	1.5±0.9	1.3±0.9	1.3±0.8	1.4±0.9	0.2828
Range	0-3.5	0-4.0	0-3.5	0-3.0	0-3.0	0-4.0	
Itchy, Watery, Red Eyes							
Mean ±SD	1.4±1.0	1.5±0.9	1.4±0.9	1.4±0.9	1.5±0.9	1.4±0.9	0.5883
Range	0-3.5	0-4.0	0-3.5	0-3.5	0-4.0	0-4.0	
TSS at Bedtime (Excluding Nasal Congestion)							
Mean ±SD	5.5±2.8	5.3±2.6	5.5±2.7	5.1±2.6	5.3±2.4	5.3±2.6	0.6102
Range	0-13	0-13	0-12	0-12	0-12	0-13	
* P value from Kruskal-Wallis test							
Supporting Data						Page	
Appendix E3 Listing 1 Kruskal-Wallis Test for Baseline Bedtime Symptom Assessments (ITT)						S8-V1 187-P22	
Appendix I2 Listing 4 Average PM Diary Listing						S8-V1 191-P354	

Table 8-252 Baseline Noon Symptom Assessments (Intent-to-Treat)							
Baseline Symptoms	Placebo BID (n=190)	MDL 16,455A (BID)				Total (n=959)	P value*
		20 mg (n=194)	40 mg (n=194)	60 mg (n=191)	80 mg (n=190)		
Nasal Congestion							
Mean±SD	1.6±0.9	1.6±0.9	1.6±1.0	1.5±0.9	1.8±0.9	1.6±0.9	0.2531
Range	0-3.0	0-4.0	0-4.0	0-4.0	0-4.0	0-4.0	
Sneezing							
Mean±SD	1.2±1.0	1.1±1.0	1.3±1.0	1.1±1.0	1.1±0.9	1.2±0.9	0.1142
Range	0-3.0	0-4.0	0-4.0	0-3.0	0-3.0	0-4.0	
Rhinorrhea							
Mean±SD	1.7±1.1	1.3±0.9	1.6±1.1	1.4±1.0	1.5±1.0	1.5±1.0	0.0025
Range	0-4.0	0-4.0	0-4.0	0-4.0	0-3.0	0-4.0	
Itchy Nose, Palate and/or Throat							
Mean±SD	1.5±1.0	1.3±1.0	1.5±1.0	1.3±1.0	1.4±1.0	1.4±1.0	0.1913
Range	0-3.0	0-4.0	0-4.0	0-4.0	0-3.0	0-4.0	
Itchy, Watery, Red Eyes							
Mean±SD	1.4±1.0	1.3±1.0	1.4±1.0	1.3±1.0	1.4±1.0	1.4±1.0	0.6870
Range	0-4.0	0-4.0	0-4.0	0-3.0	0-4.0	0-4.0	
TSS at Noon (Excluding Nasal Congestion)							
Mean±SD	5.8±3.1	5.1±2.8	5.8±3.3	5.1±2.9	5.3±2.6	5.4±3.0	0.0257
Range	0-13.0	0-13.0	0-15.0	0-12.0	0-12.0	0-15.0	
* P value from Kruskal-Wallis test							
Supporting Data						Page	
Appendix E3, Listing 2: Kruskal-Wallis Test for Baseline Noon Assessments (ITT)						S8-V1.187-P40	
Appendix 12, Listing 3: Average AM Diary Listing						S8-V1.191-P285	

Table 8-253 Baseline Physician's Rating of Symptoms (Intent-to-Treat)							
Baseline Symptoms	Placebo BID (n=190)	MDL 16,455A (BID)				Total Active (n=962)	P value*
		20 mg (n=194)	40 mg (n=195)	60 mg (n=191)	80 mg (n=192)		
Nasal Congestion							
Mean±SD	2.0±0.8	2.0±0.8	2.2±0.7	1.9±0.8	2.1±0.7	2.1±0.7	0.0744
Range	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	
Sneezing							
Mean±SD	1.7±0.9	1.9±0.8	1.9±0.8	1.8±0.8	1.7±0.8	1.8±0.8	0.0722
Range	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	
Rhinorrhea							
Mean±SD	2.1±0.7	2.2±0.7	2.2±0.7	2.1±0.7	2.3±0.7	2.2±0.7	0.0970
Range	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	
Itchy Nose, Palate and/or Throat							
Mean±SD	1.9±0.8	1.9±0.8	2.0±0.8	1.9±0.7	1.9±0.8	1.9±0.8	0.5484
Range	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	
Itchy, Watery, Red Eyes							
Mean±SD	1.8±0.9	2.1±0.8	2.1±0.8	1.9±0.9	1.8±0.9	1.9±0.9	0.0070
Range	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	0-3.0	
TSS (Excluding Nasal Congestion)							
Mean±SD	7.6±1.8	8.0±1.8	8.2±1.9	7.8±1.8	7.8±1.9	7.9±1.9	0.0265
Range	4-12.0	4-12.0	4-12.0	4-12.0	4-12.0	4-12.0	
* P value from Kruskal-Wallis test							
Supporting Data						Page	
Appendix E3, Listing 3: Kruskal-Wallis Test for Baseline Physician's Rating of Symptoms (ITT)						S8-V1.187-P57	
Appendix 12, Listing 5: Physician's Rating of Individual Symptoms						S8-V1.192-P1	

Reviewer Comments Regarding Baseline Symptom Assessments

For baseline patient's bedtime symptom assessments, there were no statistically significant differences observed across the treatment groups. For baseline noon symptom assessments there were statistically significant differences observed for rhinorrhea and TSS across the treatment groups; and for baseline physician's rating of symptoms there were statistically significant differences observed for all symptoms except for Itchy Nose, Palate and/or Throat.

Results - Patient Compliance with Study Procedures

The sponsor summarizes duration of exposure to double-blind treatment which was estimated using the first and last date of symptom assessments during the double-blind period. The sponsor reports that six subjects had inadequate information to compute the duration of exposure but that the mean duration of exposure was 14 ± 2 days with a range of 1 to 16 days.

The sponsor's table indicates that compliance with double blind treatment was 99-100% for each treatment with the broadest range for the 80mg dose (62-175%) and that 18 subjects had compliance below 80% or above 120%. Compliance was computed by dividing the total number of doses taken during the double-blind period by the total number of doses that should have been taken based on the number of days the patient was exposed to double-blind study medication.

We asked the sponsor to provide a summary of subject's compliance with diary symptom assessments. On December 13, 1995 the sponsor reported that compliance in completing diary symptom assessments for the ITT population was $99.8 \pm 1.1\%$ for protocol #PJPR0009.

For major protocol violations based on concomitant medications, the sponsor reports that 24 subjects (24/782 - 3.0%) receiving fexofenadine and 8 subjects (8/193 - 4.0%) receiving placebo had such violations - Placebo-8; 20mg-7; 40mg-6; 60mg-8; 80mg-3.

Reviewer Comment Regarding Patient Compliance

It does not appear that any of these factors were substantially imbalanced across study treatments.

Results - Efficacy

Results - Primary Efficacy Parameter (Average Bedtime TSS) - Intent-To-Treat Analysis

The pre-defined primary assessment of efficacy was the subject's change in bedtime TSS from baseline in the ITT population compared to placebo. The change from baseline was computed by subtracting the average Bedtime TSS during the placebo lead-in period from the average bedtime TSS during the double-blind period. These results were summarized by the sponsor in Table 8-257 and Figure 8-123 reproduced below. The 80mg and 40mg treatments were statistically significant over placebo with the 40mg dose exhibiting a slightly larger numerical reduction in symptom scores compared to all other active treatments. The 60mg and 20mg did not reach statistical significance over placebo but the trend was toward statistical significance with $p=0.0907$ and $p=0.0515$, respectively.

Table 8-257. Intent-to-Treat Analysis of Bedtime TSS (N=962)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean ±SE</i>		
		<i>Baseline</i>	<i>Double Blind Period</i>	<i>Change from Baseline*</i>
Placebo	190	5.47±0.20	4.75±0.19	-0.66±0.14
20 mg MDL 16,455A	194	5.30±0.19	4.28±0.18	-1.03±0.13
40 mg MDL 16,455A	195	5.52±0.19	3.98±0.17	-1.46±0.13
60 mg MDL 16,455A	191	5.14±0.19	4.23±0.17	-0.98±0.14
80 mg MDL 16,455A	192	5.31±0.18	4.00±0.18	-1.32±0.13
<i>Treatment Comparison</i>		<i>Mean ±SE* (Active-Placebo)</i>		<i>P value*</i>
Overall Treatment Differences				0.0002
Dose Response (Linear Trend)				0.0028
20 mg MDL 16,455A vs Placebo		-0.37±0.19		0.0515
40 mg MDL 16,455A vs Placebo		-0.80±0.19		0.0001
60 mg MDL 16,455A vs Placebo		-0.32±0.19		0.0907
80 mg MDL 16,455A vs Placebo		-0.66±0.19		0.0005
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
<i>Supporting Data:</i>				<i>Page</i>
Appendix E3, Listing 4: <i>Intent-to-Treat Analysis of Bedtime TSS</i>				S8-V1.187-P73
Appendix I2, Listing 4: <i>Average PM Diary Listing</i>				S8-V1.191-P354

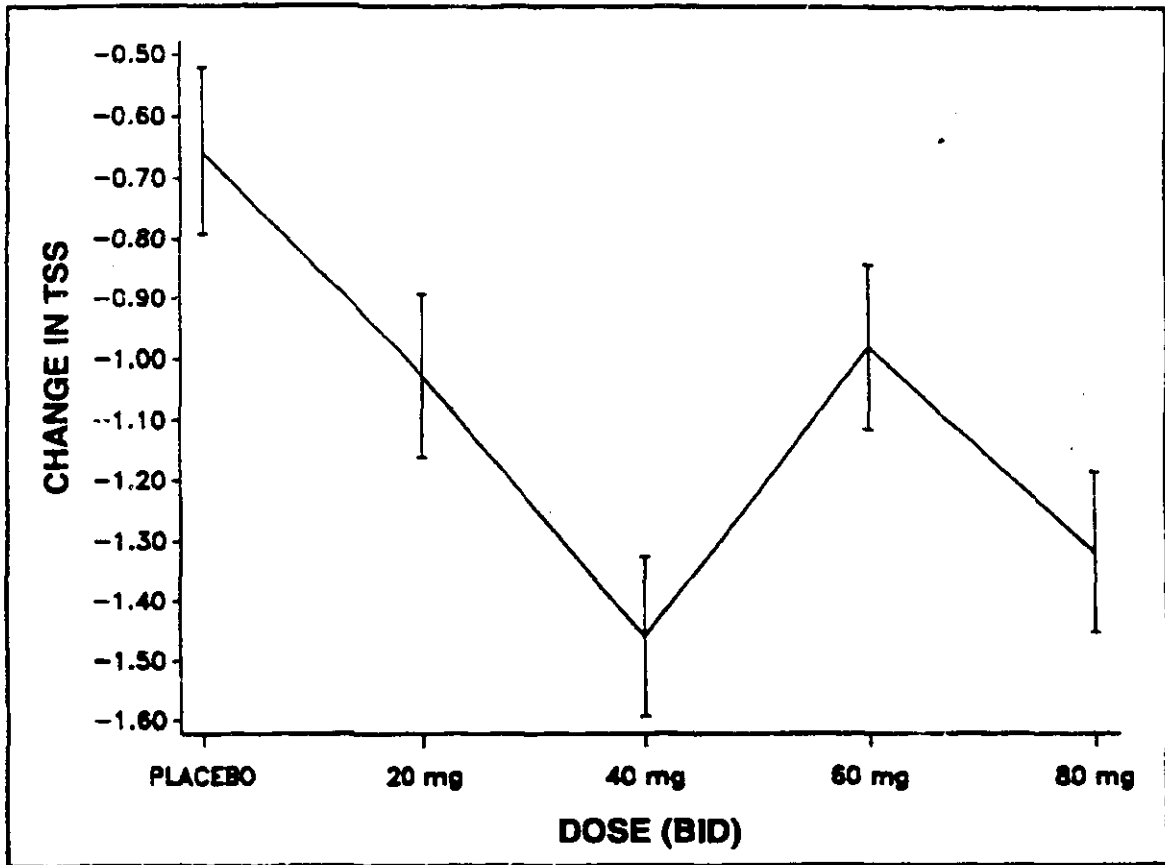


Figure 8-123. Change From Baseline in TSS. Mean $\pm$ SE (Intent-to-Treat)

Supporting Data:	Page
Appendix E3, Listing 4: Intent-to-Treat Analysis of Bedtime TSS	S8-V1.187-P73
Appendix I2, Listing 4: Average PM Diary Listing	S8-V1.191-P354

Results - Primary Efficacy Parameter (Average Bedtime TSS) - Protocol Correct Analysis

The sponsor performed a secondary analysis using 915 patients with no major protocol violations and summarized the results in Table 8-258 and Figure 8-124, reproduced below. The results from the protocol correct analysis are very similar to those from the ITT analysis.

Table 8-258. Protocol Correct Analysis of Bedtime TSS (N=915)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean ± SE</i>		
		<i>Baseline</i>	<i>Double Blind Period</i>	<i>Change from Baseline*</i>
Placebo	181	5.42±0.21	4.69±0.19	-0.67±0.13
20 mg MDL 16,455A	186	5.26±0.19	4.27±0.18	-0.99±0.13
40 mg MDL 16,455A	185	5.52±0.20	3.98±0.17	-1.46±0.13
60 mg MDL 16,455A	181	5.04±0.19	4.16±0.17	-0.97±0.13
80 mg MDL 16,455A	182	5.34±0.18	3.96±0.18	-1.37±0.13
<i>Treatment Comparison</i>	<i>Mean ± SE*</i> <i>(Active-Placebo)</i>		<i>P value *</i>	
Overall Treatment Differences			0.0001	
Dose Response (Linear Trend)			0.0012	
20 mg MDL 16,455A vs Placebo	-0.32±0.19		0.0871	
40 mg MDL 16,455A vs Placebo	-0.79±0.19		0.0001	
60 mg MDL 16,455A vs Placebo	-0.30±0.19		0.1147	
80 mg MDL 16,455A vs Placebo	-0.70±0.19		0.0002	
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
<i>Supporting Data:</i>			<i>Page</i>	
<i>Appendix E3, Listing 5: Protocol Correct Analysis of Bedtime TSS</i>			<i>S8-V1.187-P78</i>	
<i>Appendix I2, Listing 4: Average PM Diary Listing</i>			<i>S8-V1.191-P354</i>	

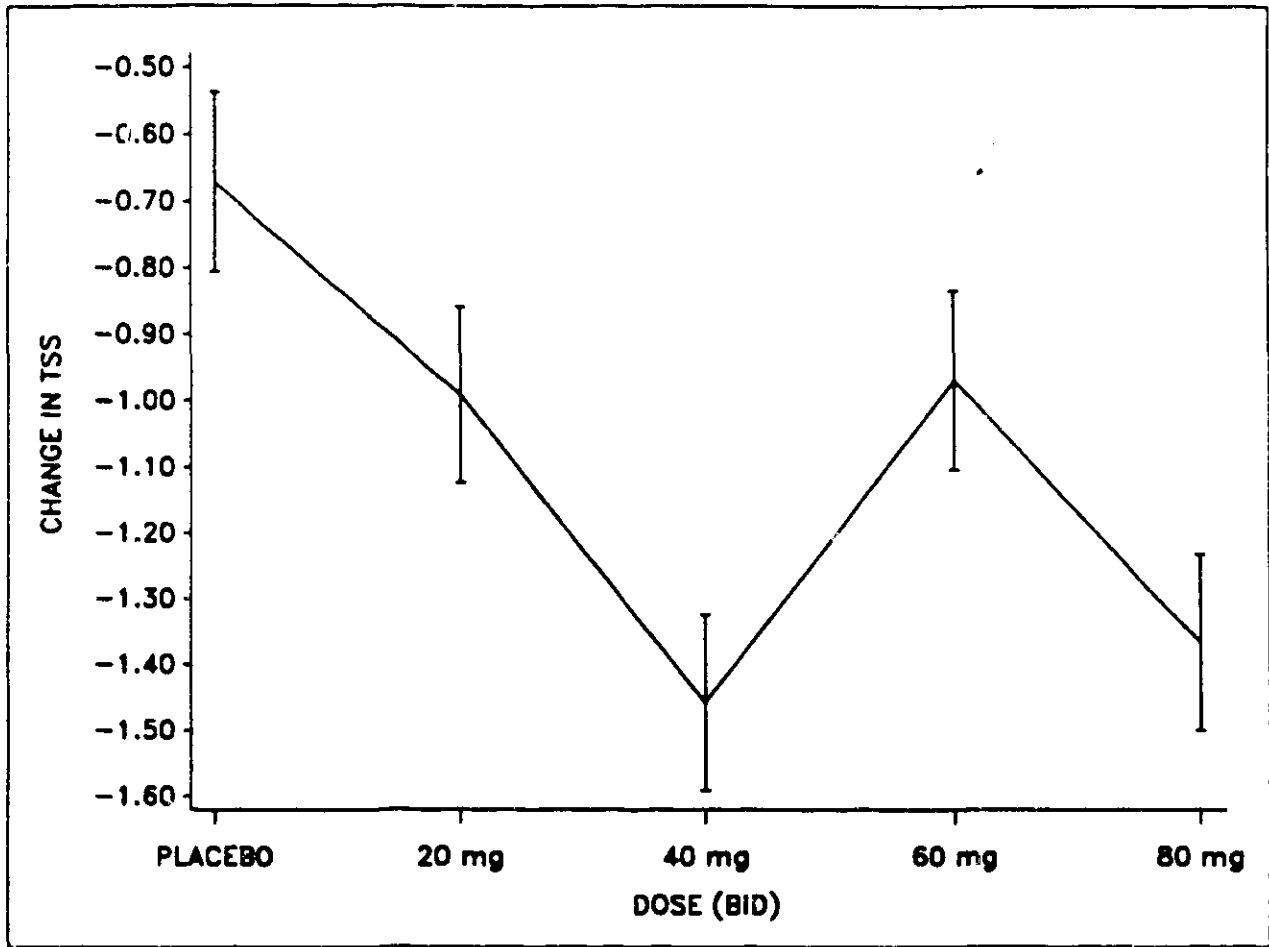


Figure 8-124. Change From Baseline in TSS. Mean ± SE (Protocol Correct)

Supporting Data:	Page
Appendix E3, Listing 5: Protocol Correct Analysis of Bedtime TSS	S8-V1.187-P78
Appendix I2, Listing 4: Average PM Diary Listing	S8-V1.191-P354

Reviewer Comment Regarding Results of the Primary Efficacy Parameter

The results from the primary pre-planned efficacy parameter in the ITT population support the assertion that fexofenadine in doses of 40mg and 80mg can mitigate the symptoms of seasonal allergic rhinitis. It is difficult to understand why the 60mg dose was unable to reach statistical significance. The results from the protocol correct analysis are in agreement with those from the ITT analysis.

The sponsor indicates that a dose response (linear trend) was also statistically significant ($p=0.0028$). The question regarding the inclusion of zero in the statistical computation and the appropriateness of this test for linear response will need examination by the statistical reviewer.

Results - Secondary Efficacy Parameters - Alternative Analysis of Efficacy

For bedtime reflective TSS using the ITT population, the sponsor calculated the number and percentage of subjects with greater than 20% reduction in bedtime TSS. They are: Placebo=41%; 20mg=52%; 40mg=57%; 60mg=49%; and 80mg=56%.

Reviewer Comment Regarding Alternative Analyses

At our request the sponsor submitted on December 22, 1995 additional calculations for larger reductions in bedtime reflective TSS. The table below displays the sponsor's calculations for the percentage of subjects with greater than 20% and 50% reduction in bedtime TSS. All active treatments exhibit a larger response than placebo. The magnitude of percentages at the 50% level of response is in general less than half that of the 20% level with a slightly larger reduction in the 20mg and 60mg groups in the number of subjects responding at the 50% level. The statistical significance levels are with respect to placebo.

Symptom Improvement Above A Fixed Level			
PJPR0009	N	≥20%	≥50%
Placebo	190	41%	14%
20mg	194	52% p=0.029	19% p=0.219
40mg	195	57% p=0.001	30% p<0.001
60mg	191	49% p=0.092	19% p=0.188
80mg	192	56% p=0.002	26% p=0.003

An alternative definition of response was also provided by the sponsor - improvement greater than the average improvement in the placebo treated subjects. The table below summarizes the results for this alternative definition. The magnitude of response at the 50% level is only slightly less than that at the 20% level.

Symptom Improvement Above Placebo			
PJPR0009	N	≥20%	≥50%
Placebo	190	45%	43%
20mg	194	55% p=0.053	51% p=0.114
40mg	195	63% p<0.001	60% p=0.001
60mg	191	53% p=0.102	50% p=0.177
80mg	192	58% p=0.009	55% p=0.020

The response rates observed in the examination of these data suggest that 40mg and 80mg treatments are more effective than placebo.

Results - Secondary Efficacy Parameters - Daily Bedtime TSS

The sponsor provided an analysis of response compared to placebo for each day for change from baseline in daily bedtime TSS using the ITT population. The sponsor's table is reproduced below. All active treatments reach statistical significance by Day 1 but only the 40mg and 80mg doses sustain statistical significance through to Day 14, with statistical significance on 12 of 14 days for the 40mg dose and statistical significance on 9 of 14 days for the 80mg dose. The 20mg and 60mg doses each reach statistical significance on only 3 of the 14 days.

Day		Mean Change from Baseline					Dose Response P value*
		Placebo BID (N=196)	MIL 16 455A (BID)				
			20 mg (N=197)	40 mg (N=196)	60 mg (N=198)	80 mg (N=195)	
1	n	190	192	194	191	192	0.0001
	Mean ± SE	-0.02 ± 0.16	-0.96 ± 0.16	-0.94 ± 0.16	-0.88 ± 0.16	-1.07 ± 0.16	
	P value*		0.0001	0.0001	0.0001	0.0001	
2	n	186	194	195	191	192	0.0003
	Mean ± SE	-0.37 ± 0.17	-0.91 ± 0.17	-1.36 ± 0.17	-1.01 ± 0.17	-1.30 ± 0.17	
	P value*		0.0275	0.0001	0.0092	0.0001	
3	n	188	191	193	191	191	0.0032
	Mean ± SE	-0.60 ± 0.18	-0.88 ± 0.18	-1.55 ± 0.18	-1.12 ± 0.18	-1.31 ± 0.18	
	P value*		0.2652	0.0002	0.0346	0.0052	
4	n	189	190	193	190	190	0.0608
	Mean ± SE	-0.64 ± 0.18	-1.23 ± 0.18	-1.63 ± 0.18	-0.84 ± 0.18	-1.40 ± 0.18	
	P value*		0.0289	0.0072	0.4933	0.0045	
5	n	186	189	193	189	190	0.2244
	Mean ± SE	-0.72 ± 0.19	-1.21 ± 0.19	-1.68 ± 0.19	-0.86 ± 0.19	-1.25 ± 0.19	
	P value*		0.0689	0.0004	0.5830	0.0063	
6	n	184	187	190	186	190	0.1393
	Mean ± SE	-0.86 ± 0.20	-0.97 ± 0.20	-1.44 ± 0.19	-1.24 ± 0.20	-1.03 ± 0.19	
	P value*		0.6890	0.0357	0.1760	0.3540	
7	n	178	180	184	181	182	0.1314
	Mean ± SE	-0.81 ± 0.20	-1.05 ± 0.20	-1.17 ± 0.20	-1.10 ± 0.20	-1.26 ± 0.20	
	P value*		0.3833	0.1674	0.3078	0.4072	
8	n	181	183	188	185	184	0.0610
	Mean ± SE	-0.91 ± 0.20	-0.87 ± 0.20	-1.27 ± 0.19	-1.08 ± 0.20	-1.39 ± 0.20	
	P value*		0.8659	0.1986	0.5627	0.0055	
9	n	182	185	186	185	185	0.1684
	Mean ± SE	-0.71 ± 0.20	-1.21 ± 0.19	-1.55 ± 0.19	-0.78 ± 0.19	-1.35 ± 0.19	
	P value*		0.0690	0.0023	0.7977	0.0004	
10	n	181	183	186	186	184	0.0469
	Mean ± SE	-0.88 ± 0.20	-1.07 ± 0.20	-1.61 ± 0.20	-1.01 ± 0.20	-1.54 ± 0.20	
	P value*		0.5025	0.0101	0.6461	0.0200	
11	n	181	185	186	186	182	0.1306
	Mean ± SE	-0.93 ± 0.20	-1.12 ± 0.20	-1.51 ± 0.20	-0.98 ± 0.20	-1.47 ± 0.20	
	P value*		0.4912	0.0377	0.8404	0.0538	
12	n	178	182	183	182	178	0.1638
	Mean ± SE	-0.90 ± 0.20	-1.24 ± 0.20	-1.58 ± 0.20	-1.13 ± 0.20	-1.40 ± 0.20	
	P value*		0.2454	0.0175	0.4261	0.0027	
13	n	133	133	136	118	111	0.0121
	Mean ± SE	-0.54 ± 0.25	-1.16 ± 0.25	-1.31 ± 0.25	-0.84 ± 0.27	-1.73 ± 0.28	
	P value*		0.0765	0.0277	0.4133	0.0012	
14	n	70	75	69	64	64	0.0060
	Mean ± SE	0.12 ± 0.38	-0.94 ± 0.35	-1.72 ± 0.38	-0.81 ± 0.39	-1.77 ± 0.39	
	P value*		0.1003	0.0016	0.1805	0.0015	

* P value, mean and associated standard error from an ANCOVA model containing investigative site, treatment and baseline

Reviewer Comment Regarding Daily Bedtime TSS

These data suggest that the durable doses are 40mg and 80mg. It is difficult to understand the failure of the 60mg dose to mimic the responses observed for the 40mg dose.

Results - Secondary Efficacy Parameters - Bedtime Individual Symptoms and TSS

The sponsor provided an analysis of change from baseline compared to placebo in bedtime individual symptom assessments using the ITT population. No dose level achieved statistical significance over placebo for nasal congestion. The 40mg and 80mg doses levels achieved statistical significance for all symptoms while 20mg and 60mg dose levels achieved statistical significance only for sneezing.

Symptoms		Placebo BID (N=190)	MDL 16 455A (BID)				Dose Response P Value*
			20 mg (N=194)	40 mg (N=195)	60 mg (N=191)	80 mg (N=192)	
Nasal Congestion	n	190	194	195	191	192	0.5231
	Mean ±SE	-0.18±0.04	-0.15±0.04	-0.25±0.04	-0.20±0.04	-0.20±0.04	
	P value*		0.6238	0.2212	0.7829	0.7408	
Sneezing	n	190	194	195	191	192	0.0018
	Mean ±SE	-0.07±0.04	-0.20±0.04	-0.25±0.04	-0.24±0.04	-0.24±0.04	
	P value*		0.0201	0.0012	0.0016	0.0022	
Rhinorrhea	n	190	194	195	191	192	0.0325
	Mean ±SE	-0.15±0.04	-0.21±0.04	-0.33±0.04	-0.22±0.04	-0.29±0.04	
	P value*		0.2997	0.0029	0.2296	0.0212	
Itchy Nose, Palate and/or Throat	n	190	194	195	191	192	0.1731
	Mean ±SE	-0.23±0.04	-0.34±0.04	-0.44±0.04	-0.24±0.04	-0.35±0.04	
	P value*		0.0664	0.0005	0.9509	0.0182	
Itchy, Watery, Red Eyes	n	190	194	195	191	192	0.0012
	Mean ±SE	-0.21±0.04	-0.29±0.04	-0.44±0.04	-0.30±0.04	-0.42±0.04	
	P value*		0.1786	0.0002	0.1233	0.0004	
TSS (Excluding Nasal Congestion)	n	190	194	195	191	192	0.0028
	Mean ±SE	-0.66±0.14	-1.03±0.13	-1.46±0.13	-0.98±0.14	-1.32±0.13	
	P value*		0.0515	0.0001	0.0907	0.0005	

* P value, mean and associated standard error from an ANCOVA model containing investigative site, treatment, and baseline

Supporting Data	Page
Appendix E3, Listing 7 Intent-to-Treat Analysis of Bedtime Individual Symptoms and TSS	S6-V1 187-P126
Appendix I2, Listing 4 Average PM Diary Listing	S6-V1 191-P354

Results - Secondary Efficacy Parameters - Noon TSS

The sponsor also provided an analysis of change from baseline for noon TSS using the ITT population. Only the 40mg dose achieved statistical significance from placebo with the 80mg dose approaching statistical significance.

Table 8-262. Intent-to-Treat Analysis of Noon TSS (N=959)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean ± SE</i>		
		<i>Baseline</i>	<i>Double Blind Period</i>	<i>Change from Baseline*</i>
Placebo	190	5.75 ± 0.23	4.79 ± 0.18	-0.76 ± 0.14
20 mg MDL 16.455A	194	5.06 ± 0.20	4.34 ± 0.17	-0.89 ± 0.14
40 mg MDL 16.455A	194	5.82 ± 0.23	4.16 ± 0.16	-1.43 ± 0.14
60 mg MDL 16.455A	191	5.06 ± 0.21	4.35 ± 0.17	-0.88 ± 0.14
80 mg MDL 16.455A	190	5.34 ± 0.19	4.23 ± 0.17	-1.12 ± 0.14
<i>Treatment Comparison</i>		<i>Mean ± SE *</i> <i>(Active-Placebo)</i>		<i>P value *</i>
Overall Treatment Differences				0.0047
Dose Response (Linear Trend)				0.1022
20 mg MDL 16.455A vs Placebo		-0.13 ± 0.19		0.4985
40 mg MDL 16.455A vs Placebo		-0.67 ± 0.19		0.0006
60 mg MDL 16.455A vs Placebo		-0.12 ± 0.20		0.5367
80 mg MDL 16.455A vs Placebo		-0.36 ± 0.20		0.0640
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
<i>Supporting Data:</i>				<i>Page</i>
<i>Appendix E3, Listing 8: Intent-to-Treat Analysis of Noon TSS</i>				<i>S8-VI.187-P151</i>
<i>Appendix I2, Listing 3: Average AM Diary Listing</i>				<i>S8-VI.191-P285</i>

Reviewer Comment Regarding Individual Symptom Scores and Noon Symptom Scores

The results of these analyses suggest that the 40mg and 80mg doses are superior to the other doses in controlling all the symptoms of SAR except nasal congestion. Noon symptom scores continue to support the efficacy of the 40mg dose.

Results - Secondary Efficacy Parameters - Average Morning Predose TSS

The sponsor provides an analysis of change from baseline for average morning predose TSS using the ITT population. This analysis was included in the protocol to represent trough levels (i.e. end-of-dosing interval). Only the 40mg dose reached statistical significance from placebo (p=0.0002) with 80mg the nearest other dose level (p=0.0990). The sponsor also conducted a supportive analysis excluding patients with the minor protocol violation of less than 8 hours or more than 16 hours from the time of the last dose to the morning predose symptom assessment. With this enriched population only the 40mg dose attained statistical significance (p=0.0007) with the 80mg dose approaching statistical significance (p=0.0541).

Results - Secondary Efficacy Parameters -**Physician's Assessment of Individual Symptoms and TSS**

The sponsor provides an analysis of change from baseline compared to placebo for the physician's assessment of individual symptoms and TSS using the ITT population. For nasal congestion no dose achieved statistical significance. For TSS all doses achieved statistical significance ($P = 0.0425, 0.0119, 0.0142, 0.0050$ for 20mg, 40mg, 60mg, 80mg respectively). The 80mg dose achieved statistical significance only for sneezing and rhinorrhea ($p = 0.0283, 0.0108$, respectively). The 60mg dose achieved statistical significance for sneezing, rhinorrhea, and itchy nose/palate/throat ($p = 0.0143, 0.0380, 0.0346$, respectively) but not for itchy/watery/red eyes. The 40mg dose achieved statistical significance only for itchy nose/palate/throat and itchy/watery/red eyes ($p = 0.0225, 0.0085$, respectively). The 20mg dose achieved statistical significance only for itchy nose/palate/throat ($p = 0.0500$).

Results - Secondary Efficacy Parameters -**Physician's Evaluation of Overall Effectiveness**

Responders were defined as subjects having moderate, marked or complete relief of symptoms. Only the 20mg ($p = 0.037$) and 40mg ($p = 0.004$) dose levels achieved statistical significance. The reported response rates were: Placebo-45.3%; 20mg-56.0%; 40mg-59.8%; 60mg-54.5%; and 80mg-50.5%.

Results - Secondary Efficacy Parameters -**Patient's Willingness to Take Study Medication Again**

All active dose groups had a greater percentage of patients compared to placebo willing to take the study medication again (Placebo-55.3%; 20mg-57.2%; 40mg-62.9%; 60mg-57.6%; and 80mg-58.9%) but none of the active treatments achieved statistical significance.

Results - Subgroup Analyses

The sponsor provides the results of additional analyses using the ITT population for interaction using subgroup factors and bedtime TSS. The sponsor reports that the analyses were not statistically significant for interaction between treatment and investigative site ($p = 0.3988$); age ($p = 0.3390$); gender ($p = 0.5230$); race ($p = 0.1754$); and weight ($p = 0.7908$).

Results - By-Weekly Symptom Analysis for Efficacy

On December 8, 1995, at our request, the sponsor submitted analyses of individual symptoms and TSS over each week of the study. After examining each individual symptom score and TSS for statistical significance ($p \leq 0.05$) and trend in statistical significance ($p \leq 0.1$) the following general patterns were observed.

None of the doses demonstrated efficacy for nasal congestion for either week.

For bedtime individual symptoms and TSS, the 40mg and 80mg doses maintained efficacy over both weeks; while the 60mg dose maintained efficacy only for sneezing and the 20mg dose only for sneezing and itchy nose.

For noon individual symptoms and TSS, only the 40mg dose maintained efficacy for each symptom for both weeks for each individual symptom except rhinorrhea.

For morning predose individual and TSS, only the 40mg dose maintained efficacy for both weeks, while the 60mg and 20mg dose maintained efficacy for only sneezing

- ++ = Statistically Significant i.e. ≤ 0.05
- + = Trend i.e. > 0.05 and < 0.10
- = Statistically Insignificant i.e. ≥ 0.10

Bedtime Individual Symptoms and TSS for PIPR0009

Symptoms Week 1	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	++	++
Rhinorrhea	-	++	-	++
Itchy Nose	+	++	-	++
Itchy Eyes	+	++	+	++
TSS	++	++	++	++
Symptoms Week 2	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	++	++
Rhinorrhea	-	++	-	+
Itchy Nose	+	++	-	++
Itchy Eyes	-	++	-	++
TSS	-	++	-	++

Noon Individual Symptoms and TSS for PIPR0009

Symptoms Week 1	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	++	++
Rhinorrhea	-	-	-	-
Itchy Nose	-	++	-	+
Itchy Eyes	-	++	-	++
TSS	-	++	-	++
Symptoms Week 2	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	+	++	-	-
Rhinorrhea	-	-	-	-
Itchy Nose	-	++	-	-
Itchy Eyes	-	++	-	-
TSS	-	++	-	-

Morning Predose Individual Symptoms and TSS for PIPR0009

Symptoms Week 1	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	++	-
Rhinorrhea	-	++	-	-
Itchy Nose	-	++	-	-
Itchy Eyes	-	++	-	-
TSS	-	++	-	-
Symptoms Week 2	20mg	40mg	60mg	80mg
Nasal Congestion	-	-	-	-
Sneezing	++	++	+	++
Rhinorrhea	-	++	-	-
Itchy Nose	++	++	-	-
Itchy Eyes	-	++	-	+
TSS	-	++	-	++

Safety Results - Adverse Events

A total of 975 patients were exposed to double-blind study medication during the study of which 972 were considered safety evaluable because 3 patients were lost to follow-up after the Entry Visit. Overall the sponsor reports that the total number of patients with 1 or more adverse event was: Placebo-73 (38%); 20mg-63 (32%); 40mg-67 (34%); 60mg-67 (34%); 80mg-56 (29%). The table below condenses the sponsor's table of the incidence of all adverse events to show those events which occurred at a rate of 1% or greater in the total active group.

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (<i>BID</i>) (<i>N</i> = 192) <i>N</i> (%)	MDL 16,455A (<i>BID</i>)				Total Active (<i>N</i> = 780) <i>N</i> (%)
		20 mg (<i>N</i> = 195) <i>N</i> (%)	40 mg (<i>N</i> = 196) <i>N</i> (%)	60 mg (<i>N</i> = 196) <i>N</i> (%)	80 mg (<i>N</i> = 193) <i>N</i> (%)	
HEADACHE	18 (9.4)	22 (11.3)	20 (10.2)	23 (11.7)	14 (7.3)	7 (10.1)
DROWSINESS	3 (1.6)	3 (1.5)	4 (2.0)	5 (2.6)	3 (1.6)	15 (1.9)
THROAT IRRITATION	2 (1.0)	6 (3.1)	1 (0.5)	2 (1.0)	3 (1.6)	12 (1.5)
EPISTAXIS	1 (0.5)	0 (0.0)	2 (1.0)	4 (2.0)	2 (1.0)	8 (1.0)
NAUSEA	3 (1.6)	1 (0.5)	4 (2.0)	4 (2.0)	0 (0.0)	9 (1.2)
DIARRHEA	0 (0.0)	2 (1.0)	3 (1.5)	2 (1.0)	1 (0.5)	8 (1.0)
BACK PAIN	1 (0.5)	4 (2.1)	2 (1.0)	3 (1.5)	1 (0.5)	10 (1.3)
MYALGIA	1 (0.5)	3 (1.5)	0 (0.0)	5 (2.6)	1 (0.5)	9 (1.2)
INFECTION VIRAL	1 (0.5)	4 (2.1)	4 (2.0)	6 (3.1)	4 (2.1)	18 (2.3)
URINARY TRACT INFECTION	3 (1.6)	1 (0.5)	1 (0.5)	3 (1.5)	4 (2.1)	9 (1.2)

Reviewer Comment Regarding Adverse Events

From the table above the following events may have occurred slightly more frequently in the active treatment group than in the placebo group: headache, throat irritation, epistaxis, diarrhea, back pain, myalgia, infection viral.

Deaths and Discontinuations Due to Adverse Events

The sponsor reports no deaths occurred during this trial. One patient (014-007) who was taking fexofenadine was hospitalized for a broken leg on Day 6 of treatment with 40 mg MDL 16,455A BID. This event was assessed by the investigator as not related to study medication. The sponsor summarizes information regarding subjects who had discontinued medication due to adverse events in the table reproduced below.

Table 8.274 Summary of Patients Who Discontinued Study Medication Due to Adverse Events

Patient	Age	Sex	Treatment (BID)	Adverse Event (Preferred Term)	Duration of Double Blind Treatment Prior to Discontinuation (days)	Severity	Study Drug Relation	Outcome
019-014								
019-015								
019-016								
019-017								
019-018								
019-019								
019-020								
019-021								
019-022								
019-023								
019-024								
019-025								
019-026								
019-027								
019-028								
019-029								
019-030								
019-031								
019-032								
019-033								
019-034								
019-035								
019-036								
019-037								
019-038								
019-039								
019-040								
023-055								
024-029								
024-051								
024-069								
025-038								
026-021								
026-056								
Patient was hospitalized and discontinued the study due to this adverse event.								
Supporting Data								Page
Appendix 13 Listing 8 Adverse Events Meeting the Serious Criteria								58-V1 193-P167

Reviewer Comment Regarding Discontinuations Due to Adverse Events

In reviewing the narratives for these subjects it is difficult to ascribe causality of the adverse event to active treatment or placebo.

Other Adverse Event Information

During the study, one patient (019-014) receiving 20 mg MDL 16,455A BID became pregnant as confirmed by a serum pregnancy test at the Final Visit. As of the date of this report the patient has not delivered the baby. Additional information will be reported when it becomes available.

Clinical Laboratory Evaluation

The sponsor reports that two laboratory parameters had statistically significant mean change from baseline compared to placebo: SGPT (p=0.0162; r=0.0774) with the largest change in the 60mg group of -1.2 ± 0.36 U/L and albumin (p=0.0036, r=-0.0938) with the change in all dose groups of -0.1 ± 0.01 or 0.02 g/dL.

Vital Signs

The sponsor reports no statistically significant change in SBP, DBP, or HR from baseline to the final visit in patients treated with fexofenadine compared to placebo.

Pharmacokinetic Results

A limited number plasma samples were collected for analysis of fexofenadine plasma concentration. One patient (023-057), who received placebo instead of the randomized 80 mg BID dose, had a plasma concentration level that was below the lower level of quantitation for the assay method (1.00 ng/ml) and was not included in the pharmacokinetic analysis. The results are summarized by the sponsor in the table reproduced below.

Treatment (BID)	1-3 Hours Postdose		5-9 Hours Postdose	
	N	Mean (% CV)	N	Mean (% CV)
20 mg MDL 16,455A	5	71.23 (65)	4	36.15 (58)
40 mg MDL 16,455A	6	138.66 (106)	5	79.19 (68)
60 mg MDL 16,455A	10	126.92 (54)	3	56.68 (62)
80 mg MDL 16,455A	6	245.46 (50)	6	129.19 (73)

Supporting Data: Appendix M2. Pharmacokinetic Listings

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Reviewer Comment Regarding Pharmacokinetic Results

Although the number of samples analyzed is very small, the apparent lack of consistent efficacy results for the 60mg and 20mg dose may be partially explained by the relatively lesser drug plasma concentration observed in the patients taking these doses. By a submission to the NDA on February 21, 1996, the sponsor provided a response to our inquiry about this issue. They indicated they have reexamined the process of packaging of drug and could find no abnormalities in the process. They also comment that they believe the small number of samples and the degree of variability in the peak concentrations in pharmacokinetic trials are the reasons for the lower concentrations observed in the 60mg dose group than the 40mg dose group.

Division of Scientific Investigations Audit (DSI) Results for Protocol PJPR0009 (Please refer to DSI audit results for the NDA for results regarding other protocols)

Material Reviewed: NDA 20-625 - Amendment Dated January 19, 1996

Discrepant Treatment Assignments

On January 18, 1996 the sponsor initiated a teleconference with the Agency to report a discrepancy in treatment assignment involving 10 patients from protocol PJPR0009. The sponsor reported that a discrepancy was found on January 10, 1996 by an FDA auditor conducting an investigative site inspection at site 21. The auditor noted that the by-patient tabulation from the NDA (V1.335-P128) listed patient #021-064 as having received fexofenadine 40mg BID while another data listing indicated the patient was on placebo. The sponsor investigated how the discrepancy occurred for patient #021-

064 and noted that 9 other patients had similar discrepancies which occurred by the same kind of error. On January 19, 1996 the sponsor submitted an amendment to the NDA explaining the nature of the discrepancy and the circumstances under which it occurred. The following is a summary of the sponsor's explanation.

A randomization schedule for double-blind treatment assignment was generated by the sponsor's statistics department. It relates the Treatment Assignment Number (TAN) to the randomized double-blind treatment. The packaging of clinical supplies was conducted using the randomization schedule.

At the time of the Entry Visit, investigators assigned patients to double-blind treatment according to a TAN and recorded the TAN in the patient's case report form (CRF) by using a PC-based computer system (i.e. remote study monitoring system). At the same time a portion of the label from the double-blind treatment supply, which also had the TAN preprinted on it, was affixed to the patient's medication card which was then forwarded to the sponsor by mail. Information from the medication card was entered by the sponsor and compared to the TAN which had been recorded in the CRF by the investigative site at the time of the Entry Visit using the remote study monitoring system. In preparation for data unblinding, a comparison was made between TANs in the CRF and the TANs on the patient medication cards when the sponsor noted that the medication cards for 10 patients from site 27 had not been received and entered. Consequently, verbal confirmation was obtained by the sponsor from site 27 for the TANs from the medication cards of the 10 patients at site 27. In cases where the TAN in the CRF and the TAN on the medication card were different, the sponsor used the TAN preprinted on the portion of the label affixed to the patient's medication card. At the time the computer program was written to select the TANs for each patient prior to unblinding, the 10 TANs verbally communicated from site 27 were incorrectly incorporated into the program for patients 061 through 070 at site 21.

The sponsor declares that for other patients for whom TANs were verbally communicated to the sponsor from the sites have been confirmed to be correctly unblinded and that all patients in other double-blind studies were also correctly unblinded. The sponsor further declares that this confirmation was conducted by a comparison of the TANs on the patient's medication card labels, the TANs in the CRFs, and the TANs from the randomization schedule. The sponsor also declares that all programs used to unblind treatment in the adequate and well controlled studies have been reevaluated to confirm that the error in unblinding is an isolated event that occurred in only protocol PJPR0009.

The sponsor has submitted a summary table of discrepant assignments in protocol PJPR0009, reproduced below. From this table it can be observed that for 4 subjects the incorrect TAN yielded the same treatment as the actual TAN the patient received, so that faulty unblinding yielded a discrepant assignment for only 6 subjects. For these 10 subjects the statistical reviewer, Barbara Bono, and I have confirmed that the listings in the table below for the correct treatments received by the patients match the treatments for the corresponding TANs in the randomization schedule for protocol PJPR0009 (Attachment 1 of the amendment) and the TANs received match the TANs and corresponding patient identification number on the photocopies of the patients medication cards (Attachment 2 of the amendment). Additionally for these 10 patients, we have confirmed that the listed incorrect treatments match the corresponding treatments for the listed incorrect TANs in the randomization schedule and that the listed incorrect treatments match the treatments listed in the statistical (SAS) database for each patient.

Summary of Discrepant Treatment Assignments in PJPR0009				
Patient Number	Treatment Actually Received*		Incorrect Treatment Information **	
	TAN Received	Correct Unblinded Treatment Received	Incorrect TAN	Incorrect Unblinded Treatment
PJST0021-061	971	60mg BID	991	80mg BID
PJST0021-062	972	Placebo	992	40mg BID
PJST0021-063	973	80mg BID	993	60mg BID
PJST0021-064	974	40mg BID	994	Placebo
PJST0021-065	975	20mg BID	995	20mg BID
PJST0021-066	976	80mg BID	996	Placebo
PJST0021-067	977	60mg BID	997	60mg BID
PJST0021-068	978	40mg BID	998	40mg BID
PJST0021-069	979	20mg BID	999	20mg BID
PJST0021-070	980	Placebo	1000	80mg BID

* Correct treatment assignment displayed in by-patient tabulations in Section 11 of NDA 20-625
** Incorrect treatment assignment used in efficacy and safety analyses reported in NDA 20-625

The sponsor has also submitted the results of a reanalysis of the primary parameter, 12 hour reflective total symptom score (TSS), using the corrected database (i.e. correct treatment assignments for the 6 discrepant patients). The results are summarized in the comparative table below. From this table it becomes apparent that with the reanalysis the changes from baseline in TSS are only marginally different and that there is no substantive change in statistical inference for the comparison between each dose level and placebo which would alter the conclusions drawn from the trial.

Primary Efficacy Analysis - Bedtime Reflective ISS - Intent-To-Treat				
Protocol PJPR0009	As Presented in NDA 20-625		Reanalysis- Corrected Treatments	
Treatment	N	Change from Baseline		Change from Baseline
Placebo BID	190	-0.66 ± 0.14		-0.69 ± 0.14
20mg BID	194	-1.03 ± 0.13		-1.03 ± 0.13
40mg BID	195	-1.46 ± 0.13		-1.43 ± 0.13
60mg BID	191	-0.98 ± 0.14		-0.97 ± 0.14
80mg BID	192	-1.32 ± 0.13		-1.32 ± 0.13
Treatment Comparison	Mean ± SE (Active-Placebo)	P Value*	Mean ± SE (Active-Placebo)	P Value*
Overall Treatment Differences		0.0002		0.0007
Dose Response (linear trend)		0.0028		0.0045
20mg vs Placebo	-0.37 ± 0.19	0.0515	-0.34 ± 0.19	0.0767
40mg vs Placebo	0.80 ± 0.19	0.0001	-0.74 ± 0.19	0.0001
60mg vs Placebo	-0.32 ± 0.19	0.0907	-0.28 ± 0.19	0.1471
80mg vs Placebo	-0.66 ± 0.19	0.0005	-0.63 ± 0.19	0.0009
*P values and means from ANCOVA model containing site, treatment and baseline.				

The sponsor also provides copies of the line listings from V1.334 for adverse events for these 10 subjects (Attachment 5 of the amendment). The adverse events noted in patients which received active treatment are few and not particularly concerning.

Patient ID	Treatment	Adverse Event	Intensity	Duration
021-062	Placebo	Thirst	Moderate	Throughout Study
021-063	80mg BID	(Muscle aches) Myalgia from working in yard	Moderate	6 hours
021-064	40mg BID	Constipation	Moderate	20 hours
021-65	20mg BID	(Muscle Aches) Myalgia from golfing	Moderate	2 days
		(Muscle aches) Myalgia	Moderate	< 1 day
021-070	Placebo	Nausea and Vomiting	Moderate	10 hours

The sponsor also provides the laboratory line listings (Attachment 6 of the amendment) for these 10 patients. I have examined the results and have noted minor postbaseline urinalysis changes for 5 subjects (i.e. trace WBCs or RBCs). I have also examined the results for shifts from normal baseline

values to abnormal postbaseline values and have found the following shifts which do not appear to be of magnitudes for clinical concern.

- 021-064 Alk Phosphatase(U/L) 37 to 30(L)
- 021-067 Neutrophils, absolute (X10E3/ul) 3.15 to 1.82(L)
- 021-068 Cholesterol (mg/dL) 156 to 140(L)
- 021-069 Albumin (g/dL) 3.9 to 3.7(L)
Cholesterol (mg/dL) 195 to 202(H)

In this amendment the sponsor also reports that by-line tabulations for 4 additional patients (PJST0016-018; PJST0016-030; PJST0017-034; PJST0024-055) in PJPR0009 are incorrectly reported in Section 11 of NDA 20-625 because the TANs listed are those which were incorrectly recorded in the CFR. However, the sponsor declares that these patients are accurately represented in the reports and summary documents in the NDA because TANs used for these patients were the TANs from the patient medication card labels. We have confirmed for each of these subjects that the corresponding treatments for the TANs on the photocopies of the patients medication cards (Attachment 3 of the amendment) match the treatments listed for these patients in the SAS database.

In this amendment the sponsor also reports that one patient (PJST0023-057) who was randomized to 80mg BID treatment received placebo treatment during week 2 of the study from the treatment supply for another patient (PJST0023-055) who had been randomized to treatment but discontinued from the study before week 2. The sponsor indicates that subject #PJST0023-057 was treated in the analyses as an 80mg BID patient so that the overall effect on study results should not bias the results in favor of active treatment. We have confirmed for these subjects that the corresponding treatments for the TANs recorded on the photocopies of the patients medication cards (Attachment 4 of the amendment) match the treatments listed in the SAS database.

Reviewer Comment Regarding Discrepant Treatment Assignments

The sponsor appears to have adequately explained the events surrounding the occurrence of the discrepant listings discussed above and declares that they have confirmed the accuracy of the databases. Further the sponsor declares that they have reevaluated all programs used to unblind treatments in the other well controlled clinical trials to confirm the isolated nature of the event in protocol PJPR0009.

Considering the marginal influence observed on the efficacy results from the reanalysis of the database for the primary endpoint with the inclusion of the corrected treatments, it does not seem necessary to subject the entire corrected database to reanalysis for efficacy. Furthermore, the efficacy results from the other three well controlled clinical trials without the results from protocol PJPR0009 would appear adequate to support efficacy. Additionally, examination of the safety data from these patients does not reveal large numbers of clinically concerning adverse events or laboratory abnormalities that would alter the interpretation of the safety database for this NDA which includes data from over 2000 patients exposed to fexofenadine during controlled clinical trials.

Final Reviewer Comment Regarding Protocol #PJPR0009: Protocol #PJPR0009 fulfills the criteria for a well controlled clinical trial in support of safety and efficacy of fexofenadine.

Reviewer's Determinations

- 1) The results of the primary pre-defined endpoint of this study support the assertion that compared to placebo treatment fexofenadine is efficacious for the mitigation of the symptoms associated with seasonal allergic rhinitis in doses of 40mg BID and 80mg BID in patients greater than 12 years of age.
- 2) The magnitude of symptom reduction was not demonstrated to be comparable across the doses studied, with only the 40mg and 80mg dose exhibiting statistically significant symptom reduction compared to placebo. It is difficult to explain the inability of the 60mg dose to achieve statistical significance.
- 3) Based on by-weekly analysis of individual symptom scores and TSS, 40mg and 80mg dose sustained efficacy for both weeks for bedtime symptom scores; only the 40mg dose sustained efficacy for both weeks for noon symptom scores except rhinorrhea; and the 40mg dose only sustained efficacy for both weeks for morning predose symptom scores.
- 4) Based on the analysis of bedtime symptoms scores, onset of action within 12 hours can be supported by this trial.
- 5) The very limited morning predose symptom assessments are supportive of end-of-dosing interval efficacy.
- 6) Examination of the safety profile of fexofenadine compared to placebo does not reveal any obvious significant toxicities with doses up to 80mg BID after two weeks administration. EKGs were not measured during this trial.
- 7) There does not appear to be an interaction between fexofenadine and age, gender, race or weight.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: Protocol PJPR0023 from NDA 20-625

Protocol No. PJPR0023 - conducted from August 15 to November 19, 1994.

Title

"A Double-Blind, Randomized, Placebo-Controlled, Parallel Study Comparing the Efficacy and Safety of Three Dosage Strengths of MDL-16,455A (60, 120, and 240 mg BID) in the Treatment of Fall Allergies."

Objectives

"The primary objective was to determine the efficacy and safety of MDL-16,455A at 60 mg BID, 120 mg BID, and 240 mg BID compared to placebo in the treatment of fall seasonal allergic rhinitis."

"A secondary objective was to determine the dose proportionality of MDL-16,455A at 60mg BID, 120mg BID, and 240mg."

Although not specifically listed as a study objective by the sponsor, a secondary objective of this protocol was to examine population pharmacokinetics and the pharmacodynamic relationship of dose to symptom reduction. The results for this secondary objective was reported by the sponsor in a separate report which combines the PK/PD data from protocol PJPR0023 and PJPR0024 since the two protocols are of identical design, except for drug dose ranges.

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel study with a 3-day single-blind placebo lead-in followed by 2 weeks of double-blind randomized treatment, in patients (ages 12-65 years) with fall seasonal allergic rhinitis (SAR). A single-blind placebo lead-in was used in an attempt to reduce the number of placebo responders entered into the double-blind period of the study. A placebo control was incorporated in the study design as a comparator for the active doses. A 2-week treatment period was chosen to facilitate an extensive evaluation of the effectiveness of the doses tested, and to reduce the effect of daily variations in pollen counts. The study consisted of four visits over a total of 17 days. There were 3 days between visit 1 and visit 2 (single-blind placebo lead-in period), and 7 days between visit 2 and visit 3 and between visit 3 and visit 4 (weeks 1 and 2 of double-blind randomized treatment). At return visits patients had their compliance assessed, had their diaries reviewed, and were issued new study supplies. It was conducted at 16 sites with patients randomized to 4 study treatments. Qualifying patients (see inclusion/exclusion criteria) were randomized at visit 2 using stratified randomization based on severity (high vs low baseline 12 hour reflective symptom scores of placebo lead-in) of total symptom score (TSS) to assure similar baseline TSS across double-blind treatment groups (See Treatment Assignment and Protocol Amendment #5 below regarding randomization).

At visit 1, patients were instructed to take the initial dose of study medication at 7 PM (± 1 hour) the

evening of visit 1 and then daily at 7 AM (± 1 hour) and 7 PM (± 1 hour), including the 7 AM dose on the day of subsequent clinic visits. They were to assess the r SAR symptoms prior to each dose (at 7 AM and 7 PM) - reflectively (for the previous 12-hour period) and instantaneously (for the previous 1-hour period). Additionally, they assessed their SAR symptoms instantaneously daily at 1-3 hours after taking the 7 PM dose ("Bedtime"). Severity assessments were to be recorded on daily diaries, a Daily Symptom Diary and a Bedtime Symptom Diary. Patients rated the severity of the following five individual symptoms: nasal congestion; sneezing; rhinorrhea; itchy nose, palate, and/or throat; and itchy, watery, red eyes. Each symptom was evaluated by the patient using the following scale.

- 0 Absent - Symptom not present
- 1 Mild - Symptom was present but was not annoying or troublesome
- 2 Moderate - Symptom was frequently troublesome but did not interfere with either normal daily activity or sleep
- 3 Severe - Symptom was sufficiently troublesome to interfere with normal daily activity or sleep
- 4 Very Severe - Symptom was so severe as to warrant an immediate visit to the physician.

The total symptom score (TSS) was calculated by adding the individual symptom scores, excluding nasal congestion. Nasal congestion was not included in the TSS because relief of nasal congestion was not expected with an H₁-antagonist.

At the final study visit, the investigator performed an overall assessment of the study treatment effectiveness according to the following 5-point scale:

- 0 = Complete Relief - Symptoms not present
- 1 = Marked Relief - Symptoms are vastly improved and, although still present and may be troublesome.
- 2 = Moderate Relief - Symptoms are noticeably improved but are still present and may be troublesome
- 3 = Slight Relief - Symptoms are present and only minimal improvement has been obtained
- 4 = No Relief/Worse - Patient's symptoms are unchanged or worse.

Study Treatments

Single-Blind Placebo Lead-In:

Placebo BID - 4-60 mg size placebo capsules

Double-Blind Treatment :

MDL 16,455A 240 mg BID - 4-60 mg MDL 16,455A capsules

MDL 16,455A 120 mg BID - 2-60 mg MDL 16,455A capsules
2-60 mg size placebo capsules

MDL 16,455A 60 mg BID - 1-60 mg MDL 16,455A capsule
3-60 mg size placebo capsules

Placebo BID - 4-60 mg size placebo capsules.

Treatment Appearances:

- a) MDL 16,455A 60 mg capsules (size #0)
- b) Placebo capsules identical in appearance to MDL 16,455A 60 mg capsules (size #0).

The medication used in the study was packaged in unit dose cards. Its identity, was stated on the label under a silver cover which was covered by a clear protective laminate. Each site was instructed that tampering with the cover will cause unblinding and that unblinding whether intentional or otherwise must be accompanied by a full explanation by the investigator and mandated patient withdrawal from the study.

Treatment Assignment:

Double-blind treatments were randomized across all study sites. A treatment assignment number (TAN) was assigned to each double-blind unit dose according to the randomization schedule. Treatments were randomized in blocks of four with each treatment group represented once. At visit 1 a patient number was assigned in sequential order (eg, 001, 002...). At visit 2 a TAN was also assigned which randomized each patient to double-blind treatment. The TAN, along with the patient number, and the site study number were used for patient identification.

Stratified randomization (high vs low) was used to ensure similar baseline total symptom scores (TSS) across treatment groups based on the baseline 12-hour PM reflective TSS.

- Low: Baseline 12-hour PM reflective TSS ≥ 10 and < 17
- High: Baseline 12-hour PM reflective TSS ≥ 17 and ≤ 24 .

If the patient's baseline TSS was Low, a TAN was dispensed in ascending order beginning with the lowest TAN shipped to the investigative site. If the patient's baseline TSS was High, a TAN was dispensed in descending order beginning with the highest TAN shipped to the investigative site.

Treatment Lot Numbers:

Table 8-342. Lot Numbers of Study Medication	
Study Medication	Lot Number(s)
MDL 16,455A 60 mg capsules (size #0)	RF9414
Placebo 60 mg capsules (size #0)	RF9413, RG9424

Efficacy Parameters

The pre-defined **primary analysis variable for efficacy** was the change in average daily 7 PM reflective TSS (average 7 PM reflective TSS during the 2-week double-blind dosing period) from average baseline 7 PM reflective TSS (average 7 PM reflective TSS during the 3-day placebo lead-in period). The 7 PM symptom assessment collected immediately prior to administration of the first double-blind dose was excluded when calculating both the average baseline and double-blind symptom scores.

Secondary analysis variables were:

Change from baseline in average daily 7 PM reflective TSS over time for: 1) week 1 vs baseline, 2) week 2 vs baseline, and 3) all days of double-blind dosing period vs baseline

Changes in average daily TSS in other scheduled assessments (average during the double-blind dosing period) from the average baseline TSS (average of the three corresponding assessments during the placebo lead-in period), including 7 AM reflective, 7 PM instantaneous, 7 AM instantaneous, and Bedtime assessments

Changes in the patient's assessment of severity of individual symptoms at 7 AM reflective, 7 AM instantaneous, 7 PM reflective, 7 PM instantaneous, and Bedtime instantaneous assessments

Physician's assessment of overall effectiveness of study drug at final visit.

Safety Parameters

Safety parameters included physical examinations, vital signs, adverse events, laboratory panel, and 12-lead ECGs. Adverse events were collected on an Adverse Event Diary with treatment emergent adverse events, as determined by the investigator, entered into the database.

Statistical Methods

An analysis of covariance (ANCOVA) model with baseline 7 PM reflective TSS as a covariate and investigative site and treatment as predictor variables was used to analyze the primary efficacy variable, change in 7 PM reflective TSS. The primary analysis was conducted using the Intent-to-Treat population. (See below, Protocol Amendment #5, dated November 15, 1995, regarding modification of the analysis procedures.) Secondary symptom assessments were analyzed with similar methods. The sponsor indicates that all symptom scores used the average of available data; if a patient had no available data for a variable the patient was excluded from the intent-to-treat analysis for that variable.

Pharmacokinetic Methods

A plasma sample for the measurement of MDL 16,455 was collected 1-3 hours after the morning dose of study drug on the day of the final visit (visit 4 or Early Discontinuation). Protocol Amendment 3, which was implemented at three study sites, added the collection of a second sample 9-11 hours after the morning dose on the day of the final visit.

Patient Inclusion Criteria

1. Fall SAR patients ≥ 12 and ≤ 65 years of age.
2. Males and females could participate. Females could not be pregnant, lactating, or likely to become pregnant.
3. History of SAR during the fall season for the previous two years. Ragweed must have been a major allergen associated with the patient's history of allergic rhinitis. The specific type of ragweed to which the patient was allergic must have been indigenous to the study site area.
4. Positive epicutaneous skin test response (wheal with a diameter at least 5 mm greater than that obtained with diluent, developing within 15 minutes) to ragweed at visit 1 or during the previous 15-month period. A skin test performed in the previous 15 months could be used to qualify the patient if it was performed at the investigator's site and recorded in the patient's medical record.
5. History of positive response to antihistamines for symptoms of SAR.
6. At visit 1 the patient's reflective total symptom score (TSS; equal to the sum of the scores for the individual symptoms except nasal congestion) for the previous 12 hours must have met the following criteria:
 - TSS ≥ 6 (excluding nasal congestion), and
 - Two or more symptoms (excluding nasal congestion) rated as "moderate" or "severe," and
 - No symptom (including nasal congestion) rated as "very severe."

At visit 2, all three PM and all three AM reflective SAR assessments from the week 1 Daily Symptom Diary must have been completed. The reflective SAR assessments from the placebo lead-in must have met the following criteria:

- TSS ≥ 5 (excluding nasal congestion) for all PM assessments, and
- TSS ≥ 4 (excluding nasal congestion) for all AM assessments, and
- Two or more symptoms, excluding nasal congestion, rated as "moderate" or "severe" at all PM and AM assessments, and
- No symptom, including nasal congestion, rated as "very severe" at any PM or AM assessment.

The patient was not to be entered into the study if any reflective symptom (including nasal congestion) was rated as "very severe" at visit 1 or visit 2. Instantaneous symptom assessment data was not used as criteria for study entry or randomization.

7. Written informed consent was obtained from the patient (and a parent or legal guardian if the patient was a minor) at visit 1

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: Protocol PJPR0004 from NDA 20-625

Protocol No. PJPR0004 - conducted from August 23, 1993 to December 6, 1993 in Leeds, England

Note: MDL-16,455 is the designation for the acid metabolite of terfenadine; and MDL-16,455A, fexofenadine, is the designation for MDL-16,455 from the synthetic source.

Title

"Multiple Dose Pharmacokinetics and Pharmacodynamics of Terfenadine and Its Major Metabolite."

Objectives

- (A) "to determine the effect of multiple dosing of terfenadine and MDL 16,455A on QTc interval";
- (B) "to determine the extent and duration of inhibition of skin wheal and skin flare area from terfenadine or MDL 16,455A";
- (C) "to characterize the multiple dose plasma and urine pharmacokinetics of terfenadine and MDL 16,455A";
- (D) "to determine the steady-state relative bioavailability of plasma MDL 16,455 area under the curve (AUC) after dosing with MDL 16,455A as compared to MDL 16,455 from terfenadine metabolism";
- (E) "to determine whether a relationship exists between plasma MDL 16,455 concentrations and changes in QTc interval duration and inhibition of the skin wheal and flare areas."

Study Design

This study was an open-label, randomized, four period (11 days per period with subjects sequestered in clinic for the first 9 days of each period), four-way complete crossover (>13 but <28 day washout) design conducted in 24 healthy males who were between 18 and 55 years of age.

- Treatment E: An oral dose of 60 mg terfenadine (1x60 mg Seldane tablets) every 12 hours for thirteen doses (Days 2-8).
- Treatment F: An oral dose of 180 mg terfenadine (3x60 mg Seldane tablets) every 12 hours for thirteen doses (Days 2-8).
- Treatment G: An oral anhydrous dose of 60 mg MDL 16,455A every 12 hours for thirteen doses (Days 2-8)
- Treatment H: An oral anhydrous dose of 180 mg MDL 16,455A every 12 hours for thirteen doses (Days 2-8)

No drug was administered on Day 1 of each period. MDL 16,455A was administered as an oral

solution of MDL 16,455A in a propylene glycol-acetic acid vehicle. Marketed 60 mg Seldane tablets were used for the terfenadine treatment.

Study Measurements

ECGs:

- Serial 12-lead electrocardiograms (ECGs) were obtained for -
- 72 hours after the final dose on Day 8 (0, 2, 4, 8, 12, 24, 48, 72 hours);
 - 12 hours after treatment on Days 1 and 2 (0, 2, 4, 8, 12 hours);
- A single ECG was obtained at -
- 4 hours after the morning dose on Days 3-7.

Plasma Samples:

- Serial blood samples were collected for 72 hours (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours) after the last dose on Day 8;
- trough blood samples were collected prior to the morning dose on Days 6-8;
- a pre-dose blood sample was obtained on Day 2.

In subjects receiving terfenadine, plasma was quantitated for MDL 16,455 and terfenadine and urine was quantitated for MDL 16,455, terfenadine, MDL 17,523 (alcohol metabolite of terfenadine), and MDL 4,829 (dealkylated metabolite of terfenadine). In subjects receiving MDL 16,455A, plasma and urine was quantitated for MDL 16,455.

Urine Samples:

Urine samples were collected from 0 to 12 hours after the morning treatment administration times on Days 1, 2 and 8.

Wheal and Flare Measurements:

- Serial wheal and flare areas were measured for -
- 72 hours after the final dose on Day 8 (0, 2, 4, 6, 8, 12, 24, 48, 72 hours);
 - 12 hours after the treatment administration time on Days 1 and 2 (0, 2, 4, 6, 8, 12 hours).

Safety Measurements:

All subjects were monitored by lead-II telemetry from Day 1 until Day 9. Vital signs were measured three times a day throughout the study. Clinical laboratory measurements were conducted pre- and post-study. Reports of adverse events were collected.

Subject Inclusion Criteria

- healthy, nonsmoking males between the ages 18 and 55 years and not more than 15% from the ideal weight and age
- no clinically significant abnormalities before study initiation for the following: clinical laboratory measurements; ECG; medical history, physical exam,
- histamine wheal area must be approximately three times subject's own saline wheal area

Subject Exclusion Criteria

- hypersensitivity reaction to terfenadine or MDL 16,455A
- significant organ abnormality or disease
- treatment with either prescription or **nonprescription (OTC)** medication within 14 days of trial initiation
- hepatic or renal clearance altering agents (eg, erythromycin, cimetidine, barbiturates, phenothiazines, etc) within 30 days of study initiation
- ketoconazole or itraconazole within three months of study initiation
- astemizole (Hismanal[®]) within six months of study initiation.
- QTc interval of greater than 440 msec or with any underlying conditions known to prolong the QTc
- a flare area greater than 2 cm² after intradermal injection with normal saline

Results - Patient Accounting

The sponsor reports that 24 subjects were enrolled; 23 subjects received MDL-16,455A 180mg Q12H, terfenadine 60mg Q12H, and terfenadine 180mg Q12H; 22 subjects completed the study. Two subjects were withdrawn due to adverse events prior to completing treatment with MDL-16,455A 60mg Q12H (see discontinuations below).

Results - Pharmacokinetic Parameters

The sponsor summarized the pharmacokinetic results in tabular and figure format, reproduced below. In general the AUC_{ss}(0-12 h) following administration of MDL-16,455A was smaller (67%- 60mg; 75%-180mg) than that observed following terfenadine administration. The sponsor reports the following pharmacokinetic results for MDL-16,455A:

- A) An 80mg dose of MDL-16,455A Q12H would result in an AUC_{ss}(0-12 h) for MDL-16,455A equivalent to a 60mg dose of terfenadine;
- B) Following terfenadine and MDL-16,455A administration, the AUC_{ss}(0-12h), C_{max}-ss and C_{min}-ss for MDL-16,455 were dose proportional;
- C) The T_{max} following MDL-16,455A (1-1.2h) was more rapid compared to that for terfenadine (2.3-4 h);
- D) The steady state ratio of C_{max} to C_{min} was greater following MDL-16,455A administration compared to that following terfenadine administration;
- E) Steady state for MDL-16,455 is achieved by day 5 following both MDL-16,455A and terfenadine administration;
- F) The half-life of MDL-16,455 is somewhat shorter following MDL-16,455A (11.8-14.0 h) administration compared to that following terfenadine administration (17.6-20.1 h).

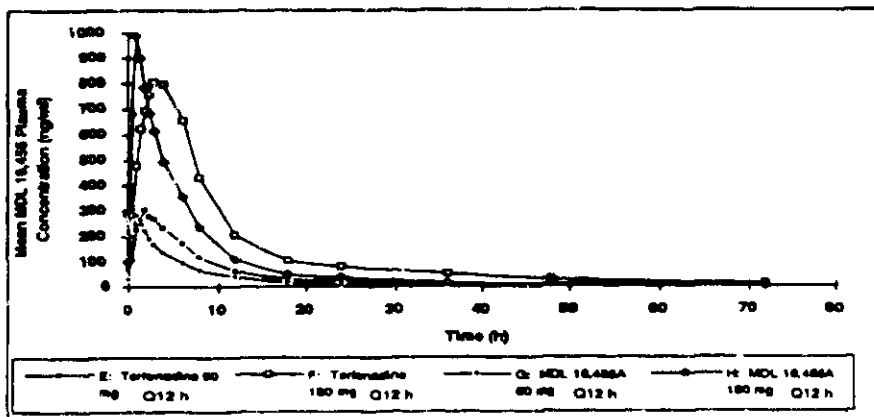


Figure 8-58. Mean Plasma MDL 16,455 Concentration as a Function of Time Following Administration of MDL 16,455A and Terfenadine

Supporting Data:
Appendix A1: Plasma

Page
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Patient Exclusion Criteria

- a. Females who were pregnant, lactating, or were likely to become pregnant during the study period. Females in certain categories, eg. not sexually active, could be admitted at the discretion of the investigator. Sexually active females of childbearing potential were expected to use one of several specified contraceptive regimens throughout the study.
- b. Upper respiratory tract infection within 30 days prior to visit 1.
- c. Evidence of sinusitis within 30 days prior to visit 1.
- d. Any of the following underlying conditions known or suspected to be present:
 - malnutrition
 - blood dyscrasia
 - renal or hepatic insufficiency
 - chronic infection
 - drug abuse or alcoholism
 - malignancy
 - malabsorption.
- e. Clinically significant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the results difficult.
- f. Serum sodium < 132 mEq/L or > 147 mEq/L.
- g. Serum potassium < 3.4 mEq/L or > 5.4 mEq/L.
- h. Serum bicarbonate < 17.0 mEq/L or > 30.6 mEq/L.
- i. Serum chloride < 94 mEq/L or > 112 mEq/L.
- j. Serum magnesium < 1.2 mEq/L or > 2.5 mEq/L.
- k. Serum calcium < 8.4 mg/dL or > 10.3 mg/dL.
- l. Serum SGPT (ALT) ≥ 41 U/L for females or ≥ 52 U/L for males (added by Amendment 1).
- m. Any disease state or surgery known to affect the gastrointestinal absorption of drugs.
- n. Mental capacity limited to the extent the patient could not provide legal consent or information regarding efficacy and side effects/tolerance of drug.
- o. Patients receiving immunotherapy except those on stable maintenance therapy for at least 6 months prior to visit 1.
- p. Hypersensitivity to terfenadine, MDL 16,455A, or the capsule ingredients (cellulose, lactose, cornstarch, gelatin, croscarmellose sodium).
- q. Use of any of the following drugs within the time indicated prior to visit 1:

Drug	Time Prior to Visit 1
Parenteral corticosteroids: long-acting, intra-articular or intramuscular	≤ 90 days
Parenteral corticosteroids: short-acting, iv push (per Amendment 1)	≤ 14 days
Oral corticosteroids	≤ 30 days
Nasal or inhaled corticosteroids	≤ 14 days
Nedocromil or cromolyn sodium	≤ 14 days
Astemizole (Hismanal®)	≤ 90 days

Loratadine (Claritin®)	≤7 days
Other H ₁ and H ₂ - antagonists	48 hours
Oral decongestants, decongestant nasal sprays or drops, including all OTC preparations - cough/cold preparations and sleep aids	48 hours
Hydroxyzine	≤72 hours
Alpha adrenergic (eg, decongestants or drugs which produce adrenergic activity)	≤48 hours
Anticholinergic agents, sedatives or hypnotics	≤3 days
Antidepressant medications (eg, serotonin-noradrenaline reuptake inhibitors (Prozac®, Paxil®, Zoloft®, Effexor®), and tricyclics)	≤21 days
Phenothiazines, benzodiazepines	≤7 days
Reserpine or reserpine products (eg, Ser-Ap-Es®, Hydropres®, etc)	≤14 days
Oral and parenteral macrolide antibiotics (eg, erythromycin, troleandomycin, azithromycin, clarithromycin)	≤7 days
Oral and parenteral ketoconazole, fluconazole, or itraconazole	≤90 days
Topical azole antifungals (eg, clotrimazole, miconazole, etc)	≤14 days
- r. Use of an investigational drug within 30 days prior to visit 1.
- s. At visit 2, any of the following manifested on the ECG:
- Rhythm disturbance (other than sinus arrhythmia)
 - PR interval < 120 msec or > 200 msec
 - QRS interval > 120 msec
 - QT interval > 440 msec.
- t. HR < 50 bpm on ECG or physical examination (added by Amendment 1).
- u. At visit 2, patient had taken < 5 of the six doses of single-blind medication.

Concomitant Medications

Patients were not to take any of the medications proscribed by the Exclusion Criteria for the duration of the study. Other medications considered important for the patient's welfare could be continued.

Protocol Amendments

There were five protocol amendments of which Amendment #5 is most significant because it modified the analysis procedures for the assessment of efficacy. Dated November 15, 1994 (prior to study closure and unblinding), it added the use of covariate adjustment for baseline symptom scores instead of an adjustment for baseline strata (low or high) and added an adjustment for treatment by investigative site and treatment by baseline symptom score interactions if either was significant at the $\alpha = .10$ level.

RESULTS

Results - Patient Accounting

The sponsor reports the following patient tally:

Screened-----1498
 Screening Failures-----425
 Exposed to Single Blind Med-----1073
 Placebo Lead-in Discontinuation-----498
 Randomized-----575
 Discontinued Prior to D-B Exposure--3
 Exposed to Double-Blind Med-----572
 Double-Blind Discontinuation-----28
 Completed-----544

The sponsor prepared 4 tables reproduced below to summarize patient disposition and distribution of patients exposed to double-blind study medication a) across treatment groups and investigative sites, b) who had major protocol violations, and c) who discontinued early. All 572 exposed patients were used in the safety analyses; and 570 were identified as Intent-to-Treat (patients with baseline and postbaseline 7 PM reflective symptom assessments) for the Intent-to-Treat analyses. The remaining two safety evaluable patients (047-147 and 019-145) had missing postbaseline symptom scores (patient had no symptom assessment while on double-blind medication). Patient 047-147 also violated noncompliance with study medication.

<i>Treatment (BID)</i>	<i>Randomized N (%)</i>	<i>Exposed N (%)</i>	<i>Safety Evaluable N (%)</i>	<i>Intent-to-Treat N (%)</i>	<i>Protocol Correct N (%)</i>
Placebo	143 (25%)	142 (25%)	142 (25%)	141 (25%)	128 (25%)
60 mg MDL 16,455A	142 (25%)	141 (25%)	141 (25%)	141 (25%)	132 (25%)
120 mg MDL 16,455A	144 (25%)	144 (25%)	144 (25%)	144 (25%)	133 (26%)
240 mg MDL 16,455A	146 (25%)	145 (25%)	145 (25%)	144 (25%)	128 (25%)
Total	575	572	572	570	521
<i>Supporting Data:</i>					<i>Page</i>
<i>Appendix F1, Summary 2: Summary of Patient Disposition</i>					<i>S8-V1.223-P276</i>
<i>Appendix F2, Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group</i>					<i>S8-V1.223-P299</i>

Table 8-347. Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group

Investigative Site	Placebo (BID)	MDL 16.455A (BID)			Total
		60 mg	120 mg	240 mg	
134	9	10	9	9	37
135	12	13	12	13	50
136	8	9	7	9	33
137	16	16	16	16	64
138	4	4	4	3	15
139	7	7	8	8	30
140	3	8	7	9	32
141	12	12	14	12	50
142	14	15	14	14	57
143	6	6	7	6	25
144	3	4	4	4	15
145	10	9	8	10	37
146	8	7	8	9	32
147	11	9	12	11	43
148	10	9	11	10	40
149	4	3	3	2	12
TOTAL	142	141	144	145	572

Supporting Data: Page
 Appendix F1. Summary 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group S8-V1.223-P272
 Appendix F2. Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group S8-V1.223-P299

Table 8-349. Summary of Major Protocol Violations (Patients Exposed to Double-Blind Study Medication)†

Major Protocol Violation	Placebo (BID) (N=142)	MDL 16.455A (BID)			Total Active (N=430)	Total (N= 572)
		60 mg (N=141)	120 mg (N=144)	240 mg (N=145)		
Failure to Meet Entrance Criteria	5 (4%)	3 (2%)	8 (6%)	9 (6%)	20 (5%)	25 (4%)
Use of Prohibited Medications Prior to or During Study	6 (4%)	3 (2%)	3 (2%)	4 (3%)	10 (2%)	16 (3%)
Missing Efficacy Data (Primary Measure)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)	2 (0%)
Non-Compliance with Study Medication	2 (1%)	3 (2%)	0 (0%)	3 (2%)	6 (1%)	8 (1%)
Non-Compliance with Data Collection Procedures or Timing	0 (0%)	1 (1%)	0 (0%)	1 (1%)	2 (0%)	2 (0%)
Total Patients	14 (10%)	9 (6%)	11 (8%)	17 (12%)	37 (9%)	51 (9%)

† Patients may have had more than one major protocol violation, therefore, patient counts for Major Violations may not equal the total number of patients having major protocol violations (Total Patients).

Supporting Data: Page
 Appendix F1. Summary 3 Summary of Major Protocol Violations (Exposed Patients) S8-V1.223-P278
 Appendix F2. Listing 2. Major Protocol Violations S8-V1.223-P312

Table 8-350. Reasons for Early Discontinuation of Patients Exposed to Double-Blind Study Medication†						
<i>Primary Reason</i>	<i>Placebo (BID) (N=142)</i>	<i>MDL 16,455A (BID)</i>				<i>Total (N= 572)</i>
		<i>60 mg (N=141)</i>	<i>120 mg (N=144)</i>	<i>240 mg (N=145)</i>	<i>Total Active (N=430)</i>	
Adverse Event	6 (4%)	3 (2%)	0 (0%)	3 (2%)	6 (1%)	12 (2%)
Failed to Return to Study Site for a Scheduled Visit	1 (1%)	3 (2%)	1 (1%)	0 (0%)	4 (1%)	5 (1%)
Abnormal Lab Value (Baseline)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Treatment Failure	3 (2%)	1 (1%)	2 (1%)	2 (1%)	5 (1%)	8 (1%)
Other	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (1%)
Total Patients	12 (8%)	7 (5%)	3 (2%)	5 (4%)	16 (4%)	28 (5%)
† Patients may have had more than one reason for discontinuing the study, however, only the primary reason is summarized						
<i>Supporting Data</i>						<i>Page</i>
<i>Appendix F1. Summary 4: Summary of Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication</i>						<i>S8-V1.223-P281</i>
<i>Appendix F2. Listing 4: Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication</i>						<i>S8-V1.223-P331</i>

Reviewer Comment Regarding Patient Accounting

The distribution of patients exposed to double-blind treatments appears similar across treatments and across treatments within investigative sites. Additionally, the frequency of major protocol violations and early discontinuations appears similar across treatment groups. Examination of the randomization schedule for this trial does not reveal any repetitive patterns which would suggest a lack of randomization.

Results - Patient Baseline Demographic Characteristics

Below is the sponsor's table of baseline demographic characteristics for the Intent-To-Treat (ITT) dataset.

Table 8-351. Demographics: Intent-to-Treat Patients						
Baseline Characteristics	Placebo (<i>BID</i>) (N=141)	MDL 16.455A (<i>BID</i>)			Total (N= 570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Gender						
Male % (N)	38(54)	41(58)	41(59)	45(65)	41(236)	7050
Female % (N)	61(87)	59(83)	59(85)	55(79)	58(334)	
Age (years)						
Mean±SD	33±10	33±11	32±10	32±11	33±11	9165
Range	12-63	13-64	12-66	12-62	12-66	
Race						
Caucasian % (N)	88(124)	86(121)	91(131)	90(129)	86(505)	9310
Black % (N)	6(9)	9(12)	4(6)	6(8)	6(35)	
Hispanic % (N)	5(7)	5(7)	4(6)	5(7)	5(27)	
Other % (N)	1(1)	1(1)	1(1)	0(0)	1(3)	
Weight (kg)						
Mean±SD	74±17	74±18	74±18	73±18	74±18	.9770
Range	42-115	42-143	40-144	32-144	32-144	
Height (cm)						
Mean±SD	169±10	170±10	170±10	171±10	170±10	.5457
Range	142-196	150-188	147-198	150-196	142-198	
Years Since First Episode Occurred						
Mean±SD	17±11	17±11	17±10	17±12	17±11	.8840
Range	2- 44	2- 60	3- 52	3- 55	2- 60	
Successive Years of Fall Allergy						
Mean±SD	17±11	17±10	17±10	17±12	17±11	.9480
Range	2- 44	2- 50	3- 52	3- 55	2- 55	
* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.						
Supporting Data					Page	
Appendix G1. Summary 1: Intent-to-Treat Patients					S8-V1.224-P3	

Reviewers Comments Regarding Demographics

Although there are no statistically significant differences for any of the baseline variables examined by the sponsor, there is a slight preponderance of female patients over male patients and a marked preponderance of Caucasians. Nonetheless, these observations would not be expected to influence the study results substantially since there does not appear to be an imbalance across study treatments.

In addition to this examination of baseline characteristics we requested the sponsor to submit an analysis of baseline demographics by investigational site. The sponsor provided this information by a submission to the NDA dated December 13, 1995. Below is a table displaying the ranges across study sites for the range of baseline demographics. Although the range of percent males is broad for this trial, at 12 of the 16 sites the percent was between 31.6 and 53.1%; and although there were very few Asian subjects, Blacks were enrolled at no less than 2% at all sites other than #169.

Range of Baseline Demographics Across Study Sites - Intent-To-Treat						
PJPR0023	Age	Gender %Male	Race			Total Symptom Score
			Asian	Black	Caucasian	
High (site #)	37±9 (148)	75.7% (134)	5.6% (145)	18.4% (136)	100% (169)	10.19±1.58 (142)
Low (site #)	28±9 (140)	13.3% (144)	0.0% (all sites except 145)	0.0% (169)	81.8% (136)	7.33±1.47 (140)

Results - Baseline Symptom Assessments

Reproduced below are the sponsor's tables of baseline symptom assessments.

Table 8-352. Baseline 7 PM Reflective Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (N=141)	MDL 16.455A (BID)			Total (N=570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Nasal Congestion						
Mean±SD	2.3±0.6	2.3±0.7	2.4±0.6	2.3±0.6	2.3±0.6	0.8459
Range	0.3-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Sneezing						
Mean±SD	2.0±0.7	2.0±0.7	2.1±0.7	2.1±0.7	2.0±0.7	0.9077
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.3±0.6	2.4±0.5	2.5±0.5	2.3±0.6	2.4±0.5	0.2754
Range	0.0-3.0	0.7-3.0	0.7-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.2±0.7	2.3±0.6	2.2±0.7	2.3±0.6	2.2±0.6	0.6683
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery, Red Eyes						
Mean±SD	2.3±0.6	2.1±0.7	2.3±0.6	2.2±0.7	2.2±0.7	0.2371
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.0-3.7	0.0-3.7	
FSS (Excluding Nasal Congestion)						
Mean±SD	8.9±1.6	8.8±1.7	9.0±1.9	8.8±1.8	8.9±1.8	0.8984
Range	5.3-12	5.0-12	5.0-12	4.3-12	4.3-12	

* P value from Kruskal-Wallis test

Supporting Data	Page
Appendix E3. Listing 1 Kruskal-Wallis Test for Baseline PM Reflective Symptom Assessment (ITT)	S8-V1 221-P92
Appendix I2. Listing 1 Intent-to-Treat Reflective PM Diary Listing	S8-V1 225-P4

Table 8-353. Baseline 7 AM Reflective Symptom Assessments (Intent-to-Treat)

Baseline Symptoms	Placebo (BID) (N=141)	MDL 16 455A (BID)			Total (N=570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Nasal Congestion						
Mean±SD	2.4±0.6	2.3±0.7	2.4±0.6	2.4±0.6	2.4±0.6	0.6187
Range	0.3-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Sneezing						
Mean±SD	1.8±0.8	1.8±0.8	1.8±0.8	1.9±0.8	1.8±0.8	0.8521
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.3±0.6	2.3±0.6	2.4±0.5	2.3±0.6	2.3±0.6	0.5588
Range	0.0-3.0	0.3-3.0	0.7-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.1±0.7	2.2±0.6	2.1±0.7	2.2±0.6	2.2±0.7	0.3055
Range	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery, Red Eyes						
Mean±SD	2.2±0.6	2.0±0.8	2.2±0.7	2.1±0.7	2.1±0.7	0.3338
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
TSS (Excluding Nasal Congestion)						
Mean±SD	8.4±1.8	8.3±1.9	8.5±2.0	8.5±2.0	8.4±1.9	0.8397
Range	4.3-12	3.7-12	4.3-12	4.0-12	3.7-12	

* P value from Kruskal-Wallis test.

Supporting Data Page
 Appendix E3, Listing 2: Kruskal-Wallis Test for Baseline AM Reflective Symptom Assessment (ITT) S8-V1 221-P136
 Appendix I2, Listing 2: Intent-to-Treat Reflective AM Diary Listing S8-V1 226-P1

Table 8-354. Baseline 7 PM Instantaneous Symptom Assessments (Intent-to-Treat)

Baseline Symptoms	Placebo (BID) (N=141)	MDL 16 455A (BID)			Total (N=570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Nasal Congestion						
Mean±SD	2.3±0.5	2.2±0.8	2.3±0.6	2.3±0.6	2.3±0.7	0.6799
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.3	0.0-3.3	
Sneezing						
Mean±SD	1.8±0.8	1.7±0.8	1.6±0.8	1.8±0.8	1.8±0.8	0.8662
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.2±0.6	2.2±0.6	2.3±0.6	2.2±0.7	2.2±0.6	0.1718
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.1±0.7	2.1±0.7	2.1±0.8	2.1±0.7	2.1±0.7	0.8479
Range	0.0-3.0	0.3-3.3	0.0-3.0	0.0-3.0	0.0-3.3	
Itchy, Watery, Red Eyes						
Mean±SD	2.1±0.7	2.0±0.8	2.1±0.7	2.0±0.8	2.1±0.7	0.3607
Range	0.0-3.0	0.0-3.0	0.0-3.3	0.0-3.7	0.0-3.7	
TSS (Excluding Nasal Congestion)						
Mean±SD	8.1±2.1	8.1±2.1	8.3±2.3	8.1±2.4	8.2±2.2	0.8275
Range	3.0-12	3.0-12	3.0-12	1.7-12	1.7-12	

* P value from Kruskal-Wallis test.

Supporting Data Page
 Appendix E3, Listing 3: Kruskal-Wallis Test for Baseline PM Instantaneous Symptom Assessment (ITT) S8-V1 221-P181
 Appendix I2, Listing 3: Intent-to-Treat Instantaneous PM Diary Listing S8-V1 227-P1

Table 8-355. Baseline 7 AM Instantaneous Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (N=141)	MDL 16,455A (BID)			Total (N=570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Nasal Congestion						
Mean±SD	2.4±0.6	2.3±0.8	2.4±0.6	2.4±0.6	2.4±0.7	0.7113
Range	0.0-3.7	0.0-3.0	0.0-3.0	0.3-3.3	0.0-3.3	
Sneezing						
Mean±SD	1.7±0.9	1.7±0.9	1.7±0.9	1.7±0.8	1.7±0.9	0.9561
Range	0.0-3.0	0.0-3.7	0.0-3.0	0.0-3.3	0.0-3.7	
Rhinorrhea						
Mean±SD	2.3±0.7	2.3±0.7	2.3±0.7	2.2±0.8	2.3±0.7	0.6125
Range	0.0-3.3	0.0-3.0	0.3-3.3	0.0-3.0	0.0-3.3	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.1±0.8	2.1±0.7	2.1±0.8	2.2±0.7	2.1±0.7	0.7673
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery Red Eyes						
Mean±SD	2.2±0.7	2.0±0.8	2.2±0.7	2.0±0.8	2.1±0.8	0.0695
Range	0.0-3.0	0.0-3.0	0.0-3.3	0.0-3.0	0.0-3.3	
TSS (Excluding Nasal Congestion)						
Mean±SD	8.2±2.2	8.0±2.4	8.3±2.5	8.1±2.4	8.2±2.4	0.8172
Range	2.0-12	1.0-12	2.0-12	0.3-12	0.3-12	

* P value from Kruskal-Wallis test

Supporting Data
 Appendix E3, Listing 4 Kruskal-Wallis Test for Baseline AM Instantaneous Symptom Assessment (ITT) Page S8-V1.221-P226
 Appendix 12, Listing 4 Intent-to-Treat Instantaneous AM Diary Listing S8-V1.228-P1

Table 8-356. Baseline Bedtime Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (N=140)	MDL 16,455A (BID)			Total (N=569)	P value*
		60 mg (N=140)	120 mg (N=144)	240 mg (N=144)		
Nasal Congestion						
Mean±SD	2.2±0.7	2.2±0.8	2.3±0.7	2.2±0.7	2.2±0.7	0.6415
Range	0.3-3.0	0.0-3.0	0.0-3.3	0.0-3.3	0.0-3.3	
Sneezing						
Mean±SD	1.6±0.8	1.6±0.9	1.6±0.9	1.6±0.9	1.6±0.9	0.9982
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.0±0.7	2.1±0.8	2.2±0.7	2.0±0.8	2.1±0.8	0.5576
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean±SD	1.9±0.8	2.0±0.8	2.0±0.9	2.0±0.7	2.0±0.8	0.9011
Range	0.0-3.0	0.0-3.0	0.0-3.3	0.0-3.0	0.0-3.3	
Itchy, Watery Red Eyes						
Mean±SD	2.0±0.8	1.9±0.9	2.0±0.8	2.0±0.8	2.0±0.8	0.5263
Range	0.0-3.3	0.0-3.0	0.0-3.3	0.0-3.7	0.0-3.7	
TSS (Excluding Nasal Congestion)						
Mean±SD	7.6±2.5	7.6±2.7	7.7±2.8	7.6±2.6	7.6±2.6	0.9404
Range	0.0-12	1.0-12	2.0-12	0.7-12	0.0-12	

* P value from Kruskal-Wallis test

Supporting Data
 Appendix E3, Listing 5 Kruskal-Wallis Test for Baseline Bedtime Symptom Assessment (ITT) Page S8-V1.221-P273
 Appendix 12, Listing 5 Intent-to-Treat Bedtime Diary Listing S8-V1.229-P1

Reviewer Comment Regarding Baseline Symptom Scores

No statistically significant differences were observed across the treatment groups for any of the five patient assessments of TSS (7 PM reflective and instantaneous, 7 AM reflective and instantaneous and bedtime instantaneous); and, there was no statistical evidence of baseline imbalance for any of the individual symptom assessments (nasal congestion; sneezing; rhinorrhea; itchy nose, palate, and/or throat; and itchy, watery, red eyes).

Results - Patient Compliance With Study Procedures

The sponsor summarizes double-blind exposure which was estimated using the first and last date of symptom assessments during the double-blind period. The sponsor indicates that the mean duration of exposure was 13 days for all treatment groups, and ranged from 1 to 14 days.

The sponsor indicates that compliance with double-blind treatment was computed by dividing the total number of doses taken during the double-blind dosing period (ie, total number of doses dispensed minus the total number of doses returned) by the total number of doses that should have been taken based on the number of days the patient participated in the double-blind dosing period; and average compliance was 100% across all treatment groups.

We asked the sponsor to provide a summary of subjects compliance with diary symptom assessments. On December 13, 1995 the sponsor reported that compliance in completing diary symptom assessments for the ITT population was $99.9\% \pm 0.9$ for protocol PJPR0023.

Additionally the sponsor reports that ten patients (10/430, 2.3%) receiving MDL 16,455A and 6/142 (4.2%) of the patients receiving placebo had major protocol violations based on concomitant medication use (patient totals - Placebo-6; 60mg-3; 120mg-3; 240mg-4).

Reviewer Comment Regarding Patient Compliance With Study Procedures

It does not appear that any of these factors were significantly imbalanced across study treatments.

Results - Primary Efficacy Parameter (7PM Reflective TSS) - Intent-to-Treat Population

The primary pre-defined assessment of efficacy was an Intent-to-Treat (ITT) analysis of patient's change from baseline in 7 PM reflective TSS compared to placebo. The sponsor summarizes the results for the primary efficacy endpoint in Table 8-360 and in Figure 8-131 reproduced below.

All 3 doses of active treatment achieved statistical significance compared to placebo in the reduction of TSS. The 60mg and 240mg BID doses exhibited magnitudes of symptom reduction which were slightly larger than that observed with 120mg BID. A statistically significant difference was noted across the four treatment groups and for the test for linear dose-response (linear trend).

The sponsor indicates that interaction terms of treatment by investigative site and treatment by baseline TSS were tested at the $\alpha=0.10$ level of significance and found not to be significant.

Table 8-360. Intent-to-Treat Analysis of 7 PM Reflective TSS (N=570)				
Treatment (BID)	N	Mean±Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	141	8.88±0.14	7.35±0.19	-1.56±0.20
60 mg MDL 16,455A	141	8.81±0.14	6.25±0.21	-2.64±0.20
120 mg MDL 16,455A	144	8.96±0.15	6.54±0.22	-2.41±0.20
240 mg MDL 16,455A	144	8.82±0.15	6.31±0.22	-2.58±0.20
Treatment Comparison		Mean±Standard Error* (Active-Placebo)		P value*
Overall Treatment Differences				.0003
Dose Response (Linear Trend)				.0036
60 mg MDL 16,455A vs Placebo		-1.07±0.28		.0001
120 mg MDL 16,455A vs Placebo		-0.85±0.28		.0026
240 mg MDL 16,455A vs Placebo		-1.02±0.28		.0003
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
ing Data:				Page
Appendix E3, Listing 6: Intent-to-Treat Analysis of 7 PM Reflective TSS				S8-V1.222-P1
Appendix I2, Listing 6: Average Reflective PM Diary Listing				S8-V1.230-P1

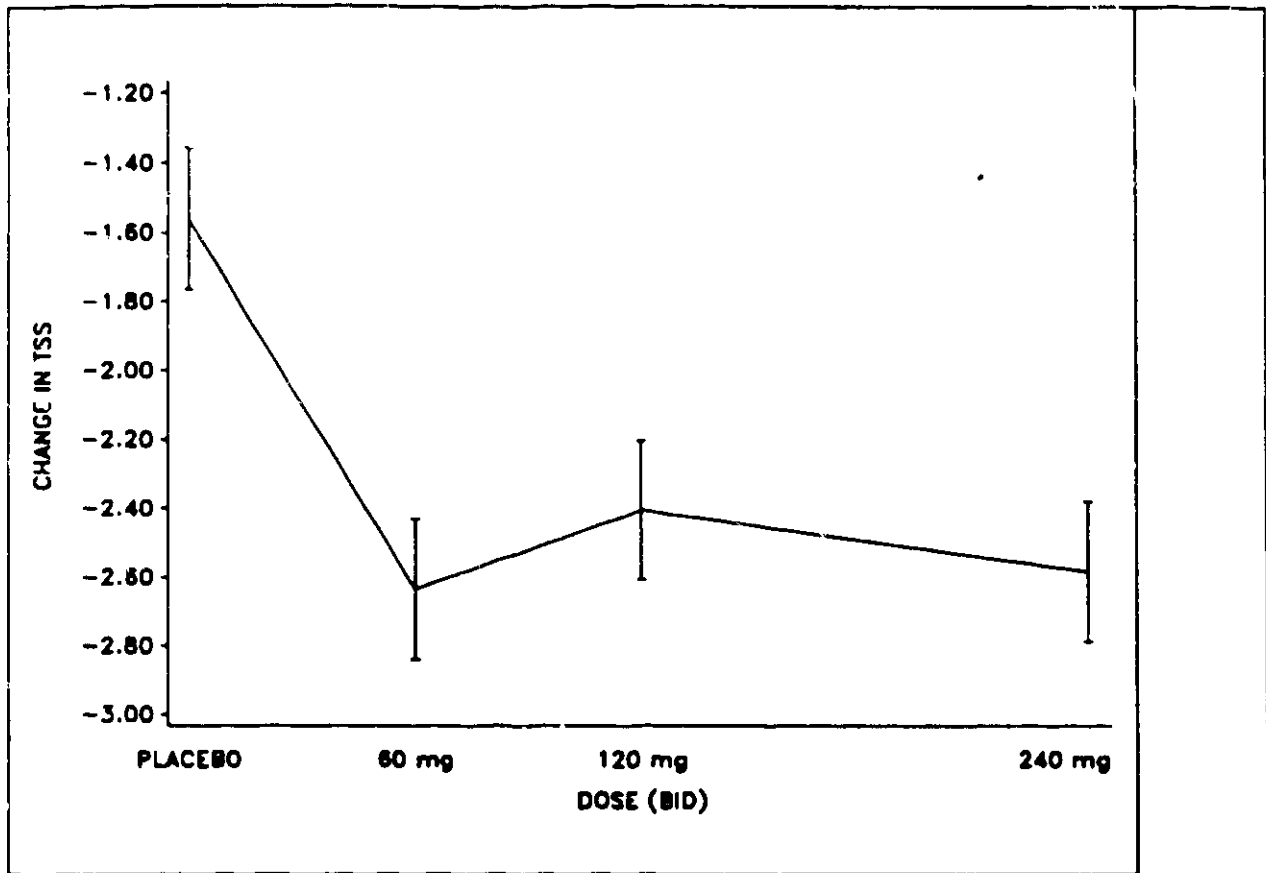


Figure 8-131. Change from Baseline in 7 PM Reflective TSS. Mean±SE (Intent-to-Treat)

Supporting Data:

Table 8-360. Intent-to-Treat Analysis of 7 PM Reflective TSS (N=570)

Page

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Results - Primary Efficacy Parameter (7PM Reflective TSS) - Protocol Correct Population

The sponsor performed a secondary analysis using 521 patients with no major protocol violations (Protocol Correct Patients). Results are presented in the sponsor's Table 8-361 and Figure 8-132. All doses produced greater reduction in TSS than placebo which was consistent with the results of the Intent-to-Treat analysis.

Table 8-361. Protocol Correct Analysis of 7 PM Reflective TSS (N= 521)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean±Standard Error</i>		
		<i>Baseline</i>	<i>Double-Blind Period</i>	<i>Change from Baseline*</i>
Placebo	128	9.06±0.13	7.35±0.20	-1.71±0.22
60 mg MDL 16.455A	132	8.90±0.15	6.29±0.22	-2.68±0.21
120 mg MDL 16.455A	133	9.08±0.16	6.59±0.23	-2.47±0.21
240 mg MDL 16.455A	128	8.89±0.16	6.30±0.24	-2.67±0.22
<i>Treatment Comparison</i>			<i>Mean±Standard Error* (Active-Placebo)</i>	<i>P value*</i>
Overall Treatment Differences				.0028
Dose Response (Linear Trend)				.0096
60 mg MDL 16.455A vs Placebo			-0.97±0.30	.0011
120 mg MDL 16.455A vs Placebo			-0.75±0.29	.0108
240 mg MDL 16.455A vs Placebo			-0.96±0.30	.0014
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
<i>Supporting Data:</i>				<i>Page</i>
<i>Appendix E3, Listing 7: Protocol Correct Analysis of 7 PM Reflective TSS</i>				<i>S8-V1.222-P6</i>
<i>Appendix I2, Listing 6: Average Reflective PM Diary Listing</i>				<i>S8-V1.230-P1</i>

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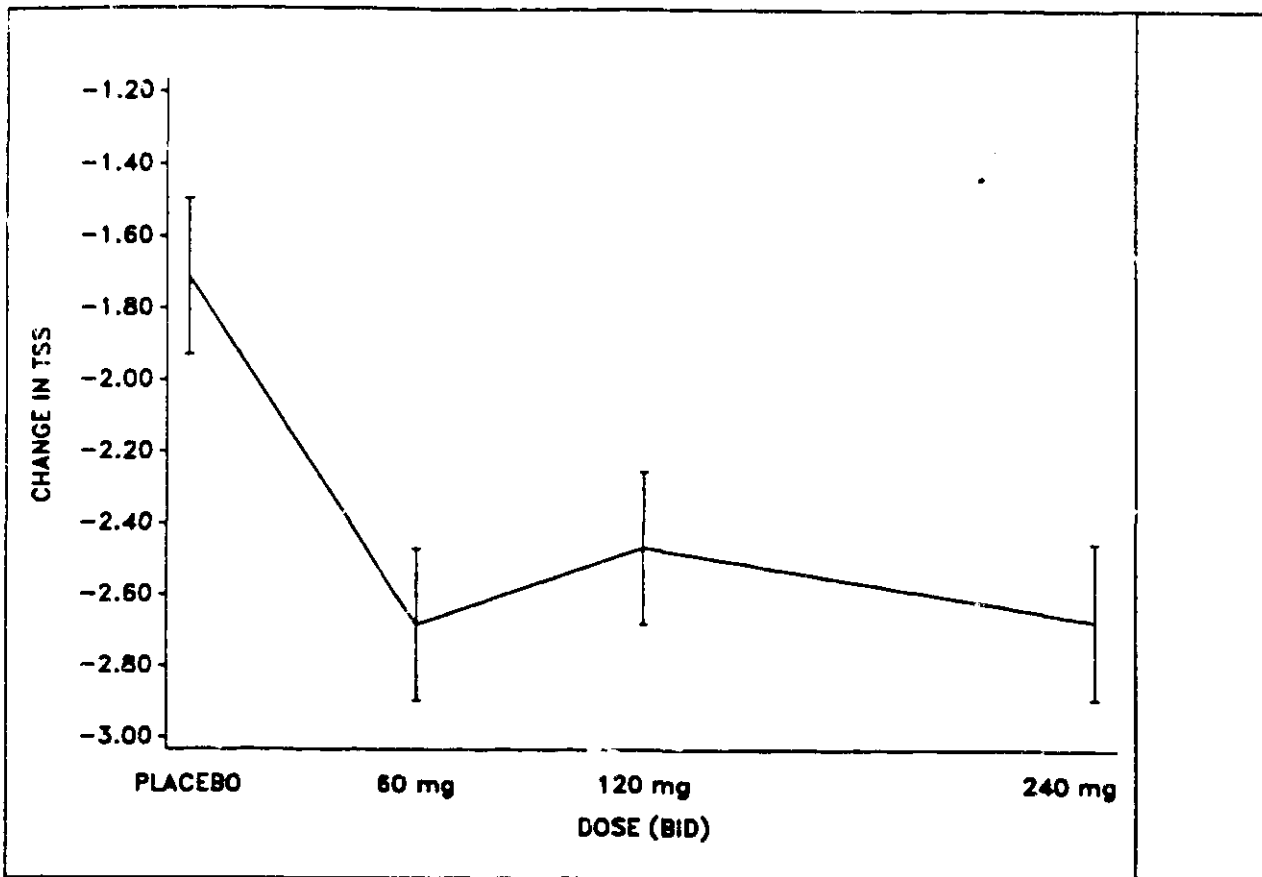


Figure 8-132. Change from Baseline in 7 PM Reflective TSS. Mean ± SE (Protocol Correct)

Supporting Data:

Table 8-361. Protocol Correct Analysis of 7 PM Reflective TSS (N= 521)

s8-v1.219-p74

Reviewer Comment On Results of Primary Efficacy Parameter

The observation that statistically significant differences from placebo were noted for each dose of fexofenadine for 7PM reflective TSS in the intent-to-treat population (the pre-defined primary efficacy analysis), supports the assertion that fexofenadine can mitigate the symptoms associated with SAR. Although the magnitude of symptom reduction appears to be approximately the same across doses, suggesting that little or no benefit is observed when doses above 60mg BID are administered, the sponsor indicates that statistically significant differences were observed among the treatment groups ($p = .0003$). The sponsor also indicates that the test for linear dose-response (linear trend) was significant as well ($p = .0036$). However, the review of the statistical reviewer, Barbara Bono, indicates that the sponsor included placebo in the model which seems inappropriate; and her recalculation excluding placebo shows a loss of statistical significance for linear trends. Using the protocol correct population, results comparable to those from the intent-to-treat population are observed.

Results - Primary Efficacy Parameter - Alternative Analysis of Efficacy

Using the primary efficacy parameter, 7PM reflective TSS, for the ITT population the sponsor calculated the number and percentage of subjects with greater than 20% reduction in TSS. They are: Placebo = 44%; 60mg = 57%; 120mg = 55%; and 240mg = 58%.

Reviewer Comment Regarding Alternative Analysis

Although the percentage of patients who exhibited a greater than 20% reduction in TSS is larger in the active treatment groups compared to the placebo group, with the largest percentage at the 240mg level, a 20% reduction seems modest. At our request the sponsor provided on December 22, 1995 additional calculations for larger reductions in TSS. The tables below display the sponsors calculations for the percentage of subjects with greater than 20% and 50% reduction in 7PM reflective TSS. Each table uses a different definition of response. The sponsor indicates that the p values provide comparison of each active dose to placebo.

For the table below, the percentages of patients at the 50% level of response is approximately one third that of the 20% level but approximately the same across all active treatments. For placebo at the 50% level the percentage is only one fifth that of the 20% level, suggesting there is greater separation of placebo from active treatments, with all 3 doses achieving statistical significance at the 50% level.

		Percent of Patients With Symptom Improvement From Baseline Above A Fixed Level	
PJPR0023	N	≥20% Improvement Level	≥50% Improvement Level
Placebo	141	44%	9%
60mg	141	57% p=0.034	23% p=0.002
120mg	144	55% p=0.094	19% p=0.016
240mg	144	59% p=0.014	20% p=0.015

Additionally the sponsor provided the results for an alternative definition of response - improvement greater than the average improvement for placebo patients. The table below summarizes the results for this alternative definition. The percent of patients at the 50% level is only slightly less than those observed at the 20% level for all treatments.

		Percent of Patients With Symptom Improvement From Baseline Above The Average Improvement For Placebo	
PJPR0023	N	≥20% Improvement Level Above Placebo	≥50% Improvement Level Above Placebo
Placebo	141	40%	35%
60mg	141	57% p=0.007	51% p=0.006
120mg	144	54% p=0.031	47% p=0.045
240mg	144	56% p=0.014	49% p=0.024

The response rates observed in the examination of these data suggest that all active treatments are more effective than placebo.

Efficacy Results - Primary Efficacy Parameter - Effect Over Time - Intent-to-Treat Population

The sponsor conducted Intent-to-Treat analyses of change from baseline TSS over time (week 1 of double-blind period vs baseline, week 2 of the double-blind baseline period vs baseline, and individual days of the double-blind dosing period vs baseline). Tables displaying results for individual days are reproduced below.

By week analysis:

Week 1 of double-blind period vs baseline (Table 8-363) - All dose groups showed statistically significant improvement over placebo (60mg, $p=0.0003$; 120mg, $p=0.0039$; 240mg, $p=0.0002$).

Week 2 of double-blind period vs baseline (Table 8-364) - All dose groups showed statistically significant improvement over placebo (60mg, $p=0.0006$; 120mg, $p=0.0120$; 240mg, $p=0.0059$).

TSS Days 1 and 2:

Table 8-365, displays symptom scores for various symptom assessments on day 1 and 2 of the double-blind period. All active dose groups achieved statistical significance compared to placebo 1-3 hours after the first dose of double-blind study medication (Bedtime symptom assessment on day 1 which was sustained (60mg, $p=0.0011$; 120mg, $p=0.0127$; 240mg, $p=0.0001$). This effect was maintained through the dosing interval as indicated by the 7 AM instantaneous and 12-hour reflective symptom assessments performed prior to the second dose of double-blind study medication (day 2).

Individual Days:

Table 8-366 displays daily change from baseline 7PM reflective TSS from day 2 to 14. Patients with missing symptom assessments are excluded from the corresponding daily analyses. All doses showed statistically significant improvement by day 2 reflective 7PM score. The 60 mg, 120 mg, and 240 mg doses showed statistical significance over placebo for 11, 7, and 13 out of 13 days of double-blind medication, respectively.

Table 8-365. Summary of Patients' TSS Assessments 24 Hours Following First Dose of Double-Blind Medication

Day*	Assessment	Change from Baseline in TSS N Mean±Standard Error P value *				Dose Response P value
		Placebo	60 mg MDL 16.455A	120 mg MDL 16.455A	240 mg MDL 16.455A	
1**	Bedtime Instantaneous	N=140 0.25±0.22	N=141 -0.74±0.22 P= 0011	N=144 -0.49±0.22 P= 0127	N=144 -0.93±0.22 P= 0001	.0008
2	7 AM Reflective	N=141 -0.02±0.20	N=141 -1.20±0.20 P= 0001	N=144 -0.89±0.20 P= 0020	N=144 -1.44±0.20 P= 0001	.0001
	7 AM Instantaneous	N=141 0.04±0.21	N=141 -0.99±0.21 P= 0004	N=144 -0.75±0.21 P= 0067	N=144 -0.91±0.21 P= 0010	.0093
	7 PM Reflective	N=141 -0.96±0.22	N=141 -1.84±0.22 P= 0036	N=144 -1.86±0.22 P= 0029	N=142 -2.23±0.22 P= 0001	.0001
2	7 PM Instantaneous	N=141 -0.36±0.22	N=141 -1.46±0.23 P= 0004	N=144 -1.46±0.22 P= 0004	N=142 -1.66±0.23 P= 0001	.0002

* P value for comparison of MDL 16.455A dose and placebo.

** First dose of double-blind medication at 7 PM.

Supporting Data:	Page
Appendix E3, Listing 30: Intent-to-Treat Analysis of 7 PM Reflective TSS Change by Day	S8-V1.223-P1
Appendix E3, Listing 32: Intent-to-Treat Analysis of 7 AM Reflective TSS Change by Day	S8-V1.223-P81
Appendix E3, Listing 33: Intent-to-Treat Analysis of 7 PM Instantaneous TSS Change by Day	S8-V1.223-P121
Appendix E3, Listing 34: Intent-to-Treat Analysis of 7 AM Instantaneous TSS Change by Day	S8-V1.223-P161
Appendix E3, Listing 35: Intent-to-Treat Analysis of Bedtime TSS Change by Day	S8-V1.223-P201
Appendix I2, Listing 1: Intent-to-Treat Reflective PM Diary Listing	S8-V1.225-P4
Appendix I2, Listing 2: Intent-to-Treat Reflective AM Diary Listing	S8-V1.226-P1
Appendix I2, Listing 3: Intent-to-Treat Instantaneous PM Diary Listing	S8-V1.227-P1
Appendix I2, Listing 4: Intent-to-Treat Instantaneous AM Diary Listing	S8-V1.228-P1
Appendix I2, Listing 5: Intent-to-Treat Bedtime Diary Listing	S8-V1.229-P1
Table 8. Summary of Patient Disposition	S8-V1.219-P59

Day	n	Mean Change from Baseline				Dose Response P value*
		Placebo (N=141)	MDL 16.455A (BID)			
			60 mg (N=141)	120 mg (N=144)	240 mg (N=144)	
2	n	141	141	144	142	0001
	Mean±SE	-0.96±0.22	-1.84±0.22	-1.86±0.22	-2.23±0.22	
	P value*		.0036	.0029	.0001	
3	n	138	141	144	144	0040
	Mean±SE	-1.09±0.23	-2.18±0.23	-1.96±0.22	-2.19±0.23	
	P value*		.0005	.0053	.0004	
4	n	136	141	144	144	0760
	Mean±SE	-1.37±0.23	-2.09±0.23	-2.01±0.23	-2.06±0.23	
	P value*		.0247	.0447	.0299	
5	n	136	138	144	144	0766
	Mean±SE	-1.07±0.24	-2.35±0.24	-1.83±0.23	-1.94±0.23	
	P value*		.0001	.0170	.0068	
6	n	137	139	143	141	0474
	Mean±SE	-1.48±0.25	-2.45±0.25	-2.27±0.25	-2.35±0.25	
	P value*		.0055	.0230	.0119	
7	n	133	135	141	139	0236
	Mean±SE	-1.66±0.25	-2.34±0.25	-1.94±0.25	-2.58±0.25	
	P value*		.0527	.4259	.0078	
8	n	131	135	140	141	0199
	Mean±SE	-1.68±0.26	-2.37±0.26	-2.33±0.25	-2.60±0.25	
	P value*		.0516	.0659	.0092	
9	n	130	135	141	140	1066
	Mean±SE	-1.87±0.27	-2.98±0.26	-2.54±0.26	-2.71±0.26	
	P value*		.0025	.0855	.0212	
10	n	131	135	140	141	0293
	Mean±SE	-1.85±0.26	-3.06±0.26	-2.87±0.26	-2.86±0.26	
	P value*		.0008	.0044	.0047	
11	n	131	135	141	141	0516
	Mean±SE	-1.94±0.28	-3.30±0.28	-3.08±0.27	-2.95±0.27	
	P value*		.0004	.0026	.0079	
12	n	130	135	141	140	2205
	Mean±SE	-2.26±0.28	-3.47±0.27	-2.98±0.27	-3.02±0.27	
	P value*		.0016	.0584	.0472	
13	n	123	128	128	132	1075
	Mean±SE	-2.30±0.29	-3.52±0.29	-3.03±0.29	-3.22±0.29	
	P value*		.0025	.0687	.0214	
14	n	92	97	105	104	0891
	Mean±SE	-2.37±0.35	-3.40±0.34	-3.25±0.33	-3.35±0.33	
	P value*		.0295	.0591	.0363	

* P value, mean and associated standard error from the analysis of change from baseline in daily TSS using an ANCOVA model containing investigative site, treatment, and baseline.

Supporting Data:	Page
Appendix E3, Listing 30: Intent-to-Treat Analysis of 7 PM Reflective TSS Change by Day	S8-V1.223-P1
Appendix I2, Listing 1: Intent-to-Treat Reflective PM Diary Listing	S8-V1.225-P4

Reviewer Comment On Results of Effect Over Time

The results displayed in Table 8-365, summary of TSS assessments for day 1 and 2, suggest that fexofenadine onset of action does occur by approximately 1-3 hours (bedtime instantaneous score) after the first dose and that this action is sustained through the 12 hour dosing interval (7AM instantaneous and 7AM reflective). The sponsor has conducted a trial specifically to assess onset of action; and it should be the primary source of data to assess onset of action.

Table 8-366, which displays 7PM reflective TSS (ITT population) by day for 14 days, shows that the impact of fexofenadine observed on this endpoint on day 1 is sustained over the 14 day period. Statistically significant different differences from placebo are observed for all days for 240mg dose, and for 60mg on days 1 through 6 and 9 through 14, while approaching very closely to statistical significance on days 7 and 8 (P=0.0527; P= 0.0516). For the 120mg dose statistical significance is observed for days 1 through 6 and days 10 and 11 while approaching statistical significance on days 8,9,12,13 and 14 (P=0.0659; P=0.0655; P=0.0584; P=0.0687; P=0.591). Only for day 7 does the 120mg dose not approach statistical significance (P=0.4259). These data support the assertion that the pharmacodynamic effect of fexofenadine on the mitigation of SAR symptoms, is sustained for at least 2 weeks.

Results -7AM Reflective TSS; 7AM/7PM Instantaneous TSS - Intent-to-Treat Population

Reproduced below are tables displaying the results of analyses of (7AM reflective, 7PM instantaneous and 7AM instantaneous symptom scores. All dose groups achieved statistical significance over placebo for all these analyses.

Table 8-367. Intent-to-Treat Analysis of 7 AM Reflective TSS (N= 570)				
Treatment (BID)	N	Mean±Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	141	8.36±0.15	7.35±0.18	-1.05±0.20
60 mg MDL 16.455A	141	8.31±0.16	6.22±0.22	-2.16±0.20
120 mg MDL 16.455A	144	8.53±0.17	6.56±0.21	-1.92±0.20
240 mg MDL 16.455A	144	8.46±0.16	6.30±0.21	-2.16±0.20
Treatment Comparison		Mean ±Standard Error (Active-Placebo)		P value *
Overall Treatment Differences				.0001
Dose Response (Linear Trend)				.0010
60mg MDL 16.455A vs Placebo			-1.11±0.27	.0001
120mg MDL 16.455A vs Placebo			-0.86±0.27	.0015
240mg MDL 16.455A vs Placebo			-1.10±0.27	.0001
* P values, means and associated standard errors from an ANCOVA model containing, investigative site, treatment, and baseline.				
Supporting Data:				Page
Appendix E3, Listing 8 Intent-to-Treat Analysis of 7 AM Reflective TSS				S8-V1 222-P11
Appendix I2, Listing 7 Average Reflective AM Diary Listing				S8-V1 230-P28

Table 8-368. Intent-to-Treat Analysis of 7 PM Instantaneous TSS (N=570)				
Treatment (BID)	N	Mean±Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	141	8.15±0.17	7.03±0.20	-1.14±0.21
60 mg MDL 16.455A	141	8.08±0.18	5.95±0.22	-2.19±0.21
120 mg MDL 16.455A	144	8.31±0.19	6.28±0.23	-1.96±0.21
240 mg MDL 16.455A	144	8.15±0.20	6.07±0.23	-2.10±0.21
Treatment Comparison		Mean±Standard Error (Active-Placebo)		P value *
Overall Treatment Differences				0008
Dose Response (Linear Trend)				0087
60 mg MDL 16.455A vs Placebo		-1.05±0.29		0003
120 mg MDL 16.455A vs Placebo		-0.81±0.28		0044
240 mg MDL 16.455A vs Placebo		-0.96±0.28		0008
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline				
Supporting Data				Page
Appendix E3, Listing 9: Intent-to-Treat Analysis of 7 PM Instantaneous TSS				S8-V1.222-P16
Appendix I2, Listing 8: Average Instantaneous PM Diary Listing				S8-V1.230-P55

Table 8-369. Intent-to-Treat Analysis of 7 AM Instantaneous TSS (N=570)				
Treatment (BID)	N	Mean±Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	141	8.18±0.18	7.34±0.19	-0.82±0.20
60 mg MDL 16.455A	141	8.03±0.20	6.24±0.22	-1.84±0.20
120 mg MDL 16.455A	144	8.32±0.20	6.70±0.22	-1.51±0.19
240 mg MDL 16.455A	144	8.10±0.20	6.37±0.23	-1.74±0.20
Treatment Comparison		Mean±Standard Error (Active-Placebo)		P value *
Overall Treatment Differences				0007
Dose Response (Linear Trend)				0088
60 mg MDL 16.455A vs Placebo		-1.02±0.27		0002
120 mg MDL 16.455A vs Placebo		-0.69±0.27		0107
240 mg MDL 16.455A vs Placebo		-0.92±0.27		0007
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline				
Supporting Data				Page
Appendix E3, Listing 10: Intent-to-Treat Analysis of 7 AM Instantaneous TSS				S8-V1.222-P21
Appendix I2, Listing 9: Average Instantaneous AM Diary Listing				S8-V1.230-P82

**Reviewer Comment On Results of Secondary Analyses - 7AM Reflective;
7PM/7AM Instantaneous**

Statistically significant differences from placebo are noted for all doses for in all three analyses and support the findings from the pre-planned analysis of the primary efficacy variable.

Results - 7PM Reflective Individual Symptoms - Intent-to-Treat Population

The table reproduced below displays the results of this analysis which shows that all dose groups achieved statistical significance over placebo in the relief of all individual symptoms (nasal congestion; sneezing; rhinorrhea; itchy, watery, and red eyes; itchy nose, palate, and/or throat).

Symptoms		Mean Change from Baseline				Dose Response P Value*
		Placebo (BID) (N=141)	MDL 16,455A (BID)			
			60 mg (N=141)	120 mg (N=144)	240 mg (N=144)	
Nasal Congestion	n	141	141	144	144	.0307
	Mean ±SE	-0.14±0.05	-0.40±0.05	-0.31±0.05	-0.35±0.05	
	P value*		.0003	.0177	.0032	
Sneezing	n	141	141	144	144	.0041
	Mean ±SE	-0.34±0.06	-0.51±0.06	-0.60±0.06	-0.61±0.06	
	P value*		.0007	.0010	.0006	
Rhinorrhea	n	141	141	144	144	.0015
	Mean ±SE	-0.33±0.06	-0.64±0.06	-0.56±0.06	-0.64±0.06	
	P value*		.0001	.0025	.0001	
Itchy Nose, Palate and/or Throat	n	141	141	144	144	.0153
	Mean ±SE	-0.44±0.06	-0.68±0.06	-0.61±0.06	-0.68±0.06	
	P value*		.0028	.0287	.0026	
Itchy, Watery, Red Eyes	n	141	141	144	144	.0777
	Mean ±SE	-0.46±0.06	-0.70±0.06	-0.63±0.06	-0.65±0.06	
	P value*		.0030	.0320	.0166	
TSS (Excluding Nasal Congestion)	n	141	141	144	144	.0036
	Mean ±SE	-1.56±0.20	-2.64±0.20	-2.41±0.20	-2.58±0.20	
	P value*		.0001	.0026	.0003	

* P value, mean and associated standard error from the analysis using an ANCOVA model containing investigative site, treatment, and baseline.

Supporting Data	Page
Appendix E3, Listing 15: Intent-to-Treat Analysis of 7 PM Reflective Individual Symptoms and TSS	S8-V1.222-P61
Appendix I2, Listing 6: Average Reflective PM Diary Listing	S8-V1.230-P1

Reviewer Comment On Results of 7PM Reflective Individual Symptoms

Statistically significant differences from placebo were noted for all doses of fexofenadine for each individual symptom for the 7PM reflective assessments. This suggests that the pharmacodynamic activity of fexofenadine is not directed toward only certain symptoms but rather most or all SAR symptoms.

Results -Physician's Evaluation of Overall Effectiveness - Intent-to-Treat Population

Results of the Physician's Evaluation of Overall Effectiveness, which classed patients as responders, defined as patients having moderate, marked or complete relief of symptoms, showed that no dose group produced statistically significant differences from placebo (60 mg, p = .720; 120 mg, p = .176; and 240 mg, p = .351)

Reviewer Comment Regarding Physicians Overall Assessment

The lack of agreement of the physician's overall assessment with the results from the patients' assessments does not invalidate the results of the trial; it may simply reflect the lack of sensitivity of the physician's assessment as a metric of efficacy.

Results - Subgroup Analyses - Intent-to-Treat Population

The sponsor provides the results of additional subgroup analysis for the ITT population for the 7PM reflective TSS by age, gender, race, weight and investigative site. The sponsor reports that the subgroup analyses were not statistically significant for treatment interaction between investigative site (p=0.2132); age (p=0.2225); gender (p=0.9027); race (p=0.7302); and weight (p=0.3883).

Results - By-Weekly Individual Symptom and TSS Analysis for Efficacy

On December 8, 1995, at our request, the sponsor submitted analyses of individual symptoms and TSS each of the 5 symptom assessments (7PM /7AM reflective, 7AM/7PM instantaneous, Bedtime) over each week of the study. After examining each individual symptom score and TSS for statistical significance (p≤0.05) and trend in statistical significance (p≤0.1) the following general patterns were observed where trend and statistical significance are both considered indicative of efficacy.

The **60mg** dose maintained efficacy over both weeks for each individual symptom and TSS. The **120mg** dose also maintained efficacy over both week for each individual symptom and TSS with the exception of week 2 itchy nose for 7PM instantaneous assessment and week 2 rhinorrhea for 7AM instantaneous assessment and bedtime assessment. The **240mg** dose also maintained efficacy over both weeks for each individual symptom and TSS with the exception of week 2 itchy eyes for 7PM reflective assessment and 7PM instantaneous assessment, week 2 itchy nose for 7PM instantaneous assessment, and week 2 rhinorrhea for 7AM instantaneous assessment. The following symbols are used in the tables below and are defined as:

- ++ = Statistically Significant i.e. ≤ 0.05
- + = Trend i.e. > 0.05 and < 0.10
- = Statistically insignificant i.e. ≥ 0.10

7pm Reflective Individual Symptoms and TSS for PJPR0023

Symptoms Week 1	60mg	120 mg	240 mg
Nasal Congestion	++	++	++
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	+	++
Itchy Eyes	++	++	++
TSS	++	++	++
Symptoms Week 2	60mg	120 mg	240 mg
Nasal Congestion	++	+	++
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	++	++
Itchy Eyes	++	+	-
TSS	++	++	++

7am Reflective Individual Symptoms and TSS for PJPR0023

Symptoms Week 1	60mg	120 mg	240 mg
Nasal Congestion	++	++	++
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	++	++
Itchy Eyes	++	++	++
TSS	++	++	++
Symptoms Week 2	60mg	120 mg	240 mg
Nasal Congestion	++	++	+
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	++	++
Itchy Eyes	++	++	++
TSS	++	++	++

7pm Instantaneous Individual Symptoms and TSS for PJPR0023

Symptoms Week 1	60mg	120 mg	240 mg
Nasal Congestion	++	++	++
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	++	++
Itchy Eyes	++	+	++
TSS	++	++	++
Symptoms Week 2	60mg	120 mg	240 mg
Nasal Congestion	++	++	+
Sneezing	++	++	++
Rhinorrhea	++	+	++
Itchy Nose	++	-	-
Itchy Eyes	++	+	-
TSS	++	+	++

Bedtime Individual Symptoms and TSS for PJPR0023

Symptoms Week 1	60mg	120 mg	240 mg
Nasal Congestion	++	--	++
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	++	++
Itchy Eyes	++	+	++
TSS	++	++	++
Symptoms Week 2	60mg	120 mg	240 mg
Nasal Congestion	++	+	++
Sneezing	++	++	++
Rhinorrhea	++	-	++
Itchy Nose	++	+	++
Itchy Eyes	++	++	++
TSS	++	++	++

7am Instantaneous Individual Symptoms and TSS for PJPR0023

Symptoms Week 1	60mg	120 mg	240 mg
Nasal Congestion	++	++	++
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	++	++	++
Itchy Eyes	++	+	++
TSS	++	++	++
Symptoms Week 2	60mg	120 mg	240 mg
Nasal Congestion	++	++	++
Sneezing	++	+	++
Rhinorrhea	++	-	-
Itchy Nose	+	+	+
Itchy Eyes	++	++	+
TSS	++	+	++

Reviewer Comment Regarding By-Weekly Individual Symptom and TSS Analysis for Efficacy

The results of this examination of the data support the efficacy of 60mg, 120mg and 240mg doses of fexofenadine to mitigate all the symptoms associated with SAR. Although it is difficult to explain why a few assessments of individual symptoms sporadically did not achieve statistical significance or trend during the second week of treatment for the two higher doses, the overall tendency could be viewed as sustained efficacy for all three doses.

Safety Results - Adverse Events

A total of 572 patients were exposed to double-blind study medication during the study and were evaluable for safety. Overall the sponsor reports that the total number of patients with one or more adverse event was: Placebo-64 (45.1%); 60mg- 43 (30.5%); 120mg-38 (26.4%); 240mg- 45(31.0%). The sponsor provides the incidence of all adverse events in Table 8-379. From that table only those adverse events which occurred a rate of 1% or greater in the total active group were extracted and placed in the table below.

INCIDENCE OF ALL ADVERSE EVENTS					
		Fexofenadine BID			
PREFERRED TERM	Placebo BID (N = 142) N(%)	60mg (N = 141) N(%)	120mg (N = 144) N(%)	240mg (N = 145) N(%)	Total Active (N = 430) N(%) ⁰
Headache	13 (9.2)	10 (7.1)	9 (6.3)	6 (4.1)	25 (5.8)
Fatigue	0 (0.0)	1 (0.7)	0 (0.0)	5 (3.4)	6 (1.4)
Throat Irritation	5 (3.5)	2 (1.4)	3 (2.1)	4 (2.8)	9 (2.1)
Sinusitis	4 (2.8)	1 (0.7)	1 (0.7)	3 (2.1)	5 (1.2)
Leukopenia	4 (2.8)	3 (2.1)	4 (2.8)	2 (1.4)	9 (2.1)
Infection Viral	4 (2.8)	3 (2.1)	4 (2.8)	7 (4.8)	14 (3.3)
Hyperlipemia	2 (1.4)	1 (0.7)	0(0.0)	5 (3.4)	6 (1.4)

Reviewer Comment Regarding Adverse Events

From this table only fatigue stands out as occurring more frequently in the active treatment groups than in the placebo group. This observation will need to be examined in the databases across all trials.

Deaths and Discontinuations Due to Adverse Events

The sponsor reports no deaths during this trial. One 18 year old Caucasian male (137-057) who was taking fexofenadine was hospitalized for closed reduction of a fractured right arm after 7 days of treatment with 240mg BID. The subject was involved in a four-wheeler accident on day 3 of treatment. The event was assessed by the investigator as not related to study drug. With regard to patients who discontinued medication due to adverse events, the sponsor provides Table 8-383 reproduced below, which lists 12 individual patients and reasons for discontinuation.

Table 8-383. Summary Of Patients Who Discontinued Study Medication Due To Adverse Events								
<i>Patient</i>	<i>Age</i>	<i>Sex</i>	<i>Treatment (BID)</i>	<i>Adverse Event (preferred Term)</i>	<i>Duration of Treatment Prior to Discontinuation (days)</i>	<i>Severity</i>	<i>Study Drug Relation</i>	<i>Outcome</i>
134-063								
136-012								
137-001								
137-057								
138-003								
138-033								
142-015								
142-022								
142-026								
146-040								
147-006								
147-047								
* Patient was also hospitalized								
Supporting Data							Page	
Appendix J3. Listing 8 Adverse Events Meeting the Serious Criteria							S8-V1 230-P268	

Reviewer Comment

In reviewing the narratives for these 12 subjects, it becomes apparent that it is difficult to ascribe causality of the event with either active treatment or placebo treatment.

Clinical Laboratory Evaluation

The sponsor reports that a statistically significant correlation ($p=0.0017$; $r=0.1316$) between dose and change from baseline was observed for SGPT with small increases in SGPT (ALT) in all fexofenadine dose groups. The 240 mg BID dose group produced the maximum average increase of 2.745 ± 0.60 U/L. There was no statistically significant correlation between dose and change from baseline for the other laboratory parameters.

Reviewer Comment

This observation for SGPT will need to be examined in the databases across all trials. This observation will need to be examined in the databases across all trials

Vital Signs

The sponsor reports that there was no statistically significant change in SBP, DBP or HR from baseline to the final visit in the patients treated with fexofenadine compared to placebo.

EKG Measurements

The sponsor reports that there was no statistically significant mean change in PR, QT, QT_c, QRS, or RR intervals from baseline to the Final Visit in patients treated with fexofenadine compared to placebo. There was a statistically significant (P= .0461) dose response in the change from baseline in RR, which reflects a maximum mean change in heart rate of only one beat per minute between baseline and Final Visit in any dose group. Reproduced below is the sponsor's table which displays this information.

Measurement	Treatment (BID)	N	Mean±Standard Error			P value* (Active vs Placebo)
			Baseline	Final	Change from Baseline	
PR (msec)	Placebo	141	154±1.5	153±1.7	-1.0±1.2	
	60 mg MDL 16.455A	141	152±1.8	153±1.7	1.0±1.2	2579
	120 mg MDL 16.455A	144	153±1.7	154±1.6	0.1±1.2	5227
	240 mg MDL 16.455A	145	152±1.7	152±1.8	-0.5±1.2	7676
	Overall Treatment Differences P value**= 7001			Dose Response (Linear Trend) P value**= 9886		
QT (msec)	Placebo	141	391±2.2	392±2.4	0.9±1.9	
	60 mg MDL 16.455A	141	390±2.2	393±2.3	2.7±1.9	5280
	120 mg MDL 16.455A	144	392±2.2	393±2.3	1.3±1.9	9011
	240 mg MDL 16.455A	145	395±2.4	393±2.3	-2.2±1.9	2537
	Overall Treatment Differences P value**= 3358			Dose Response (Linear Trend) P value**= 1493		
QT _c (msec)	Placebo	141	411±2.4	409±2.3	-2.3±2.1	
	60 mg MDL 16.455A	141	408±2.2	408±1.9	0.0±2.1	4316
	120 mg MDL 16.455A	144	408±1.9	409±2.0	1.7±2.1	1739
	240 mg MDL 16.455A	145	409±2.1	409±2.1	0.1±2.0	4122
	Overall Treatment Differences P value**= 5976			Dose Response (Linear Trend) P value**= 4480		
QRS (msec)	Placebo	141	84±0.7	84±0.7	-0.0±0.6	
	60 mg MDL 16.455A	141	86±0.9	85±0.9	-1.2±0.6	1837
	120 mg MDL 16.455A	144	84±0.8	84±0.7	0.4±0.6	6416
	240 mg MDL 16.455A	145	85±0.8	85±0.7	-0.3±0.6	7891
	Overall Treatment Differences P value**= 3224			Dose Response (Linear Trend) P value**= 8036		
RR (msec)	Placebo	141	918±11.8	934±12.8	15±10.1	
	60 mg MDL 16.455A	141	925±10.8	938±12.2	13±10.1	8444
	120 mg MDL 16.455A	144	934±11.7	934±12.4	0±10.0	2761
	240 mg MDL 16.455A	145	945±12.0	935±12.5	-10±9.9	0724
	Overall Treatment Differences P value**= 2442			Dose Response (Linear Trend) P value**= 0461		
* P value from an ANOVA analysis adjusting for treatment						
Supporting Data						Page
Appendix E3 Listing 26 Intent-to-Treat Analysis of QT _c and QT Change						S8-V1 222-P256
Appendix E3 Listing 27 Intent-to-Treat Analysis of PR and QRS Change						S8-V1 222-P265
Appendix E3 Listing 28 Intent-to-Treat Analysis of RR and HR Change						S8-V1 222-P274
Appendix L1 Listing 2 Patient ECG Listing						S8-V1 238-P198

For QTc, the sponsor defined patients who exhibited a interval >440 msec and an increase >10 msec as an outlier. The number exhibiting this change from baseline to final visit for each treatment group were: Placebo = 8; 60mg = 7; 120mg = 10; 240mg = 8.

Reviewer Comment

These data suggest that fexofenadine does not tend to prolong QTc intervals in patients taking fexofenadine in doses up to 240mg BID. Corroboration of this observation with observations from other clinical trials will be needed for greater assurance that this phenomenon does not occur.

Pharmacokinetics/Pharmacodynamics

The data from Protocol PJPR0023 were combined with that from Protocol PJPR0024, and have been reviewed separately.

Final Reviewer Comments Regarding Protocol PJPR0023:

Protocol PJPR0023 fulfills the requirements for a well controlled clinical trial. The study objectives are clearly stated. The study subjects are well defined by appropriate inclusion and exclusion criteria. It was placebo-controlled and double-blinded with random assignment of subjects to study treatments. The baseline characteristics of the treatment groups were comparable without any obvious clinically important differences between groups. The methods for observation, recording, quantification and evaluation of data are described along with statistical methods used and statistical comparisons between active treatments and placebo.

Reviewer's Determinations:

- 1) The results of this study support the assertion that compared to placebo treatment fexofenadine is efficacious for the mitigation of the symptoms associated with SAR in doses of 60mg BID, 120mg BID and 240mg BID in patients greater than 12 years of age.
- 2) Based on the analyses of the primary parameter, the magnitude of symptom reduction is comparable across the doses studied, suggesting that there is little if any additional symptom reduction by increasing the dose above 60mg BID in most patients.
- 3) Based on the analysis of effect over time, all three doses exhibited an onset of action in 1-3 hours, maintained efficacy at the end of the dosing interval, and maintained efficacy for two weeks.
- 4) The lowest effective dose of fexofenadine was not observed, since no dose in this trial failed to demonstrate efficacy nor did any dose demonstrate a substantially lesser effect in symptom reduction than higher other doses.
- 5) Examination of the safety profile of fexofenadine compared to that of placebo does not reveal any obvious toxicities with doses up to 240mg BID administered for 2 weeks. Particular attention was focused on QTc interval measurements with no obvious greater propensity for prolongation than placebo. The observance of a small but statistically significant increase in SGPT relative to baseline will need further confirmation from other clinical trials.
- 6) There does not appear to be an interaction between fexofenadine and age, gender, race or weight.

Conclusions: The results of this study support the assertion that fexofenadine in doses of 60mg BID, 120mg BID and 240mg BID are safe and effective for the mitigation of symptoms associated with SAR in patients 12 years of age and older.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted July 31, 1995
Material Reviewed: Protocol PJPR0024 from NDA 20-625

Protocol No. PJPR0024 - conducted from August 12, 1994 to November 30, 1994

Title

"A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of three dosage strengths of MDL-16,455A (40, 60, and 120mg BID) in the treatment of Fall allergies."

Objectives

"The primary objective was to determine the efficacy and safety of MDL-16,455A at 40 mg BID, 60 mg BID, and 120 mg BID doses compared to placebo in the treatment of fall seasonal allergic rhinitis."

"A secondary objective was to determine the dose proportionality of MDL-16,455A at 40 mg BID, 60 mg BID, and 120 mg BID."

Study Design

The study design and plans for data analysis for this protocol are identical to that for Protocol #PJPR0023. The reader is referred to Medical Officer review for Protocol #PJPR0023 for review of the study design and plans for the analysis of data.

I have compared the two protocols and found them to be identical for schematics, protocol amendments, number of treatment groups, duration of treatments, number of investigational sites, numbers of patients planned for enrollment at each site, patient inclusion and exclusion criteria, restrictions for concomitant medication use, blinding technique, packaging and labeling of study medication, randomization plan, efficacy and safety variables and assessments, timing of assessments, collection of pollen counts, scheduling of study procedures, patient disposition, definition of primary and secondary parameters, and plan for data analysis.

I note that the two protocols differ in the doses of study treatments, study investigators, lot numbers of study medications, and capsule sizes. The analysis of data also differed in that protocol PJPR0024 excluded data from one investigative site (# 0155) from the efficacy analysis because of the sponsor's discovery of protocol violations relating to patient enrollment. The sponsor questioned the integrity of the data from that site upon discovering that data in the symptom diaries had been altered to allow patients to qualify for the study and subsequently discontinued further patient enrollment. Nonetheless, the sponsor also provides an additional analysis of the primary efficacy parameter which includes the questionable data. The sponsor's concern about data integrity from site #0155 was communicated to the Agency's Division of Scientific Investigations by letter, dated September 28, 1995 from the sponsor, from Cynthia Kirk-Yourtee, Ph.D to Mr. Gurston Turner.

Study Treatments

Single-Blind Placebo Lead-In:

Placebo BID 2-40 mg size placebo capsules
 2-20 mg size placebo capsules

Double-Blind Treatment :

MDL 16,455A 120 mg BID 2-40 mg MDL 16,455A capsules
 2-20 mg MDL 16,455A capsules

MDL 16,455A 60 mg BID 1-40 mg MDL 16,455A capsule
 1-20 mg MDL 16,455A capsule
 1-40 mg size placebo capsule
 1-20 mg size placebo capsule

MDL 16,455A 40 mg BID 1-40 mg MDL 16,455A capsule
 1-40 mg size placebo capsule
 2-20 mg size placebo capsules

Placebo BID 2-40 mg size placebo capsules
 2-20 mg size placebo capsules.

<i>Study Medication</i>	<i>Lot Number(s)</i>
MDL 16,455A 40 mg capsules (size #1)	RF9422
MDL 16,455A 20 mg capsules (size #3)	RB9434
Placebo 40 mg capsules (size #1)	RF9423
Placebo 20 mg capsules (size #3)	RB9408

Reviewer Comment

According to the biopharmaceutics reviewer, Brad Gillespie, the 20mg and 40mg capsule formulations are considered bioequivalent when administered in equivalent doses.

Efficacy Parameters - The efficacy parameters are reproduced for reference, if needed.

Primary Parameter - The primary efficacy analysis variable was change in the average daily 7 PM reflective TSS. This TSS was computed by summing the individual symptom scores (excluding nasal congestion) as recorded on the patient's symptom diary card. If any of the individual symptoms used in calculating the TSS were missing then that TSS evaluation was also treated as missing. Further, the change in the TSS assessment is defined as follows:

Average Double-Blind 7 PM Reflective TSS - Average Baseline 7 PM Reflective TSS

Note, the 7 PM symptom assessment collected immediately prior to administration of the first double-blind dose was excluded when calculating both the average baseline and double-blind symptom scores.

Secondary Parameters -

The following variables were used for secondary evaluations of efficacy.

1. Change in average daily 7 PM reflective TSS over time (week 1 vs baseline, week 2 vs baseline, and all days of double-blind dosing period vs baseline).
2. Change in average daily 7 AM reflective TSS (average of the 7 AM reflective TSS during the double-blind dosing period) from average baseline 7 AM reflective TSS (average of the three 7 AM reflective TSS during the placebo lead-in period).
3. Change in average daily 7 PM instantaneous TSS (average of the 7 PM instantaneous TSS during the double-blind dosing period) from average baseline 7 PM instantaneous TSS (average of the three 7 PM instantaneous TSS during the placebo lead-in period).
4. Change in average daily 7 AM instantaneous TSS (average of the 7 AM instantaneous TSS during the double-blind dosing period) from average baseline 7 AM instantaneous TSS (average of the three 7 AM instantaneous TSS during the placebo lead-in period).
5. Change in average daily bedtime instantaneous TSS (average of the bedtime instantaneous TSS during the double-blind dosing period) from average baseline bedtime instantaneous TSS (average of the three bedtime instantaneous TSS during the placebo lead-in period).
6. Change in the patient's assessment of severity of individual symptoms for the 7 AM reflective, 7 AM instantaneous, 7 PM reflective, 7 PM instantaneous, and bedtime instantaneous assessments.
7. Physician's evaluation at the final visit of the overall effectiveness of study medication.

Results - Patient Accounting

The sponsor reports the following patient tally:

Screened-----	1345
Screening Failures-----	299
Exposed to Single Blind Med-----	1046
Placebo Lead-in Discontinuation-----	457
Randomized-----	589
Discontinued Prior to D-B Exposure--	1
Exposed to Double-Blind Med-----	588
Double-Blind Discontinuation-----	38
Completed-----	550

The sponsor prepared 4 tables reproduced below to summarize patient disposition and distribution of patients exposed to double-blind study medication a) across treatment groups and investigative sites, b) who had major protocol violations, and c) who discontinued early. There is a discrepancy of 43 in the number of patients in the exposed-population and the intent-to-treat (ITT) population, 39 of which the sponsor attributes to exclusion from site #0155 due questionable data integrity and 4 of which had no symptom assessments while on double-blind medication.

The tables below show that the distribution of patients exposed to double-blind treatment is similar across treatments and across treatments within investigative sites. Similarly, the number of major protocol violations and early discontinuations are similar across treatments for each type of violation and each reason for discontinuation; these occurred in 5% or less of the patients assigned to any one study treatment, with the exception of 7% for patients who were at site #0155. The 39 patients, excluded from the intent-to-treat population, is evenly distributed across treatments (i.e. 10, 10, 9, 10) so that their exclusion does not cause imbalance across treatments.

It is interesting to note that study PJPR0024 had fewer screening failures than PJPR0023 (299 vs 425) to obtain approximately the same number of patients entering the single-blind phase (1046 vs 1073) and approximately the same number of patients entering the double-blind phase (589 vs 575).

Table 8-401. Summary of Patient Disposition					
<i>Treatment (BID)</i>	<i>Randomized N (%)</i>	<i>Exposed N (%)</i>	<i>Safety Evaluable N (%)</i>	<i>Intent-to-Treat N (%)</i>	<i>Protocol Correct N(%)</i>
Placebo	148 (25%)	148 (25%)	148 (25%)	137 (25%)	126 (25%)
40 mg MDL 16,455A	146 (25%)	145 (25%)	145 (25%)	135 (25%)	126 (25%)
60 mg MDL 16,455A	148 (25%)	148 (25%)	148 (25%)	138 (25%)	130 (25%)
120 mg MDL 16,455A	147 (25%)	147 (25%)	147 (25%)	135 (25%)	129 (25%)
Total	589	588	588	545	517
<i>Supporting Data:</i>					<i>Page</i>
<i>Appendix F1, Summary 2: Summary of Patient Disposition</i>					<i>S8-V1.243-P156</i>
<i>Appendix F2, Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group</i>					<i>S8-V1.243-P179</i>

Table 8-400. Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group					
Investigative Site	Placebo (BID)	MDL 16 455A (BID)			Total
		40 mg	60 mg	120 mg	
149	10	10	9	12	41
150	12	11	12	12	47
151	7	8	8	7	30
152	12	12	12	12	48
153	10	10	10	9	39
154	14	14	14	14	56
155	10	10	9	10	39
156	9	10	11	10	40
157	11	11	10	10	42
158	9	10	11	9	39
159	6	5	6	6	23
160	12	12	12	12	48
161	5	3	4	4	16
162	3	3	3	3	12
163	7	5	5	6	23
167	11	11	12	11	45
TOTAL	148	145	148	147	588

Supporting Data: Page
 Appendix F1, Summary 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group S8-V1.243-P152
 Appendix F2, Listing 1: Distribution of Patients Exposed to Double-Blind Study Medication by Investigative Site and Treatment Group S8-V1.243-P179

Table 8-402. Summary of Major Protocol Violations (Patients Exposed to Double-Blind Study Medication)						
Major Protocol Violation	Placebo BID (N=143)	MDL 16.455A (BID)				Total (N= 588)
		40 mg (N=145)	60 mg (N=148)	120 mg (N=147)	Total Active (N=440)	
Failure to Meet Entrance Criteria	7 (5%)	4 (3%)	4 (3%)	2 (1%)	10 (2%)	17 (3%)
Use of Prohibited Medications Prior to or During Study	5 (3%)	6 (4%)	4 (3%)	5 (3%)	15 (3%)	20 (3%)
Missing Efficacy Data (Primary Measure)	1 (1%)	0 (0%)	1 (1%)	2 (1%)	3 (1%)	4 (1%)
Non-Compliance with Study Medication	5 (3%)	4 (3%)	3 (2%)	2 (1%)	9 (2%)	14 (2%)
Non-Compliance with Data Collection Procedures or Timing	10 (7%)	10 (7%)	9 (6%)	10 (7%)	29 (7%)	39 (7%)
Total Patients	22 (15%)	19 (13%)	18 (12%)	18 (12%)	55 (13%)	77 (13%)

Patients may have had more than one major protocol violation, therefore, patient counts for Major Violations may not equal the total number of patients having major protocol violations (Total Patients)

Supporting Data Page
 Appendix F1, Summary 3 Summary of Major Protocol Violations (Exposed Patients) S8-V1 243-P158
 Appendix F2, Listing 2 Major Protocol Violations S8-V1 243-P193

Table 8-403. Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication						
<i>Primary Reason</i>	<i>Placebo BID (N=148)</i>	<i>MDL 16 455A (BID)</i>				<i>Total (N= 588)</i>
		<i>40 mg (N=145)</i>	<i>60 mg (N=148)</i>	<i>120 mg (N=147)</i>	<i>Total Active (N=440)</i>	
Adverse Event	3 (2%)	3 (2%)	2 (1%)	1 (1%)	6 (1%)	9 (2%)
Elected to Discontinue	1 (1%)	3 (2%)	1 (1%)	0 (0%)	4 (1%)	5 (1%)
Use of Prohibited Medications	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Failed to Return to Study Site for a Scheduled Visit	3 (2%)	0 (0%)	4 (3%)	7 (5%)	11 (3%)	14 (2%)
Treatment Failure	1 (1%)	2 (1%)	1 (1%)	1 (1%)	4 (1%)	5 (1%)
Other	0 (0%)	0 (0%)	0 (0%)	4 (3%)	4 (1%)	4 (1%)
Total Patients	8 (5%)	9 (6%)	8 (5%)	13 (9%)	30 (7%)	38 (6%)
Patients may have had more than one reason for discontinuing the study; however, only the primary reason is summarized.						
<i>Supporting Data:</i>						<i>Page</i>
<i>Appendix F1 Summary 4: Summary of Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication</i>						<i>S8-V1.243-P161</i>
<i>Appendix F2. Listing 4: Reasons for Early Discontinuation in Patients Exposed to Double-Blind Study Medication</i>						<i>S8-V1.243-P217</i>

Results - Patient Baseline Demographics

The sponsor summarizes baseline demographic characteristics in Table 8-404 reproduced below. Of the baseline factors presented only height demonstrates a statistically significant difference ($p = 0.016$) across treatment groups. It is difficult to ascribe a clinical significance to the observed small differences in means across treatments for height.

Baseline Characteristics	Placebo (n=137)	MDL 16,455A (BID)			Total (n=545)	P value*
		40 mg (n=135)	60 mg (n=138)	120 mg (n=135)		
Gender						
Male % (N)	42(57)	46(62)	34(47)	36(49)	39(215)	.1809
Female % (N)	58(80)	54(73)	66(91)	64(86)	61(330)	
Age (years)						
Mean±SD	33±11	33±11	33±11	34±10	33±11	.8452
Range	12-60	12-63	13-62	13-59	12-63	
Race						
Caucasian % (N)	82(113)	84(114)	78(107)	75(101)	80(435)	.3536
Black % (N)	7(10)	7(9)	7(10)	7(10)	7(39)	
Hispanic % (N)	10(14)	7(9)	12(16)	15(20)	11(59)	
Other % (N)	0(0)	2(3)	4(5)	3(4)	2(12)	
Weight (kg)						
Mean±SD	72±17	75±18	72±19	73±17	73±18	.3351
Range	43-140	44-122	33-135	42-118	33-140	
Height (cm)						
Mean±SD	170±10	170±9	167±10	169±10	169±10	.0161
Range	152-193	152-189	145-203	150-193	145-203	
Years Since First Episode Occurred						
Mean±SD	19±11	17±11	18±11	17±10	18±11	.3512
Range	3- 52	2- 56	3- 50	2- 52	2- 56	
Successive Years of Fall Allergy						
Mean±SD	18±11	17±11	17±11	18±10	17±11	.5288
Range	3- 52	2- 56	2- 50	2- 52	2- 56	
* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors						
Supporting Data.					Page	
Appendix G1, Summary 1: Intent-to-Treat Patients					S8-V1 243-P281	

Reviewer Comment Regarding Patient Baseline Demographics

It is difficult to ascribe a clinical significance to the observed small differences in means across treatments for height.

In addition to this examination of baseline characteristics we requested the sponsor to submit an analysis of baseline demographics by investigational site. The sponsor provided this information by a submission to the NDA dated December 13, 1995. Below is a table displaying the ranges across study sites for the range of baseline demographics.

Range of Baseline Demographics Across Study Sites - Intent-To-Treat							
PJPR0024	Age	Gender %Male	Race				Total Symptom Score
			Asian	Black	Caucasian	Other	
High (site #)	39 ± 12 (151)	59.5% (157)	10.3% (153)	31.3% (160)	100% (149, 161, 162)	2.6% (153)	10.33 ± 1.38 (157)
Low (site #)	28 ± 9 (162) 28 ± 8 (163)	18.2% (162)	0.0% (all sites except 151, 154, 159)	0.0% (149, 152, 153, 161, 162)	68.8% (160)	0.0% (All sites except 152, 153)	7.83 ± 1.85 (150)

Results - Baseline Symptom Assessments

Baseline symptom assessments for the 7PM reflective symptom assessments for the ITT population are summarized by the sponsor in Table 8-405, reproduced below. No statistically significant difference was noted across treatments for any one symptom or total symptom score. Similar tables, reproduced below, were presented by the sponsor for the other symptom parameters - 7AM reflective scores, 7AM and 7PM instantaneous scores, and bedtime scores. Similarly, no statistically significant difference was observed across the treatment groups for any one symptom or total symptom score for any of the other symptom parameters (i.e. 7AM reflective scores, 7AM and 7PM instantaneous scores, and bedtime scores) with the lowest p value (0.2524) for bedtime score for assessment of nasal congestion for the bedtime symptom assessment.

Table 8-405. Baseline 7 PM Reflective Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (n=137)	MDL 16 455A (BID)			Total (n=545)	P value*
		40 mg (n=135)	60 mg (n=138)	120 mg (n=135)		
Nasal Congestion						
Mean ±SD	2.3±0.6	2.2±0.7	2.3±0.6	2.3±0.6	2.3±0.6	5777
Range	0.7-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
Sneezing						
Mean ±SD	2.0±0.6	2.1±0.7	1.9±0.7	2.0±0.7	2.0±0.7	6191
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean ±SD	2.3±0.5	2.3±0.6	2.3±0.5	2.4±0.5	2.3±0.5	8045
Range	0.7-3.0	0.7-3.0	0.7-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean ±SD	2.2±0.6	2.2±0.6	2.2±0.6	2.3±0.6	2.2±0.6	8409
Range	0.7-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery, Red Eyes						
Mean ±SD	2.1±0.6	2.1±0.7	2.2±0.7	2.0±0.8	2.1±0.7	2989
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
TSS (Excluding Nasal Congestion)						
Mean ±SD	8.7±1.5	8.7±1.9	8.7±1.5	8.6±1.7	8.7±1.7	9712
Range	5.7-12	5.0-12	5.0-12	5.0-12	5.0-12	
* P value from Kruskal-Wallis test						
Supporting Data:						Page
Appendix E3, Listing 1 Kruskal-Wallis Test for Baseline PM Reflective Symptom Assessment (ITT)						S8-V1 241-P18
Appendix 12, Listing 1 Intent-to-Treat Reflective PM Diary Listing						S8-V1 245-P4

Table 8-406. Baseline 7 AM Reflective Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (n=137)	MDL 16 455A (BID)			Total (n=545)	P value*
		40 mg (n=135)	60 mg (n=138)	120 mg (n=135)		
Nasal Congestion						
Mean±SD	2.4±0.6	2.3±0.6	2.3±0.6	2.3±0.7	2.3±0.6	7477
Range	0.7-3.3	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.3	
Sneezing						
Mean±SD	1.9±0.7	1.7±0.8	1.8±0.8	1.7±0.8	1.8±0.8	4223
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.3±0.6	2.2±0.6	2.3±0.5	2.3±0.6	2.3±0.6	2698
Range	0.3-3.0	0.0-3.0	0.7-3.0	0.3-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.1±0.6	2.1±0.7	2.2±0.6	2.2±0.6	2.2±0.6	3083
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery, Red Eyes						
Mean±SD	2.0±0.6	2.0±0.7	2.1±0.7	1.9±0.7	2.0±0.7	3321
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
TSS (Excluding Nasal Congestion)						
Mean±SD	8.3±1.7	8.0±1.9	8.4±1.8	8.2±1.8	8.2±1.8	2675
Range	4.0-12	4.7-12	4.7-12	5.0-12	4.7-12	
* P value from Kruskal-Wallis test						
Supporting Data:						Page
Appendix E3, Listing 2 Kruskal-Wallis Test for Baseline AM Reflective Symptom Assessment (ITT)						S8-V1 241-P62
Appendix 12, Listing 2 Intent-to-Treat Reflective AM Diary Listing						S8-V1 246-P1

Table 8-407. Baseline 7 PM Instantaneous Symptom Assessments (Intent-to-Treat)

Baseline Symptoms	Placebo (BID) (n=137)	MDL 16 455A (BID)			Total (n=545)	P value*
		40 mg (n=135)	60 mg (n=138)	120 mg (n=135)		
Nasal Congestion						
Mean±SD	2.3±0.6	2.1±0.8	2.2±0.7	2.3±0.6	2.2±0.7	3101
Range	0.3-3.3	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.3	
Sneezing						
Mean±SD	1.8±0.8	1.7±0.9	1.8±0.8	1.7±0.8	1.7±0.8	8168
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.2±0.7	2.1±0.7	2.2±0.6	2.2±0.6	2.2±0.6	7339
Range	0.0-3.3	0.3-3.3	0.7-3.0	0.0-3.0	0.0-3.3	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.1±0.7	2.1±0.7	2.1±0.7	2.1±0.7	2.1±0.7	7634
Range	0.0-3.3	0.0-3.3	0.0-3.0	0.0-3.0	0.0-3.3	
Itchy, Watery, Red Eyes						
Mean±SD	2.0±0.7	2.0±0.8	2.1±0.8	1.9±0.8	2.0±0.8	4954
Range	0.0-3.0	0.0-3.3	0.0-3.3	0.0-3.0	0.0-3.3	
TSS (Excluding Nasal Congestion)						
Mean±SD	8.0±2.2	7.9±2.4	8.1±1.9	7.9±2.1	8.0±2.2	8428
Range	2.0-12	2.7-13	2.3-12	1.7-12	1.7-13	

* P value from Kruskal-Wallis test

Supporting Data
 Appendix E3, Listing 3: Kruskal-Wallis Test for Baseline PM Instantaneous Symptom Assessment (ITT) Page SB-V1 241-P106
 Appendix 12, Listing 3: Intent-to-Treat Instantaneous PM Diary Listing SB-V1 247-P1

Table 8-408. Baseline 7 AM Instantaneous Symptom Assessments (Intent-to-Treat)

Baseline Symptoms	Placebo (BID) (n=137)	MDL 16 455A (BID)			Total (n=545)	P value*
		40 mg (n=135)	60 mg (n=138)	120 mg (n=135)		
Nasal Congestion						
Mean±SD	2.4±0.6	2.3±0.6	2.3±0.7	2.4±0.7	2.3±0.7	2619
Range	0.3-3.3	0.3-3.3	0.3-3.0	0.0-3.0	0.0-3.3	
Sneezing						
Mean±SD	1.8±0.8	1.6±0.9	1.6±0.9	1.6±0.9	1.6±0.9	4079
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean±SD	2.2±0.7	2.2±0.7	2.2±0.6	2.2±0.7	2.2±0.7	8072
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.3-3.3	0.0-3.3	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.0±0.7	2.0±0.7	2.1±0.7	2.1±0.7	2.1±0.7	3819
Range	0.0-3.3	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.3	
Itchy, Watery, Red Eyes						
Mean±SD	2.0±0.7	2.0±0.8	2.1±0.7	1.9±0.8	2.0±0.6	3461
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
TSS (Excluding Nasal Congestion)						
Mean±SD	8.0±2.2	7.7±2.3	8.1±2.1	7.9±2.3	7.9±2.2	5227
Range	1.5-12	2.0-12	2.0-12	1.3-12	1.3-12	

* P value from Kruskal-Wallis test

Supporting Data
 Appendix E3, Listing 4: Kruskal-Wallis Test for Baseline AM Instantaneous Symptom Assessment (ITT) Page SB-V1 241-P151
 Appendix 12, Listing 4: Intent-to-Treat Instantaneous AM Diary Listing SB-V1 248-P1

Table 8-409. Baseline Bedtime Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (n=137)	MDL 16 455A (BID)			Total (n=543)	P value*
		40 mg (n=134)	60 mg (n=137)	120 mg (n=135)		
Nasal Congestion						
Mean±SD	2.2±0.7	2.0±0.8	2.2±0.7	2.1±0.7	2.1±0.7	2524
Range	0.3-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
Sneezing						
Mean±SD	1.6±0.8	1.6±0.9	1.5±0.9	1.5±0.8	1.5±0.9	8955
Range	0.0-3.3	0.0-3.0	0.0-3.3	0.0-3.0	0.0-3.3	
Rhinorrhea						
Mean±SD	2.0±0.8	1.9±0.8	2.0±0.7	2.0±0.8	2.0±0.8	7457
Range	0.0-3.3	0.0-3.0	0.3-3.7	0.0-3.0	0.0-3.7	
Itchy Nose, Palate and/or Throat						
Mean±SD	2.0±0.7	2.0±0.7	2.0±0.7	2.0±0.8	2.0±0.7	6644
Range	0.0-3.3	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.3	
Itchy, Watery, Red Eyes						
Mean±SD	1.8±0.7	1.9±0.8	2.0±0.8	1.8±0.9	1.9±0.8	3631
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
TSS (Excluding Nasal Congestion)						
Mean±SD	7.4±2.4	7.4±2.5	7.5±2.4	7.3±2.6	7.4±2.5	9941
Range	1.0-13	1.7-12	1.7-12	1.0-12	1.0-13	
* P value from Kruskal-Wallis test						
Supporting Data:					Page	
Appendix E3, Listing 5: Kruskal-Wallis Test for Baseline Bedtime Symptom Assessment (ITT)					S8-V1.241-P198	
Appendix I2, Listing 5: Intent-to-Treat Bedtime Diary Listing					S8-V1.244-P1	

Results - Compliance

The sponsor reports the period of double-blind exposure as 13 ± 2 days with a range of 2-14 days for all treatments except the 120mg dose which had a range of 4-14 days.

The sponsor also reports that compliance with double-blind treatment across treatments to range from 100 ± 2 % for the 60mg and 120mg dose to 100 ± 7 % for the 40mg dose; and reports that 4 patients had compliance below 80% or above 120%.

We asked the sponsor to provide a summary of subjects compliance with diary symptom assessments. On December 13, 1995 the sponsor reported that compliance with diary symptom assessments for the ITT population was 99.8 ± 0.9 % for protocol PJPR0024.

The sponsor reports that a total 14 patients (6-40mg; 4-60mg; 5-120mg) on active treatment and 5 patients on placebo received concomitant medications which were pre-defined as protocol violation with not more than 3 patients in any one prohibited drug category.

Results - Primary Efficacy Parameter (7PM Reflective TSS) - Intent-to-Treat Population

The pre-defined primary assessment of efficacy was the patient's change in mean 7 PM reflective TSS from baseline in the Intent-to-Treat population; the results were summarized by the sponsor in Table 8-413 and figure 8-135 reproduced below. Patients from investigative site #0155 were excluded from the Intent-to-Treat population. An ANCOVA model containing investigative site, treatment and baseline demonstrated that all active treatments were statistically significant over placebo with the 120mg dose exhibiting a slightly larger numerical reduction in scores compared to the two lower doses which exhibited an almost identical response to each other.

For these results, the change from baseline for active treatments compared to placebo are numerically smaller for the 60mg (-0.66 ± 0.24) and similar for the 120mg (-0.91 ± 0.25) than the respective results observed in protocol PJPR0023 for the 60mg (-1.07 ± 0.28) and 120mg (0.85 ± 0.28) doses; but both 120mg dose responses remained numerically smaller than the 60mg dose observed in protocol PJPR0023.

The sponsor also reports that interaction terms of treatment by investigative site and treatment by baseline TSS were tested at the $\alpha = 0.10$ level and found not to be significant; and that the test for linear dose response was significant ($P = .0005$).

Table 8-413. Intent-to-Treat Analysis of 7 PM Reflective TSS (N=545)				
Treatment (BID)	N	Mean $\pm$ Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	137	8.66 $\pm$ 0.13	7.54 $\pm$ 0.19	-1.21 $\pm$ 0.18
40 mg MDL 16.455A	135	3.69 $\pm$ 0.16	6.93 $\pm$ 0.21	-1.86 $\pm$ 0.18
60 mg MDL 16.455A	138	8.72 $\pm$ 0.14	6.93 $\pm$ 0.19	-1.86 $\pm$ 0.18
120 mg MDL 16.455A	135	8.61 $\pm$ 0.15	6.59 $\pm$ 0.21	-2.11 $\pm$ 0.18
Treatment Comparison		Mean $\pm$ Standard Error* (Active-Placebo)		P value *
Overall Treatment Differences				.0020
Dose Response (Linear Trend)				.0005
40 mg MDL 16.455A vs Placebo		-0.65 $\pm$ 0.25		.0087
60 mg MDL 16.455A vs Placebo		-0.66 $\pm$ 0.24		.0075
120 mg MDL 16.455A vs Placebo		-0.91 $\pm$ 0.25		.0002
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
Supporting Data:				Page
Appendix E3, Listing 6: Intent-to-Treat Analysis of 7 PM Reflective TSS				S8-V1.241-P244
Appendix I2, Listing 6: Average Reflective PM Diary Listing				S8-V1.250-P1

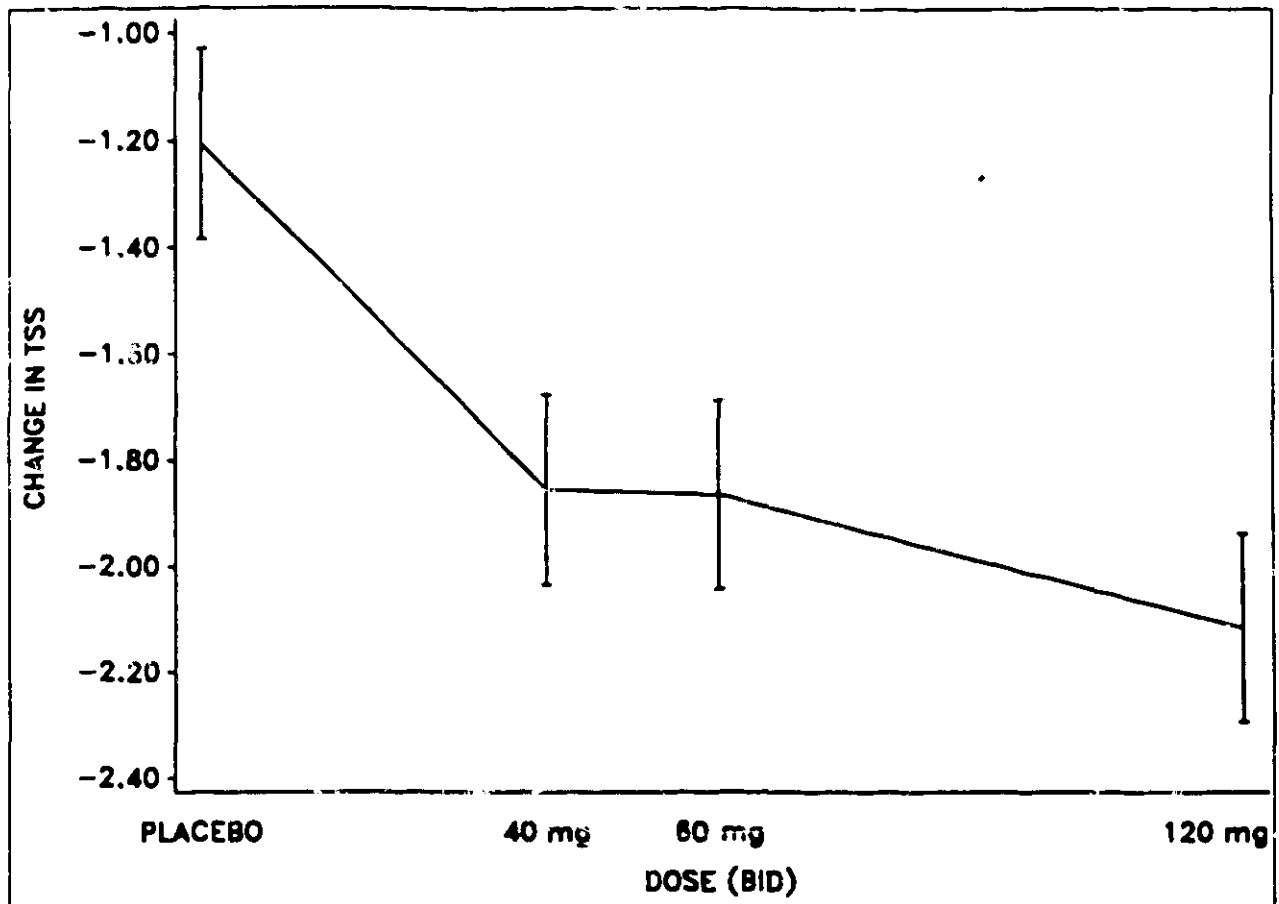


Figure 8-135. Change from Baseline in 7 PM Reflective TSS. Mean±SE (Intent-to-Treat)

Supporting Data:

Page

Table 8-413. Intent-to-Treat Analysis of 7 PM Reflective TSS (N=545)

S8-V1.239-P74

Res **Secondary Efficacy Parameter (7PM Reflective TSS) - Protocol Correct Population**

The sponsor performed a secondary analysis using 511 patients with no major protocol violations (Protocol Correct Patients) and summarized the results in Table 8-414 and figure 8-136, reproduced below. The results show that all doses demonstrated statistically significant differences from placebo and that the numerical magnitude of the difference from placebo was similar to that of the ITT population.

Table 8-414. Protocol Correct Analysis of 7 PM Reflective TSS (N=511)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean±Standard Error</i>		
		<i>Baseline</i>	<i>Double-Blind Period</i>	<i>Change from Baseline*</i>
Placebo	126	8.67±0.13	7.53±0.21	-1.22±0.19
40 mg MDL 16,455A	126	8.73±0.17	6.91±0.21	-1.91±0.19
60 mg MDL 16,455A	130	8.74±0.14	6.89±0.19	-1.90±0.19
120 mg MDL 16,455A	129	8.62±0.15	6.55±0.22	-2.16±0.19
<i>Treatment Comparison</i>		<i>Mean±Standard Error* (Active-Placebo)</i>		<i>P value *</i>
Overall Treatment Differences				.0025
Dose Response (Linear Trend)				.0007
40 mg MDL 16,455A vs Placebo		-0.69±0.26		.0080
60 mg MDL 16,455A vs Placebo		-0.67±0.26		.0093
120 mg MDL 16,455A vs Placebo		-0.94±0.26		.0003
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
<i>Supporting Data:</i>				<i>Page</i>
Appendix E3, Listing 7: Protocol Correct Analysis of 7 PM Reflective TSS				S8-V1.241-P249
Appendix I2, Listing 6: Average Reflective PM Diary Listing				S8-V1.250-P1

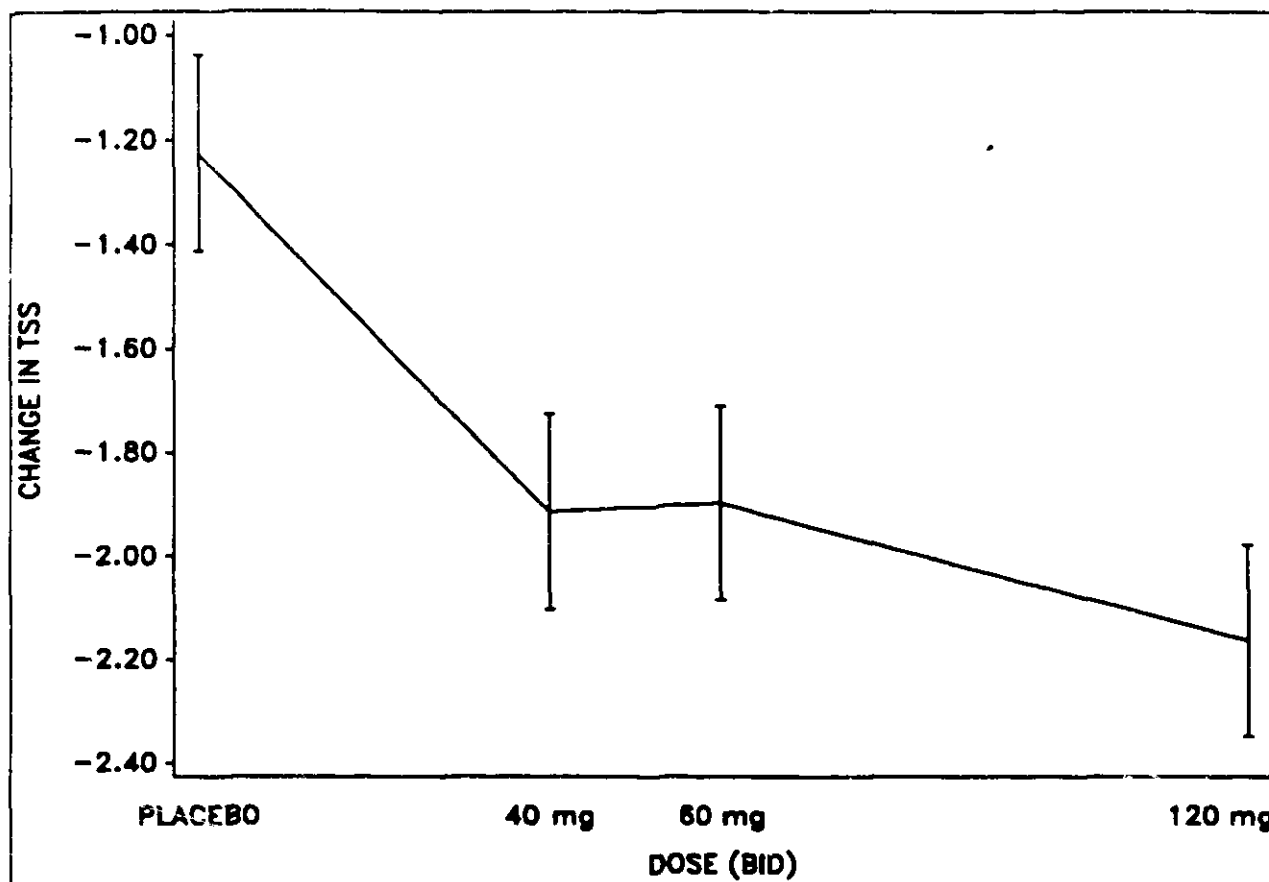


Figure 8-136. Change from Baseline in 7 PM Reflective TSS. Mean±SE (Protocol Correct)

Supporting Data:

Page

Table 8-414. Protocol Correct Analysis of 7 PM Reflective TSS (N=511)

S8-V1.239-P76

Reviewer Comment on Results of the Primary Efficacy Parameter

The results from the primary pre-planned analysis support the assertion that fexofenadine at the three doses tested can mitigate the symptoms of seasonal allergic rhinitis. The response of the 40 and 60 mg dose level numerically appear comparable while the response observed in at the 120mg dose level may confer some additional symptom control. This is in contrast to trial PJPR0023 in which the 120mg dose level did not appear to confer any additional symptom control over that seen with the 60mg dose level. This observation regarding magnitudes of symptom reduction for the primary endpoint across trials suggests that there may in fact be little additional symptom score reduction from the administration of 120mg dose compared to the 60mg dose. Examination of other dose response factors will be needed to identify the lowest effective dose. Additionally, results from the protocol correct population are similar to those from the ITT population. The sponsor indicates that the test for dose response (linear trend) was statistically significant ($p=0.0005$). However, the review of the statistical reviewer, Barbara Bono, indicates that the sponsor included placebo in the model which seems inappropriate; and her recalculation excluding placebo shows a loss of statistical significance for linear trends.

Results - Primary Efficacy Parameter - Alternative Analyses

The sponsor also presents the results of several alternative analyses.

Inclusion of Site #0155:

The sponsor conducted an alternative analysis on the primary variable which **included** the data from site #0155 (Vol. 242 - P146) and noted the increase in the level of statistical significance between each dose level and placebo (40mg - $p=0.0018$; 60mg - $p=0.0018$; 120mg - $p=0.0001$) compared to the significance levels observed during the analysis which excluded site #0155.

Responder Analysis:

Additionally data for 7PM reflective TSS using the ITT population was displayed as the percentage of patients experiencing greater than 20% reduction in TSS: Placebo = 32%; 40mg = 49%; 60mg = 50%; and 120mg = 45%.

Reviewer Comment on Alternative Analyses

The sponsor's analysis excluding the data from study site #0155 seems appropriate. The results from the reanalysis of the data which includes data from site #0155 appears to make little difference in the interpretation of the results since including the data from site #0155 increases the level of statistical significance.

With regard to the responder analysis, although the percentage of patients who exhibit greater than 20% reduction in TSS is larger in the patients on active treatment compared to placebo, a 20% reduction seems modest. At our request the sponsor provided on December 22, 1995 additional calculations for larger reductions in TSS. The tables below display the sponsor's calculations for the percentage of subjects with greater than 20% and 50% reduction in 7PM reflective TSS. Each table uses a different definition of response. The sponsor indicates that the p values provide comparison of each active dose to placebo.

For the table below, the percentages of patients at the 50% level of response is similar for the 60mg and 120mg dose with the 120mg dose achieving statistical significance, while the percentages for the 40mg dose and placebo are the same suggesting a possible dose response favoring the 120mg dose and possibly the 60mg dose.

		Percent of Patients With Symptom Improvement From Baseline Above A Fixed Level	
PJPR0024	N	≥20% Improvement Level	≥50% Improvement Level
Placebo	137	33%	9%
40mg	135	49% $p=0.008$	9% $p=0.943$
60mg	138	51% $p=0.003$	13% $p=0.291$
120mg	135	45% $p=0.045$	16% $p=0.060$

Additionally the sponsor provided the results for an alternative definition of response - improvement greater than the average improvement for placebo patients. The table below summarizes the results for

this alternative definition. The percent of patients at the 50% level is only slightly less than those observed at the 20% level for all treatments.

PJPR0024	N	Percent of Patients With Symptom Improvement From Baseline Above The Average Improvement For Placebo	
		≥20% Improvement Level Above Placebo	≥50% Improvement Level Above Placebo
Placebo	137	38%	33%
40mg	135	57% p=0.002	47% p=0.023
60mg	138	58% p=0.001	49% p=0.006
120mg	135	50% p=0.043	44% p=0.072

Results - Primary Efficacy Parameter - Effect Over Time - Intent-To-Treat Population

The sponsor conducted three Intent-To-Treat analyses of change from baseline TSS over time (week 1 of double-blind period vs baseline, week 2 of double-blind baseline period vs baseline, and each individual day of the double-blind dosing period vs baseline). Tables displaying results for the individual days are reproduced below

By week analysis :

Week 1 of double-blind period vs baseline (Table 8-416) - all dose groups showed statistically significant improvement over placebo (40 mg, P=.0054; 60 mg, P=.0135; and 120 mg P=.0011).

Week 2 of double-blind period vs baseline (Table 8-417) - all dose groups showed statistically significant improvement over placebo (40 mg, P=.0143; 60 mg, P=.0168; and 120 mg P=.0019).

TSS Days 1 and 2:

Table 8-418, reproduced below, displays the symptom scores for various symptom assessments on Day 1 and 2 of the double-blind period. Examination of this table shows that the 60mg (p=0.0395) and 120mg (p=0.0139) dose level attained statistical significance for the bedtime instantaneous score for Day 1, suggesting that these two doses have an onset of action 1 to 3 hours after the first dose and is sustained by both 7AM and 7PM instantaneous and reflective scores for Day 2. By comparison, the 40mg dose appeared to lag behind by not achieving statistical significance until Day 2 instantaneous 7AM scoring and not achieving statistical significance for 7AM reflective scoring.

Each Individual Day:

Table 8-419 displays daily change from baseline for 7PM reflective TSS from day 2 to 14. All dose groups showed statistically significant improvement by Day 2 reflective 7PM score, which was sustained for the following number of days out of 13 during the double-blind period: 7 - 40mg; 8 - 60mg; 12 - 120mg.

Table 8-418. Summary of Patients' TSS Assessments 24 Hours Following First Dose of Double-Blind Medication

Day	Assessment	Change from Baseline in TSS				Dose Response P value
		N				
		Mean ± Standard Error				
		P value				
		Placebo	40 mg MDL 16,455A	60 mg MDL 16,455A	120 mg MDL 16,455A	
1†	Bedtime Instantaneous	N=136 0.24±0.19	N=134 -0.06±0.19 P= 2501	N=137 -0.30±0.19 P= 0395	N=135 -0.41±0.19 P= 0139	.0126
2	7 AM Reflective	N=137 -0.07±0.17	N=135 -0.44±0.18 P= 1340	N=138 -0.59±0.17 P= 0323	N=135 -0.77±0.18 P= 0041	.0043
	7 AM Instantaneous	N=137 0.23±0.20	N=135 -0.43±0.18 P= 0099	N=138 -0.58±0.18 P= 0014	N=135 -0.67±0.18 P= 0004	.0007
	7 PM Reflective	N=137 -0.53±0.19	N=135 -1.39±0.19 P= 0010	N=138 -1.44±0.19 P= 0005	N=135 -1.39±0.19 P= 0010	.0030
2	7 PM Instantaneous	N=137 0.02±0.21	N=135 -0.99±0.21 P= 0005	N=138 -0.97±0.21 P= 0005	N=135 -1.23±0.21 P= 0001	.0001

* P value for comparison of MDL 16,455A dose and placebo

† First dose of double-blind medication at 7 PM

Supporting Data:	Page
Appendix E3, Listing 31: Intent-to-Treat Analysis of 7 PM Reflective TSS Change by Day	S8-V1.242-P186
Appendix E3, Listing 33: Intent-to-Treat Analysis of 7 AM Reflective TSS Change by Day	S8-V1.242-P266
Appendix E3, Listing 34: Intent-to-Treat Analysis of 7 PM Instantaneous TSS Change by Day	S8-V1.243-P1
Appendix E3, Listing 35: Intent-to-Treat Analysis of 7 AM Instantaneous TSS Change by Day	S8-V1.243-P41
Appendix E3, Listing 36: Intent-to-Treat Analysis of Bedtime TSS Change by Day	S8-V1.243-P81
Appendix I2, Listing 1: Intent-to-Treat Reflective PM Diary Listing	S8-V1.245-P4
Appendix I2, Listing 2: Intent-to-Treat Reflective AM Diary Listing	S8-V1.246-P1
Appendix I2, Listing 3: Intent-to-Treat Instantaneous PM Diary Listing	S8-V1.247-P1
Appendix I2, Listing 4: Intent-to-Treat Instantaneous AM Diary Listing	S8-V1.248-P1
Appendix I2, Listing 5: Intent-to-Treat Bedtime Diary Listing	S8-V1.249-P1
Table 8-401 Summary of Patient Disposition	8-V1.239-P61

Table 8-419. Intent-to-Treat Analysis of Daily 7 PM Reflective TSS		Mean Change from Baseline				Dose Response P value*
Day		Placebo (N=147)	MDL 16,455A (BID)			
			40 mg (N=145)	60 mg (N=147)	120 mg (N=145)	
2	n	137	135	138	135	.0030
	Mean±SE	-0.53±0.19	-1.39±0.19	-1.44±0.19	-1.39±0.19	
	P value*		0.0010	0.0005	0.0010	
3	n	136	134	137	134	.0201
	Mean±SE	-0.76±0.21	-1.70±0.21	-1.41±0.21	-1.57±0.21	
	P value*		0.0014	0.0265	0.0058	
4	n	136	134	137	135	.0247
	Mean±SE	-0.95±0.21	-1.53±0.21	-1.55±0.21	-1.66±0.21	
	P value*		0.0471	0.0414	0.0156	
5	n	136	133	137	133	.0260
	Mean±SE	-1.05±0.21	-1.61±0.22	-1.46±0.21	-1.78±0.22	
	P value*		0.0601	0.1705	0.0152	
6	n	135	133	136	133	.0031
	Mean±SE	-1.12±0.21	-1.68±0.22	-1.77±0.21	-2.03±0.21	
	P value*		0.0572	0.0272	0.0023	
7	n	133	131	136	130	.0490
	Mean±SE	-1.17±0.23	-1.57±0.23	-1.57±0.23	-1.83±0.23	
	P value*		0.2089	0.2048	0.0404	
8	n	133	127	132	125	.0042
	Mean±SE	-1.11±0.23	-2.07±0.24	-1.94±0.23	-2.14±0.24	
	P value*		0.0030	0.0089	0.0015	
9	n	133	126	132	127	.0092
	Mean±SE	-1.31±0.24	-2.10±0.25	-2.04±0.24	-2.26±0.24	
	P value*		0.0196	0.0288	0.0047	
10	n	133	125	131	126	.0026
	Mean±SE	-1.26±0.25	-2.17±0.26	-2.13±0.25	-2.40±0.25	
	P value*		0.0092	0.0122	0.0012	
11	n	131	125	132	126	.0059
	Mean±SE	-1.60±0.24	-2.38±0.25	-2.26±0.25	-2.62±0.25	
	P value*		0.0219	0.0494	0.0029	
12	n	131	125	130	126	.0511
	Mean±SE	-1.78±0.25	-2.38±0.26	-2.35±0.26	-2.52±0.26	
	P value*		0.0854	0.1026	0.0345	
13	n	125	119	122	115	.0096
	Mean±SE	-1.89±0.27	-2.27±0.28	-2.52±0.27	-2.85±0.28	
	P value*		0.3130	0.0891	0.0107	
14	n	93	91	94	89	.0724
	Mean±SE	-2.11±0.32	-2.44±0.32	-2.26±0.32	-2.88±0.32	
	P value*		0.4262	0.7203	0.0639	

* P value, mean and associated standard error from the analysis of change from baseline in daily TSS using an ANCOVA model containing investigative site, treatment, and baseline

Supporting Data	Page
Appendix E3, Listing 31 Intent-to-Treat Analysis of 7 PM Reflective TSS Change by Day	S8-V1 242-P186
Appendix I2, Listing 1 Intent-to-Treat Reflective PM Diary Listing	S8-V1 245-P4

Reviewer Comment on Effect Over Time

The analysis of 7PM reflective scores by week shows that all 3 doses exhibit a sustained effect overall for the 2 week study period. Examination of the 7PM reflective TSS (ITT population) data on a daily change from baseline basis shows that all 3 doses exhibited an onset of action by day 2 which is sustained on a daily basis, best by the 120mg dose (12 of 13 days) and by the 40mg and 60mg doses less consistently (7 and 8 respectively of 13 days). Examination of the various assessments over day 1 and 2 also suggests that the 60mg and 120mg doses have an onset of action by approximately 1-3 hours (bedtime instantaneous score) after the first dose and that this action is sustained through the 12 hour dosing interval (7AM instantaneous and 7AM reflective). The 40mg dose did not appear to have an onset of action in 1-3 hours

Results Secondary Efficacy Parameters - 7AM Reflective TSS; 7AM/7PM Instantaneous TSS - Intent-to-Treat Population

The sponsor provides the results for the analyses of these parameters in the tables reproduced below: Tables 8-420, 8-421, 8-422.

Table 8-420. Intent-to-Treat Analysis of 7 AM Reflective TSS (N=545)				
<i>Treatment (BID)</i>	<i>N</i>	<i>Mean ± Standard Error</i>		
		<i>Baseline</i>	<i>Double-Blind Period</i>	<i>Change from Baseline*</i>
Placebo	137	8.35±0.14	7.46±0.19	-0.92±0.17
40 mg MDL 16.455A	135	8.01±0.17	6.78±0.21	-1.41±0.17
60 mg MDL 16.455A	138	8.37±0.15	6.96±0.18	-1.45±0.17
120 mg MDL 16.455A	135	8.21±0.15	6.59±0.21	-1.70±0.17
<i>Treatment Comparison</i>		<i>Mean ± Standard Error (Active-Placebo)</i>		<i>P value *</i>
Overall Treatment Differences:				.0109
Dose Response (Linear Trend)				.0017
40 mg MDL 16.455A vs Placebo		-0.49±0.24		.0396
60 mg MDL 16.455A vs Placebo		-0.52±0.23		.0261
120 mg MDL 16.455A vs Placebo		-0.77±0.24		.0011
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
<i>Supporting Data:</i>				<i>Page</i>
Appendix E3. Listing 8: Intent-to-Treat Analysis of 7 AM Reflective TSS				S8-V1 241-P254
Appendix I2. Listing 7: Average Reflective AM Diary Listing				S8-V1 250-P29

Table 8-421. Intent-to-Treat Analysis of 7 PM Instantaneous TSS (N=545)				
Treatment (BID)	N	Mean±Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	137	8.04±0.19	7.28±0.21	-0.79±0.19
40 mg MDL 16.455A	135	7.91±0.21	6.63±0.22	-1.38±0.19
60 mg MDL 16.455A	138	8.12±0.17	6.63±0.20	-1.48±0.19
120 mg MDL 16.455A	135	7.92±0.18	6.31±0.21	-1.69±0.19
Treatment Comparison		Mean±Standard Error* (Active-Placebo)		P value *
Overall Treatment Differences				.0041
Dose Response (Linear Trend)				.0009
40 mg MDL 16.455A vs Placebo		-0.59±0.26		.0222
60 mg MDL 16.455A vs Placebo		-0.69±0.26		.0073
120 mg MDL 16.455A vs Placebo		-0.90±0.26		.0005
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
Supporting Data:				Page
Appendix E3, Listing 9: Intent-to-Treat Analysis of 7 PM Instantaneous TSS				S8-V1.241-P259
Appendix I2, Listing 8: Average Instantaneous PM Diary Listing				S8-V1.250-P57

Table 8-422. Intent-to-Treat Analysis of 7 AM Instantaneous TSS (N=545)				
Treatment (BID)	N	Mean±Standard Error		
		Baseline	Double-Blind Period	Change from Baseline*
Placebo	137	7.97±0.19	7.41±0.20	-0.59±0.17
40 mg MDL 16.455A	135	7.72±0.20	6.79±0.21	-1.08±0.18
60 mg MDL 16.455A	138	8.07±0.17	7.00±0.19	-1.04±0.17
120 mg MDL 16.455A	135	7.87±0.19	6.64±0.21	-1.29±0.18
Treatment Comparison		Mean±Standard Error* (Active-Placebo)		P value *
Overall Treatment Differences				.0299
Dose Response (Linear Trend)				.0063
40 mg MDL 16.455A vs Placebo		-0.49±0.24		.0426
60 mg MDL 16.455A vs Placebo		-0.46±0.24		.0579
120 mg MDL 16.455A vs Placebo		-0.70±0.24		.0038
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.				
Appendix E3, Listing 10: Intent-to-Treat Analysis of 7 AM Instantaneous TSS				
Appendix I2, Listing 9: Average Instantaneous AM Diary Listing				

Reviewer Comments On Results of Secondary Efficacy Parameters

Statistically significant differences from placebo are noted for all doses in all three analyses except for the 60mg dose for 7AM instantaneous TSS which approaches statistical significance (p=0.0579). Additionally, bedtime instantaneous TSS analysis showed statistically significant differences from placebo for all 3 doses (40mg, 60mg, 120mg - p=0.0102, 0.0210, 0.0011 respectively). All these analyses support the findings from the pre-planned analysis of the primary efficacy parameter.

Results - Secondary Analyses - Individual Symptoms - Intent-to-Treat Population

Results of the analyses of individual symptom scores for 7PM reflective symptom assessments is presented by the sponsor in Table 8-424, reproduced below. None of the doses reached statistical significance for congestion. Statistical significance was achieved for all doses for all the remaining individual symptom scores except 40mg for itchy eyes and 60mg for itchy nose.

Table 8-424. Intent-to-Treat Analysis of 7 PM Reflective Individual Symptoms and TSS						
Symptoms		Mean Change from Baseline				Dose Response P Value*
		Placebo BID (N=137)	MDL 16.455A (BID)			
			40 mg (N=135)	60 mg (N=138)	120 mg (N=135)	
Nasal Congestion	n	137	135	138	135	.1049
	Mean±SE	-0.13±0.05	-0.12±0.05	-0.18±0.05	-0.22±0.05	
	P value*		0.9246	0.4564	0.1472	
Sneezing	n	137	135	138	135	.0004
	Mean±SE	-0.24±0.05	-0.45±0.05	-0.46±0.05	-0.51±0.05	
	P value*		0.0034	0.0022	0.0001	
Rhinorrhea	n	137	135	138	135	.0169
	Mean±SE	-0.24±0.05	-0.41±0.05	-0.42±0.05	-0.42±0.05	
	P value*		0.0137	0.0093	0.0087	
Itchy Nose, Palate and/or Throat	n	137	135	138	135	.0077
	Mean±SE	-0.38±0.06	-0.54±0.06	-0.48±0.06	-0.61±0.06	
	P value*		0.0356	0.2183	0.0037	
Itchy, Watery, Red Eyes	n	137	135	138	135	.0034
	Mean±SE	-0.35±0.05	-0.46±0.06	-0.51±0.06	-0.57±0.06	
	P value*		0.1694	0.0392	0.0036	
TSS (Excluding Nasal Congestion)	n	137	135	138	135	.0005
	Mean±SE	-1.21±0.18	-1.86±0.18	-1.86±0.18	-2.11±0.18	
	P value*		0.0067	0.0075	0.0002	
* P value, mean and associated standard error from the analysis using an ANCOVA model containing investigative site, treatment, and baseline.						
Supporting Data						Page
Appendix E3. Listing 15: Intent-to-Treat Analysis of 7 PM Reflective Individual Symptoms and TSS						S8-V1.241-P303
Appendix 12. Listing 6: Average Reflective PM Diary Listing						S8-V1.250-P1

The sponsor also provides analyses for individual symptoms for the 7 AM reflective, 7 PM and 7 AM instantaneous, and bedtime instantaneous scores in Appendix E3. None of the dose levels reached statistical significance for nasal congestion whereas all dose levels reached statistical significance for TSS except 60mg for the 7AM instantaneous score (p=0.0579). The 120mg dose reached statistical significance for all scores for the 4 individual remaining symptoms. The 40mg and 60mg dose level reached statistical significance for all scores of sneezing and rhinorrhea except 40mg did not reach significance for the 7AM instantaneous score. The 60mg dose level reached statistical significance for itchy eyes for 7PM instantaneous (p=0.0241) and bedtime (p= 0.0328) scores but not for 7AM instantaneous (p=0.2714) or 7AM reflective (p=0.0873). The 60mg dose did not reach significance for itchy nose for these scores. The 40mg dose level reached significance for itchy nose only for the bedtime score and never for itchy eyes.

Reviewer Comment on Individual Symptoms

In general all doses impacted on all individual symptom scores for the 7PM reflective parameter; and all doses impacted on sneezing and rhinorrhea for 7AM reflective and 7AM and 7PM instantaneous scores. However, the 40mg and 60mg doses did not impact many 7AM reflective and 7AM and 7PM instantaneous scores for itchy nose or itchy eyes. It is still necessary to examine the data on a weekly basis to determine how these dose levels behave over time.

Results - Physician's Evaluation of Overall Effectiveness

Only the 120 mg dose group had a statistically marginal effect (as assessed by the physician) over placebo (P=.053).

Results - Subgroup Analyses

The sponsor provides the results of 5 additional analyses for interaction using subgroup factors and the 7PM reflective scores. The results of an ANCOVA which contained treatment, investigative site and baseline was not statistically significant (p=0.6259). Additionally, there was no statistically significant interaction for age (p=0.1570), gender (p=0.4738), race (p=0.5265), or weight (p=0.8383).

Results - By-Weekly Individual Symptom and TSS Analysis for Efficacy

On December 8, 1995, at our request, the sponsor submitted analyses of individual symptoms and TSS each of the 5 symptom assessments (7PM /7AM reflective, 7AM/7PM instantaneous, Bedtime) over each week of the study. After examining each individual symptom score and TSS for statistical significance (p≤0.05) and trend in statistical significance (p≤0.1) the following general patterns were observed where trend and statistical significance are both considered indicative of efficacy. All 3 doses maintained efficacy for TSS for all 5 symptom assessments over two weeks while none of the doses effected nasal congestion at any time.

The 120mg dose maintained efficacy over both weeks for each individual symptom and TSS with the exception of week 2 rhinorrhea nose for 7AM reflective assessment and week 2 sneezing, itchy nose, and itchy eyes for 7AM instantaneous assessment.

Both the 40mg and 60mg doses maintained efficacy for sneezing and rhinorrhea over two weeks for all assessments except the 40mg did not exhibit efficacy for week 1 rhinorrhea for 7AM reflective assessment and week 2 sneezing for 7AM instantaneous assessment. Both the 40mg and 60mg doses did not exhibit efficacy for itchy nose or itchy eye for any time point for any assessment except they did exhibit efficacy for the following:

60mg for week 2 itchy eye for 7PM reflective, 7PM instantaneous and bedtime assessment;

40mg for week 2 itchy eye for 7PM reflective and bedtime assessments; and weeks 1 and 2 itchy nose for 7PM reflective and bedtime assessments.

The following symbols are used in the tables below and are defined as:

++ = Statistically Significant i.e. ≤ 0.05

+ = Trend i.e. > 0.05 and < 0.10

- = Statistically Insignificant i.e. ≥ 0.10

7pm Reflective Individual Symptoms and TSS for PJPR0024

Symptoms Week 1	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	+-	-	++
Itchy Eyes	-	-	++
TSS	++	++	++
Symptoms Week 2	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	+	-	++
Itchy Eyes	+	++	++
TSS	++	++	++

7pm Instantaneous Individual Symptoms and TSS for PJPR0024

Symptoms Week 1	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	+++	++
Rhinorrhea	++	++	++
Itchy Nose	-	-	++
Itchy Eyes	-	-	++
TSS	++	++	++
Symptoms Week 2	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	-	-	++
Itchy Eyes	-	++	++
TSS	++	++	++

7am Reflective Individual Symptoms and TSS for PJPR0024

Symptoms Week 1	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	-	++	++
Itchy Nose	-	-	++
Itchy Eyes	-	-	++
TSS	+	++	++
Symptoms Week 2	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	++	-
Itchy Nose	-	-	+
Itchy Eyes	-	-	+
TSS	++	++	++

7am Instantaneous Individual Symptoms and TSS for PJPR0024

Symptoms Week 1	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	++	++
Itchy Nose	-	-	++
Itchy Eyes	-	-	+
TSS	+-	+	++
Symptoms Week 2	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	-	+	-
Rhinorrhea	++	++	++
Itchy Nose	-	-	-
Itchy Eyes	-	-	-
TSS	+	+	+

Bedtime Individual Symptoms and TSS for PJPR0024

Symptoms Week 1	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	+	+
Itchy Nose	+	-	++
Itchy Eyes	-	-	+
TSS	++	+	++
Symptoms Week 2	40mg	60 mg	120 mg
Nasal Congestion	-	-	-
Sneezing	++	++	++
Rhinorrhea	++	++	+
Itchy Nose	+	-	++
Itchy Eyes	++	++	++
TSS	++	++	++

Safety Results - Adverse Events

A total of 588 patients were exposed to double-blind treatment and were considered safety evaluable. Overall, the sponsor reports that the total number of patients with 1 or more adverse event was: Placebo 50-(33.8%); 40mg 53-(36.6%); 60mg-55 (37.2%); 120mg-50 (34.0%). The sponsor provides the incidence of all adverse events in Table 8-432. From that table only those which occurred at a rate of 1% or greater in the total active group were extracted and placed in the table below.

PREFEPRED TERM	Placebo (N=148) N(%)	Fexofenadine BID			Total Active (N=440) N(%)
		40 mg (N=145) N(%)	60 mg (N=148) N(%)	120 mg (N=147) N(%)	
HEADACHE	12 (8.1)	4 (2.8)	7 (4.7)	13 (8.8)	24 (5.5)
THROAT IRRITATION	3 (2.0)	6 (4.1)	3 (2.0)	3 (2.0)	12 (2.7)
LEUKOPENIA	2 (1.4)	5 (3.4)	3 (2.0)	2 (1.4)	10 (2.3)
HYPOCALCEMIA	2 (1.4)	3 (2.1)	3 (2.0)	3 (2.0)	9 (2.0)
UPPER RESPIRATORY TRACT INFECTION	2 (1.4)	3 (2.1)	2 (1.4)	3 (2.0)	8 (1.8)
INJURY ACCIDENTAL	1 (0.7)	1 (0.7)	5 (3.4)	2 (1.4)	8 (1.8)
INFECTION VIRAL	3 (2.0)	1 (0.7)	5 (3.4)	1 (0.7)	7 (1.6)
HYPERLIPEMIA	2 (1.4)	1 (0.7)	1 (0.7)	3 (2.0)	5 (1.1)
DYSMENORRHEA	0 (0.0)	0 (0.0)	4 (2.7)	1 (0.7)	5 (1.1)
MYALGIA	1 (0.7)	3 (2.1)	0 (0.0)	2 (1.4)	5 (1.1)

Reviewer Comment On Adverse Events

From this table, leukopenia, accidental injury, and dysmenorrhea stand out as occurring slightly more frequently in the active treatment groups than in the placebo group. Of these only leukopenia also appeared in the comparable table of adverse events in protocol PJPR0023 but in that table it did not occur more frequently in the active treatment group than in the placebo group. This observation will need to be examined in the databases across all trials. Fatigue occurred more frequently in active treatment groups compared to placebo in protocol PJPR0023 and also in PJPR0024 (placebo = none; 40mg = none; 60mg = 0.7%; 120mg = 1.4%); but in protocol PJPR0024, overall it occurred in less than 1% of the patients on active treatments.

Deaths and Discontinuations Due to Adverse Events

The sponsor reports no deaths or hospitalizations occurring during this study. The sponsor summarizes information regarding subjects who have discontinued medication due to adverse events in Table 8-436, reproduced below.

Table 8-436. Summary Of Patients Who Discontinued Study Medication Due To Adverse Events	
Patent	
152-037	
157-003	
153-062	
159-001	
159-007	
160-026	
160-063	
162-042	
163-044	
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Appendix J3 Listing 8 Adverse Events Meeting the Serious Criteria	S8-V1 250-P287

Reviewer Comment

In reviewing the narratives for these 9 subjects, it becomes apparent that it is difficult to ascribe causality of the event to active treatment or placebo treatment. The sponsor reports no deaths or hospitalizations occurring during this trial.

Clinical Laboratory Evaluation

The sponsor reports that there was a small dose dependent decrease in sodium ($p=0.0217$; $r=-0.0957$) and potassium ($p=0.0193$; $r=0.0977$) with the largest change occurring in the placebo group for potassium which amounted to less than 3% of baseline.

Vital Signs

The sponsor reports that there was no statistically significant change in SBP, DBP, or HR from baseline to the final visit in patients treated with fexofenadine compared to placebo.

ECG Measurements

The sponsor reports that there was no statistically significant change in PR, QT, QT_c, QRS, or RR intervals from baseline to the final visit in the patients treated with fexofenadine compared to placebo, for all doses. The supporting data was displayed by the sponsor in Table 8-444, reproduced below.

Measurement	Treatment (BID)	n	Mean±Standard Error			P Value* (Active vs Placebo)
			Baseline	Final	Change from Baseline	
PR (msec)	Placebo	144	160±1.7	161±1.4	0.4±1.0	
	40 mg MDL 16,455A	144	162±1.6	161±1.7	-0.5±1.0	.5045
	60 mg MDL 16,455A	142	161±1.4	161±1.5	-0.9±1.0	.3701
	120 mg MDL 16,455A	142	157±1.3	159±1.5	1.9±1.0	.3078
	Overall Treatment Differences P value*=.2217			Dose Response (Linear Trend) P value*=.2414		
QT (msec)	Placebo	144	386±2.1	389±1.8	2.9±1.7	
	40 mg MDL 16,455A	144	392±2.0	391±2.2	-0.4±1.7	.1772
	60 mg MDL 16,455A	142	389±1.9	390±2.3	1.3±1.7	.5104
	120 mg MDL 16,455A	142	388±2.1	390±2.0	2.2±1.7	.7562
	Overall Treatment Differences P value*=.5693			Dose Response (Linear Trend) P value*=.9572		
QT _c (msec)	Placebo	144	408±1.8	407±1.9	-1.0±1.8	
	40 mg MDL 16,455A	144	411±2.0	410±1.9	-1.3±1.8	.9000
	60 mg MDL 16,455A	142	412±2.0	411±1.9	-1.1±1.8	.9811
	120 mg MDL 16,455A	142	413±2.0	411±2.0	-1.1±1.8	.9642
	Overall Treatment Differences P value*=.9994			Dose Response (Linear Trend) P value*=.9849		
QRS (msec)	Placebo	144	88±0.6	88±0.5	-0.0±0.4	
	40 mg MDL 16,455A	144	88±0.7	88±0.9	-0.1±0.4	.8397
	60 mg MDL 16,455A	142	87±0.6	88±0.6	0.8±0.4	.1506
	120 mg MDL 16,455A	142	87±0.5	88±0.6	0.5±0.4	.3493
	Overall Treatment Differences P value*=.3073			Dose Response (Linear Trend) P value*=.2462		
RR (msec)	Placebo	144	907±12.3	926±12.1	19±10.8	
	40 mg MDL 16,455A	144	919±11.3	926±13.6	7±10.8	.4211
	60 mg MDL 16,455A	142	904±13.5	912±11.8	8±10.9	.4762
	120 mg MDL 16,455A	142	895±12.0	910±12.0	15±10.9	.7722
	Overall Treatment Differences P value*=.8384			Dose Response (Linear Trend) P value*=.8658		
* P value from an ANOVA analysis adjusting for treatment.						
Supporting Data:						Page
Appendix E3, Listing 27: Intent-to-Treat Analysis of QT _c and QT Change						S8-V1.242-P149
Appendix E3, Listing 28: Intent-to-Treat Analysis of PR and QRS Change						S8-V1.242-P158
Appendix E3, Listing 29: Intent-to-Treat Analysis of RR and HR Change						S8-V1.242-P167
Appendix L1, Listing 2: Patient ECG Listing						S8-V1.258-P281

The sponsor defined patients who exhibited a QT_c interval > 440 msec and an increase > 10 msec as an outlier. The number exhibiting this change from baseline to final visit were: Placebo = 6.2%; 40mg = 4.9%; 60mg = 7.7%; 120mg = 6.3%.

Final Reviewer Comments Regarding Protocol PJPR0024: Protocol PJPR0024 fulfills the criteria for a well controlled clinical trial in support of safety and efficacy.

Reviewer's Determinations:

- 1) Based on the results of the 7PM reflective total symptom scores (TSS), this study supports the assertion that compared to placebo fexofenadine in doses of 40mg BID, 60mg BID and 120mg BID are safe and effective for the mitigation of symptoms, except nasal congestion, associated with SAR in patients 12 years of age and older; and the effect is sustained over a 2 week period. This effect was also observed for all doses for individual symptom scores except itchy nose for 60mg and itchy eyes for 40mg. Compared to placebo, the magnitude of TSS reduction was comparable between 40mg and 60mg with slight additional reduction for the 120mg dose.
- 2) Based on the results from analyses of 7AM and 7PM instantaneous TSS, efficacy is maintained at the end of the dosing interval by Day 2.
- 3) Based on Day 1 bedtime instantaneous scores and Day 2 7AM reflective scores, 60mg and 120mg doses appear to exert a more rapid onset of action compared to the 40mg dose.
- 4) Based on analyses of individual symptom scores for 7AM reflective, 7AM and 7PM instantaneous and bedtime assessments, only the 120mg dose controls all the individual symptoms except nasal congestion, while the 40mg and 60mg doses control sneezing and rhinorrhea but poorly control itchy nose and itchy eyes.
- 5) Examination of the safety profile of fexofenadine compared to that of placebo does not reveal any obvious toxicities with doses up to 120mg BID administered for 2 weeks. Particular attention was focused on QTc interval measurements with no obvious greater propensity for prolongation than placebo.
- 6) There does not appear to be an interaction between fexofenadine and age, gender, race or weight.

Conclusion: Based on the results of total symptom scores, this study supports the assertion that fexofenadine in doses of 40mg BID, 60mg BID and 120mg BID are safe and effective for the mitigation of symptoms, except nasal congestion, associated with SAR in patients 12 years of age and older.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: **NDA 20-625**
Protocol # PJPR0017- conducted November 25 to December 11, 1994

Title

"A Placebo-Controlled, Double-Blind, Randomized, Parallel Study In An environmental Exposure Unit Characterizing The Onset Of Action, Efficacy and Safety of a Single Dose of 60mg or 120mg MDL-16,455A in Patients with Fall Allergies."

Objectives

"The primary objective was to characterize the time to onset of clinically important relief of symptoms of ragweed pollen-induced allergic rhinitis in patients taking a single dose of 60mg MDL 16,455A, 120mg MDL 16,455A, or placebo during exposure to ragweed pollen in an Environmental Exposure Unit (EEU)."

Study Design

This was a single center, placebo-controlled, double-blind, parallel study with a single-blind placebo lead-in period followed by randomization to one of three double-blind treatments (i.e. single dose of Placebo, 60mg, or 120mg) in approximately 100 male and female patients (12-65 years) who had at least a 2 year history of ragweed pollen-induced allergic rhinitis (RPAR) and a positive epicutaneous skin test to ragweed allergen.

The study consisted of a Screening Visit, 3 to 5 Priming Visits, a Qualifying Visit, and a Study Visit. At screening, patients underwent evaluation for compliance with entrance criteria and epicutaneous skin testing or had confirmation of positive testing during the previous 15 month period. Screened patients returned for Priming Visits during which they were exposed to controlled levels of ragweed pollen in an Environmental Exposure Unit (EEU) where they remained until adequate symptoms developed or 3 hours had lapsed. At the Qualifying Visit patients were again exposed to pollen in the EEU until adequate symptoms developed after 1 hour of exposure and then were administered a single dose of single-blind placebo. At the Qualifying Visit, if adequate symptoms did not develop by 1 hour, the subject was discontinued. At the Qualifying Visit patients who met placebo responder criteria for symptom control (3 consecutive relief assessments rated as marked or complete) were discontinued from trial; placebo non-responders were scheduled for a Study Visit. At the Study Visit, placebo non-responders entered the EEU and were randomized to double-blind study treatment and administered one dose of study treatment if adequate symptoms developed within 1 hour of entering the EEU. At the Study Visit, if adequate symptoms did not develop by 1 hour, the subject was discontinued. While in the EEU they assessed RPAR symptoms and RPAR symptom relief at 20 minute intervals for up to 3 hours during Priming Visits and up to 5 hours during Qualifying Visits. At the Study Visit the patients assessed their RPAR symptoms every 20 minutes for 1 hour before taking study medication and for 5 hours after taking the study medication.

The severity of the following individual symptoms of RPAR were rated by the subjects every 20

minutes: nasal congestion, sneezing, rhinorrhea, itchy nose/palate/throat and itchy watery red eyes.

Each symptom was evaluated by the patient on the following scale:

- 0 Absent - Symptom not present
- 1 Mild - Symptom is present but is not annoying or troublesome
- 2 Moderate - Symptom is frequently troublesome but would not interfere with either normal daily activity or sleep
- 3 Severe - Symptom is sufficiently troublesome to interfere with normal daily activity or sleep
- 4 Very Severe - Symptom is so severe as to warrant an immediate visit to the physician.

The total symptom score (TSS) was calculated by adding the individual symptom scores, excluding nasal congestion. Adequate symptoms for the Qualifying Visit and the Study Visit were defined as TSS ≥ 5 and two symptoms rated as moderate or severe or one rated as severe and none including nasal congestion as very severe.

Relief of RPAR symptoms, relative to symptoms at 0 minutes prior to dosing with study medication, was assessed every 20 minutes using the following scale:

- 0 Complete Relief - Symptoms not present
- 1 Marked Relief - Symptoms vastly improved and, although still present, are scarcely troublesome
- 2 Moderate Relief - Symptoms are noticeably improved but are still present and may be troublesome
- 3 Slight Relief - Symptoms are present and only minimal improvement has been obtained
- 4 No Relief - Symptoms are unchanged or worse

Patients were to exclude nasal congestion from their assessment of relief of symptoms.

Study Treatments:

Single-Blind Placebo Lead-In:

Placebo - 2-60 mg size placebo capsules

Double-Blind Treatment :

Fexofenadine 120 mg - 2-60 mg Fexofenadine capsules

Fexofenadine 60 mg - 1-60 mg Fexofenadine capsule

1-60 mg size placebo capsule

Placebo - 2-60 mg size placebo capsules.

Table 8-173 Lot Numbers of Study Medication	
Study Medication	Lot Number(s)
MDL 16,455A 60 mg capsules (size #0)	RH9411
Placebo 60 mg capsules (size #0)	RJ9407

Efficacy Parameters:

The pre-defined **primary efficacy parameter** was the time to onset of clinically important relief of RPAR symptoms as assessed by the patient and defined as clinically important relief which was pre-defined as the first of 3 time points at which relief was assessed as marked or complete and the two assessments immediately following the given point were also assessed as marked or complete.

Other parameters were a) time to onset of symptom relief using definitions including moderate and slight relief; b) proportion of patients experiencing relief, c) change in TSS from baseline to mean post dose TSS; and d) change in TSS at each time point post dosing.

Safety Parameters

Collection of adverse event reports.

Statistical Methods

The primary analysis for efficacy was the Intent-to-Treat analysis of the primary efficacy parameter, time to onset of clinically important relief of symptoms. The time to onset was estimated for each treatment group as the median time to onset for patients in that group and compared between treatment groups using the log-rank test in SAS PROC LIFETEST to compare survival curves. The proportion of patients achieving symptom relief was also assessed between treatment groups using Fisher's Exact test. Two secondary analyses of the data were conducted also using modified definitions of clinically important onset of relief based on moderate assessments and moderate and slight assessments.

An ANCOVA was also conducted, using baseline TSS as a covariate, for the differences between the groups for average change from baseline in mean post dose TSSs and TSSs at each time point post dosing. The TSS immediately prior to dosing was used as the baseline. An analysis at each time point was conducted also using imputed symptom scores where values were missing and imputing the most recent assessment of that symptom. The sponsor indicated that the imputed analysis was conducted to stabilize the sample sizes because 31% of the patient population left the EEU early and the impact of these early departures on interpretation of the results was unknown.

Patient Inclusion/Exclusion Criteria

The inclusion and exclusion criteria were nearly identical to those specified in the pivotal safety and efficacy trials.

A) primary inclusion criteria specified:

- 12 to 65 year of age, either gender
- 2 year history of Fall SAR with ragweed the major allergen
- positive epicutaneous skin test (skin wheal 3mm $\geq$ than diluent) at screening or recorded within the previous 15 months
- history of positive response to antihistamines
- at the Priming Visit and by 1 hour at the Qualifying and Study Visits, TSS $\geq$ 5 excluding nasal congestion with 2 symptoms rated as moderate or severe or one rated as severe but none including nasal congestion rated very severe

B) primary exclusion criteria specified:

- pregnancy
- serious or clinically significant illnesses including asthma exacerbated by ragweed pollen
- use of any drug from a list of prohibited concomitant drugs
- URI or sinusitis within 30 days of Screening or Study Visits

RESULTS

Results - Patient Accounting The sponsor reports the following patient tally:

Screened-----	163
Screening Failures-----	17
Entering Priming-----	146
Discontinued During Priming-----	10
Entering Qualifying Visit-----	136
Discontinued Prior To and During Qualifying-----	36
Patients Entering Study Visit-----	100
Discontinued Before Randomization-----	1
Randomized-----	99
Exposed to Double-Blind Med-----	99
Completed-----	99

The sponsor reports that of the patients who were exposed to double-blind treatment all 99 were considered safety evaluable and were treated as the intent-to-treat (ITT) population with 91 considered as the protocol correct population. Of the 8 subjects with major protocol violations, the distribution was: Placebo - 1; 60mg - 2; 120mg - 5.

For the subjects' baseline demographics, the sponsor reports no statistically significant differences between the treatment groups for gender, age, race, weight, height, SBP, DBP, HR or number of Priming Visits. The lowest p value reported was 0.0780, for gender, with a preponderance of females in the two active treatment groups (i.e. % female - Placebo=48%; 60mg=67%; 120mg=70%).

Results - Baseline Symptom Scores

With regard to baseline symptom assessments, the sponsor reports no statistically significant differences between the treatment groups for any individual symptom score or TSS. The p values were: Nasal Congestion=0.9465; Sneezing=0.3337; Rhinorrhea=0.2523; Itchy nose/palate/throat=0.2303; Itchy water/red eye=0.7640; TSS=0.2414.

Results - Compliance

The sponsor reports that all subjects who were randomized consumed a single dose of double-blind study treatment; only one patient was non-compliant with proscriptions for concomitant medications. Patient #175-044 ingested an antidepressant (Manerix[®]) throughout the study. **The sponsor has not provided an estimate of the subject compliance with symptom assessments but will be asked to.**

Results - Pollen Counts - Pollen counts were obtained every 20 minutes - the average pollen counts during the 7 Priming Visits ranged from 3745 to 4745 gr/m³; during the 2 Qualifying Visits from 4310 to 4427 gr/m³; during 2 Study Visits 5562 to 5887 gr/m³.

Results - Pre-Defined Primary Efficacy Parameter - Intent-to-Treat Population

In Table 8-180 reproduced below, the sponsor presents the survival data for onset of clinically important relief of symptoms for the primary pre-defined parameter using the pre-defined definition of relief and two not pre-defined relaxed definitions of relief. Using the pre-defined definition of onset

(complete/marked) in the ITT, a median time to onset and statistically significant difference from placebo could not be observed for either active treatment. This was the case also using the definition of relief, complete/marked/moderate. Using the most relaxed definition of relief, complete/marked/moderate/slight, a 60 minute median time to onset statistically significant difference from placebo was observed for the 60mg dose, with the 120mg dose approaching statistical significance at $p=0.0551$. Similarly, the parameter, proportion of patients in the ITT population experiencing relief by each of the definitions of relief, is reported to have achieved statistical significance for the combined active treatments from placebo, but not for the most relaxed definition for each dose individually.

Reviewer Comment We note in Table 8-180 that for the analysis of proportions of patients experiencing relief, for the most relaxed definition of onset, the following p values for difference from placebo are reported: 60mg - $p=0.166$; 120mg - $p=0.090$ and both active doses - $p=0.043$. The statistical reviewer will need to confirm these values. It is difficult to understand why combined active treatments achieve statistical significance when individually each does not.

Table 8-180 Analysis for Time to Onset and Proportion of Patients Receiving Clinically Important Relief							
Analysis	Comparison	Time to Onset (minutes)			P-value* for Treatment Comparisons		
		Placebo	60 mg	120 mg	Active Doses vs Placebo	MDL 16,455A 60 mg vs Placebo	MDL 16,455A 120 mg vs Placebo
Relief Scores of Complete and Marked							
Intent-to-Treat	Median time to onset of clinically important relief for Intent-to-Treat patients (minutes postdose)	>300 minutes	115 minutes	139 minutes	1765	1317	3315
	Proportion of Intent-to-Treat patients receiving clinically important relief	15% (5/33)	23% (11/33)	27% (9/33)	141	150	367
Protocol Correct	Median time to onset of clinically important relief for protocol correct patients (minutes postdose)	>300 minutes	130 minutes	130 minutes	1051	0904	2968
	Proportion of protocol correct patients receiving clinically important relief	13% (4/32)	35% (11/31)	25% (7/28)	073	041	318
Relief Scores of Complete, Marked and Moderate							
Intent-to-Treat	Median time to onset of clinically important relief for Intent-to-Treat patients (minutes postdose)	260 minutes	120 minutes	120 minutes	1354	2775	1303
	Proportion of Intent-to-Treat patients receiving clinically important relief	43% (15/33)	58% (19/33)	67% (22/33)	135	460	136
Relief Scores of Complete, Marked, Moderate and Slight							
Intent-to-Treat	Median time to onset of clinically important relief for Intent-to-Treat patients (minutes postdose)	100 minutes	60 minutes	80 minutes	0180	0237	0851
	Proportion of Intent-to-Treat patients receiving clinically important relief	64% (21/33)	82% (27/33)	85% (28/33)	043	166	080
* P values based on comparison of survival curves using log rank test for time to onset and on Fisher's Exact test for proportions receiving relief							
Supporting Data							Page
Appendix E3, Listing 1: Intent-to-Treat Survival Analysis							58-V1 167-P10
Appendix E3, Listing 2: Intent-to-Treat Tests of Proportions							58-V1 167-P58
Appendix E3, Listing 14: Protocol Correct Survival Analysis							58-V1 167-P180
Appendix E3, Listing 15: Protocol Correct Test of Proportions							58-V1 167-P226
Appendix 12, Listing 1: Time to Onset of Relief							58-V1 168-P80
Appendix 12, Listing 5: Relief Scores at Each Time Point							58-V1 168-P153

Results - Changes in Symptom Scores - Intent-to-Treat Population

Table 8-181, reproduced below, presents the sponsor's results from the analysis of mean change from baseline in TSS. Statistical significance from placebo was observed for each treatment for TSS and all individual symptom scores except rhinorrhea which trends toward significance (60mg p=0.0953 and 120mg p=0.1122) and itchy watery/red eyes (only 120mg p=0.0647).

Table 8-181. Intent-to-Treat Analysis of Symptom Scores						
Symptom	Mean postdose value as change from baseline* (Mean ± SE)			P value* for Treatment Comparisons		
	Placebo (N=33)	MDL 16,455A		Active Doses vs Placebo	MDL 16,455A 60 mg vs Placebo	MDL 16,455A 120 mg vs Placebo
		60 mg (N=33)	120 mg (N=33)			
Nasal Congestion	-0.3 ± 0.1	-0.4 ± 0.1	-0.4 ± 0.1	.3683	.4111	.4612
Sneezing	-0.2 ± 0.1	-0.6 ± 0.1	-0.6 ± 0.1	.0094	.0233	.0238
Rhinorrhea	-0.4 ± 0.1	-0.6 ± 0.1	-0.6 ± 0.1	.0607	.0953	.1122
Itchy nose, palate, and/or throat	-0.3 ± 0.1	-0.8 ± 0.1	-0.8 ± 0.1	.0004	.0013	.0028
Itchy, watery, red eyes	-0.3 ± 0.1	-0.8 ± 0.1	-0.6 ± 0.1	.0083	.0063	.0647
TSS (excluding nasal congestion)	-1.2 ± 0.4	-2.9 ± 0.4	-2.6 ± 0.4	.0024	.0044	.0143

* Adjusted means and P values from analysis of covariance of change from baseline using model adjusting for treatment group and baseline symptom score

Supporting Data:		Page
Appendix E3, Listing 3:	Covariance Analysis of Symptom Scores	S8-V1.167-P66
Appendix I2, Listing 2:	Baseline and Average Postdose Change in Symptom Scores	S8-V1.168-P83
Appendix I2, Listing 3:	Actual Symptom Scores at Each Time Point	S8-V1.168-P67

Results - Changes in Symptom Scores Over Time - Intent-to-Treat Population

Table 8-182, reproduced below, presents the results from an analysis for change from baseline at each time point post baseline using actual available data. For the 60mg dose, statistical significance from placebo is first achieved by 60 minutes and maintained to 240 minutes and for the 120mg dose at 80 minutes and maintained to 220 minutes. For the 60 minute time point, the overall level of statistical significance for the active treatments relative to placebo was $p=0.011$ (V1.167, p. 108). The sponsor conducted a similar analysis with imputation of missing scores (last observation carried forward) to replace those missing because patients left the EEC early, so that each time point utilized 33 observations for each treatment. These results confirm those observed from the analysis with actual data with statistical significance maintained to the 300 minute time point for both active treatments.

Table 8-182. Intent-to-Treat Analysis for Change from Baseline TSS – Actual TSSs Used							
Time (Minutes Postdose)	Size of Placebo Group N	Difference Between Active Dose and Placebo MDL 16,455A					
		60 mg (N=33)			120 mg (N=33)		
		N	Mean ± SE*	P value	N	Mean ± SE*	P value
20	33	33	0.5 ± 0.3	.1027	33	-0.1 ± 0.3	.8129
40	33	33	0.4 ± 0.5	.3954	33	0.2 ± 0.5	.5802
60	33	32	1.6 ± 0.5	.0032	33	-0.6 ± 0.5	.3025
80	31	31	1.4 ± 0.6	.0254	33	-1.4 ± 0.6	.0178
100	31	31	1.6 ± 0.7	.0169	32	-0.9 ± 0.7	.1171
120	31	31	1.5 ± 0.7	.0401	31	-0.9 ± 0.7	.2308
140	29	30	1.6 ± 0.8	.0215	32	-1.6 ± 0.8	.0399
160	29	30	1.9 ± 0.8	.0155	31	-1.9 ± 0.8	.0147
180	27	28	2.2 ± 0.8	.0080	31	-1.8 ± 0.8	.0260
200	25	28	1.9 ± 0.8	.0181	31	-1.7 ± 0.8	.0315
220	23	26	2.0 ± 0.8	.0184	28	-1.7 ± 0.8	.0390
240	21	24	2.1 ± 1.0	.0336	28	-1.1 ± 0.9	.2234
260	18	24	1.0 ± 1.0	.3323	28	-0.4 ± 1.0	.7186
280	18	24	1.5 ± 1.0	.1363	25	-0.9 ± 1.0	.3802
300	18	24	1.3 ± 1.0	.2051	26	-1.1 ± 1.0	.2580
Total symptom score excludes nasal congestion							
* Adjusted means and P values from analysis of covariance of change from baseline using model adjusting for treatment group and baseline symptom score							
Supporting Data:							Page
Appendix E3, Listing 4: Analysis of Variance for Baseline TSS							S8-V1.167-P85
Appendix E3, Listing 6: Individual Time Point Analysis of Actual TSS							S8-V1.167-P102
Appendix E3, Listing 9: Sample Sizes for TSSs at Each Time Point – Actual Data							S8-V1.167-P137
Appendix I2, Listing 3: Actual Symptom Scores at Each Time Point							S8-V1.168-P87

Safety Results - Adverse Events

The sponsor reports no deaths, hospitalizations or life threatening events, no discontinuations after randomization due to adverse events, and no adverse events assessed by the investigator as treatment related.

Final Reviewer Comments Regarding Protocol PJPR0017

This trial failed to demonstrate an onset of action based on its pre-defined primary endpoint. Four possible factors may have contributed to the failure of this analysis.

As the sponsor points out, the EEC provides a constant exposure to allergen versus fluctuating levels seen in the natural environment, possibly making the detection of complete or marked relief by the subjects overly difficult.

Although the EEC provides for more measured control of exposure to pollen, the use of the EEC may skew the population of patients willing to participate in such a study. It might be that the population enrolled, although meeting the entry criteria, may be subjectively less discriminating about changes in symptom severity compared to the entire population of patients with the disorder and might be more willing to be subjected to a five hour exposure to their allergen than some patients. Whereas, those subjects who would be unwilling to enroll, may be those who simply would not want to be exposed because of their elevated perception of the symptoms although they might be more observant to symptom changes and more discriminating in observing their response to treatment. These subjects may be more willing to participate in a trial in the natural environment simply because they would not have as much control over the natural environment as they would by simply refusing to enter an environment designed to illicit their symptoms.

Another possibility is that the patients enrolled may not in reality have been the more sensitive patients since the enrollment criteria specified only a 3mm wheal size over diluent rather than 5mm.

Finally, while the primary pre-defined parameter was unable to demonstrate onset of action compared to placebo, this metric using complete to marked relief seems challenging and restrictive. Use of the broader definition of relief, complete-slight, may be more appropriate since it includes patients with all levels of response to treatment and did result in the observance of a statistically significant onset of action of 60 minutes for the 60mg dose, with the 120mg dose approaching significance at $p=0.0551$. This observation is further supported by the examination of the change from baseline in TSS compared to placebo at each time point which shows a statistically significant difference from placebo for the 60mg dose at 60 minutes and for 120mg dose at 80 minutes.

Reviewer's Determinations

- 1) The results of this trial support the assertion that onset of action of fexofenadine 60mg occurs by one hour after the first dose, based on the results from the analysis of onset of clinically important symptom relief using the relaxed definition, complete to slight relief, and the analysis of change from baseline in TSS at each time point post dosing. The strong trend observed in these same analyses suggests that fexofenadine 120mg also exhibits an onset of action by 60 minutes.
- 2) Examination of the safety profile observed during this trial does not reveal any obvious adverse events attributable to fexofenadine administered as a single 60mg or 120mg dose.

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Table 8-141. Mean MDL 18,455 Pharmacokinetic Parameters and Treatment Comparisons Following Administration of MDL 18,455A and Terfenadine								
Parameter	Tr	Mean	%CV	Adjusted Mean*	Pairwise Comparisons			
					Par	Ratio (%)	90% CI	P value
AUC _{0-12 h} h·ng/ml	E	1872.25	19.38	1834.08				
	F	8285.92	20.81	2042.88	F/E	108.82	(84.8, 118.0)	0.414
	G	1387.08	27.71	1308.80	G/E	87.52	(80.3, 75.6)	<0.001
	H	4838.71	27.02	1847.87	H/G	118.53	(108.9, 132.7)	0.014
					H/F	78.78	(87.8, 84.7)	<0.001
C _{max-ss} ng/ml	E	341.08	38.28	323.73				
	F	870.92	21.88	283.41	F/E	87.58	(78.8, 101.8)	0.138
	G	298.42	37.84	278.31	G/E	88.04	(73.2, 98.8)	0.077
	H	1023.38	38.74	318.61	H/G	115	(98.0, 133.8)	0.125
					H/F	111.71	(98.4, 129.5)	0.218
C _{min-ss} ng/ml	E	58.02	37.82	85.83				
	F	183.38	31.84	81.24	F/E	108.87	(87.3, 123.8)	0.203
	G	28.87	27.87	27.48	G/E	48.18	(43.8, 55.8)	<0.001
	H	80.80	43.22	28.30	H/G	103.07	(81.3, 118.4)	0.879
					H/F	48.22	(41.0, 52.1)	<0.001
t _{1/2} h	E	20.18	28.17	19.48				
	F	17.82	18.3	17.84	F/E	80.14	(81.2, 100.1)	0.102
	G	14.08	22.07	13.81	G/E	70.87	(83.9, 78.8)	<0.001
	H	11.88	29.3	11.47	H/G	83.08	(74.8, 88.2)	0.004
					H/F	88.38	(88.9, 72.6)	<0.001
t _{max-ss} h	E	2.30	43.78	2.18				
	F	4.02	81.33	3.70	F/E	171.37	(142.8, 208.8)	<0.001
	G	1.08	32.7	1.00	G/E	48.08	(38.3, 58.8)	<0.001
	H	1.20	38.38	1.11	H/G	111.81	(88.8, 134.3)	0.325
					H/F	30.02	(28.0, 38.0)	<0.001
C _{Lp-ss} L/h	E	N/A	N/A					
	F	N/A	N/A					
	G	44.81	38.38					
	H	38.25	38.71					
C _{max-ss} /C _{min-ss}	E	6.14	34.88					
	F	4.84	38.80					
	G	11.18	48.40					
	H	12.78	47.02					

E = Terfenadine 60 mg Q12 h (N=23)
 F = Terfenadine 180 Q12 h (N=23)
 G = MDL 18,455A 60 mg Q12 h (N=22)
 H = MDL 18,455A 180 mg Q12 h (N=23)
 * - Adjusted mean and statistical comparisons are based on data normalized to the 60 mg dose for AUC_{0-12 h}, C_{max-ss}, and C_{min-ss}.

Supporting Data: Page
 Appendix A1: Plasma S8-V1.188-P107
 Appendix B2: MDL 18,455 Pharmacokinetic Parameters, Treatment Comparisons. 18-V1.158-P8

The sponsor also reports pharmacokinetic results for terfenadine (see table and figure reproduced below) and notes that as the dose of terfenadine was increased from 60mg to 180mg, the AUC_{0-12 h} increased by 96%, the C_{max-ss} by 40% and the C_{min-ss} by 125%; and the half-life was the same (60mg - 16.4 h; 180mg - 16.6 h).

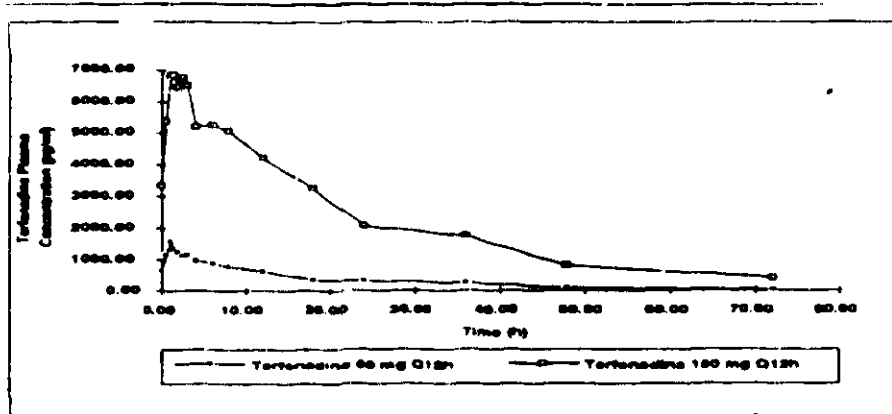


Figure 8-89. Mean Terfenadine Plasma Concentration Following Administration of Terfenadine as a Function of Time.
 Supporting Data: Appendix A1 Plasma
 Page 88-V1 188-P107

Table 8-143. Mean Terfenadine Pharmacokinetic Parameters and Treatment Comparisons Following Administration of Terfenadine

Parameter	Trt	Mean	%CV	Adjusted Mean*	Pairwise Comparisons			
					Pair	Ratio (%)	90% CI	P value
AUC _{0-12 h} (ng·h/ml)	E	10804.19	81.00	8886.16				
	F	68127.46	79.54	17440.00	F/E	188.22	(179.4,214.6)	<0.001
C _{max,0-12 h} (pg/ml)	E	1880.64	88.21	1468.74				
	F	7521.51	70.38	2041.41	F/E	140.23	(121.5,161.8)	<0.001
C _{max,24-36 h} (pg/ml)	E	883.88	102.88	437.71				
	F	3808.64	84.00	884.87	F/E	234.94	(203.1,249.1)	<0.001
t _{1/2} (h)	E	18.37	32.28	18.48				
	F	18.64	17.58	18.48	F/E	108.24	(94.5,118.4)	0.381
t _{max} (h)	E	1.15	87.88	1.00				
	F	1.88	81.88	1.88	F/E	188.08	(128.9,222.8)	0.008
CL _{0-12 h} (L/h)	E	8138.38	84.88					
	F	4215.88	87.88					
C _{max,0-12 h} /C _{max,24-36 h}	E	3.40	42.78					
	F	2.15	28.88					

E = Terfenadine 60 mg Q12 h (N=23)
 F = Terfenadine 180 mg Q12 h (N=23)
 * = Adjusted mean and statistical comparisons are based on data normalized to the 60 mg dose for AUC_{0-12 h}, C_{max,0-12 h}, and C_{max,24-36 h}.

Supporting Data: Appendix A1 Plasma
 Appendix B10: Terfenadine Pharmacokinetic Parameters, Treatment Comparisons
 Page 88-V1 188-P107
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Results - Pharmacodynamic Parameters - Wheal and Flare

The sponsor reports from the data from fitted means, that the magnitude of inhibition following dosing with the 180mg doses was greater than the 60mg doses in the range of 10.3% to 12.4% at Day 8.

Table 8-146. Wheal Average Percent Inhibition Data				
Study Day	Fitted Means and Standard Errors P value 95% Confidence Interval			
	Terfenadine 60 mg	Terfenadine 180 mg	MOL 16 488A 60 mg	MOL 16 488A 180 mg
Day 2 minus Day 1	-42.7 ± 2.7	-54.2 ± 2.7	-42.4 ± 2.6	-53.3 ± 2.7
Day 8 minus Day 1	-53.6 ± 2.7	-63.8 ± 2.7	-45.9 ± 2.7	-56.2 ± 2.7
Day 8 minus Day 2	-10.9 ± 3.6 0.0031 (-18.1, -3.7)	-9.7 ± 3.6 0.0084 (-18.9, -2.5)	-3.4 ± 3.6 0.3486 (-10.6, 3.7)	-4.9 ± 3.6 0.1824 (-12.0, 2.3)
Comparison ¹	Average Difference in Daily Means			
	Day 2 Mean ± Std Error P value ² Confidence Interval	Day 8 Mean ± Std Error P value ² Confidence Interval	Day 8 minus Day 2 Mean ± Std Error P value ² Confidence Interval	
MOL 16 488A 60 mg vs. MOL 16 488A 180 mg	-10.9 ± 3.6 0.0027 (-18.0, -3.8)	-12.4 ± 3.7 0.0010 (-19.6, -5.1)	-1.4 ± 5.1 0.7627 (-11.6, 6.7)	
Terfenadine 60 mg vs Terfenadine 180 mg	-11.5 ± 3.8 0.0019 (-18.6, -4.3)	-10.3 ± 3.8 0.0083 (-17.4, -3.1)	1.2 ± 5.1 0.6128 (-8.9, 11.3)	
MOL 16 488A 60 mg vs Terfenadine 60 mg	-0.3 ± 3.6 0.8286 (-7.4, 6.8)	-7.8 ± 3.7 0.0084 (-15.0, -0.6)	-7.5 ± 5.1 0.1478 (-17.6, 2.7)	
MOL 16 488A 180 mg vs Terfenadine 180 mg	-0.8 ± 3.6 0.6138 (-6.0, 6.3)	-8.7 ± 3.6 0.1181 (-12.9, 1.5)	-4.8 ± 5.1 0.3477 (-15.0, 5.3)	
MOL 16 488A vs Terfenadine	-0.8 ± 2.6 0.8182 (-5.6, 4.0)	-6.7 ± 2.8 0.0089 (-11.5, -1.9)	-6.1 ± 3.6 0.0882 (-13.3, 1.0)	

¹ P value is for a test of no difference based on fitted ANOVA model.
² Negative values indicate greater suppression with higher dose or with terfenadine than MOL 16 488A.

Supporting Data: Appendix A2: Skin Wheal and Flare Page 98-V1 187-P11

The sponsor reports the trough wheal area inhibition prior to the Day 8 dose was 45% (Day 8 - 0 hour) or more across treatments and at 12 hours after the last dose on Day 8 wheal area inhibition was no less than 30% across treatments suggesting the effect lasts throughout the dosing interval. The greatest degree of inhibition appears to occur at approximately 6 hours across all treatments. Note: CHG1 refers to point-adjusted means - the percent difference between corresponding time points of the treatment day and Day 1 measurements.

Table 8-147. Mean Percent Change in Wheal Area From Baseline - CHG1

HOUR	Terfenadine 60 mg Q12 h		Terfenadine 180 mg Q12 h		MDL 16,455A 60 mg Q12 h		MDL 16,455A 180 mg Q12 h	
	CHG1 Day 2	CHG1 Day 8	CHG1 Day 2	CHG1 Day 8	CHG1 Day 2	CHG1 Day 8	CHG1 Day 2	CHG1 Day 8
	0	1.09	-58.97	3.07	-61.89	-8.66	-46.30	-12.83
2	-32.72	-38.15	-37.44	-50.41	-42.54	-38.95	-53.16	-52.51
4	-44.70	-51.37	-61.83	-53.53	-38.21	-40.86	-64.11	-63.42
6	-57.03	-60.77	-69.97	-70.67	-52.01	-49.15	-62.16	-67.29
8	-42.00	-43.01	-57.31	-60.64	-49.24	-39.29	-55.11	-49.00
12	-38.99	-41.98	-58.81	-52.09	-32.70	-31.92	-53.31	-44.04

Supporting Data: Appendix A3: Skin Wheal and Flare Page SB-VI.157-P11

The sponsor reports mean maximum inhibition ranged from -75% (MDL-16,455A 60mg) to -84% (terfenadine 180mg) across treatments.

Table 8-148. Mean Wheal Area Pharmacodynamic Parameters (CHG1)

Treatment		AUEC (%·h) Day 2	AUEC (%·h) Day 8	MAXINH (%) Day 2	MAXINH (%) Day 8
Terfenadine 60 mg Q12 h N=23	Mean	-474.2	-537.4	-72.2	-78.1
	SD	219.6	333.8	13.6	16.8
	%CV	46.3	62.1	18.9	21.5
Terfenadine 180 mg Q12 h N=23	Mean	-617.7	-687.6	-60.5	-63.8
	SD	208.0	184.0	10.4	9.2
	%CV	33.3	26.8	12.9	10.9
MDL 16,455A 60 mg Q12 h day 2 N=24 day 8 N=22	Mean	-486.0	-495.8	-71.6	-75.1
	SD	215.9	197.5	10.8	14.3
	%CV	46.3	39.8	15.1	19.0
MDL 16,455A 180 mg Q12 h N=23	Mean	-612.2	-642.2	-80.3	-83.4
	SD	146.4	200.8	8.2	8.6
	%CV	23.9	31.3	10.2	10.3

Supporting Data: Appendix A3: Skin Wheal and Flare Page SB-VI.157-P11

Results - Pharmacodynamic Parameters - Cardiac Conduction

The sponsor reports the results of two analyses of QTc measurements as fitted daily means and as daily maxima. Both of these analyses are reported using the QTc values as measured by hand by Dr Joel Morganroth, an independent consultant, and as measured by the ECG machine. The sponsor indicates that the database generated by Dr Morganroth was constructed from blinded readings of ECG of intervals. These data were summarized in tabular and graphic form, reproduced below.

Morganroth Database:

Focusing on the Day 8 minus Day 1 comparisons, the fitted daily QTc means from the Morganroth database show that statistically significant increases from baseline (Day 1) were seen by Day 8 for both terfenadine doses (60mg: 9.3±2.9 msec; 180mg: 23.2±2.9 msec) but not for either dose of MDL-16,455A (60mg: 0.5±2.9 msec; 180mg: 3.3±2.9 msec). Statistically significant increases were also seen for change from baseline between terfenadine 60mg and terfenadine 180mg (13.9±4.1 msec) but not between MDL-16,455A 60mg and 180mg (2.8±4.1 msec). A statistically significant increase was also seen between terfenadine 180mg and MDL-16,455A 180mg (19.9± 4.1 msec). Although the sponsor does not report a comparison for the 60mg doses, the numerical difference was 8.8 msec.

Study Day	Fitted Means and Standard Errors P value* ‡ 90% Confidence Interval			
	Terfenadine 60 mg Q12 h	Terfenadine 180 mg Q12 h	MDL 16 455A 60 mg Q12 h	MDL 16 455A 180 mg Q12 h
	Day 1	376.4 ± 3.6	376.4 ± 3.6	361.8 ± 3.6
Day 2	360.7 ± 3.6	360.1 ± 3.6	360.2 ± 3.6	378.7 ± 3.6
Day 8	386.7 ± 3.6	396.7 ± 3.6	362.2 ± 3.6	382.6 ± 3.6
Day 2 minus Day 1	1.3 ± 2.9 0.642 (-4.3, 7.0)	-4.6 ± 2.9 0.111 (-1.1, 10.3)	-1.5 ± 2.9 0.668 (-7.1, 4.0)	-0.6 ± 2.9 0.628 (-6.3, 5.1)
Day 8 minus Day 1	9.3 ± 2.9 0.001 (3.6, 15.0)	23.2 ± 2.9 0.000 (17.5, 28.9)	0.5 ± 2.9 0.668 (-5.2, 6.1)	3.3 ± 2.9 0.255 (-2.4, 9.0)
Day 8 minus Day 2	7.9 ± 2.9 0.008 (2.3, 13.6)	18.6 ± 2.9 0.000 (12.9, 24.3)	2.0 ± 2.9 0.484 (-3.6, 7.7)	3.9 ± 2.9 0.176 (-1.6, 9.6)
Comparison [§]	Average Difference† in Daily Means			
	Day 2 minus Day 1 Mean ± Std Error P value‡ Confidence Interval	Day 8 minus Day 1 Mean ± Std Error P value‡ Confidence Interval	Day 8 minus Day 2 Mean ± Std Error P value‡ Confidence Interval	
MDL 16 455A 60 mg vs MDL 16 455A 180 mg	0.9 ± 4.0 0.623 (-7.1, 8.9)	2.8 ± 4.1 0.490 (-5.2, 10.8)	1.9 ± 4.1 0.636 (-6.1, 9.9)	
Terfenadine 60 mg vs Terfenadine 180 mg	3.3 ± 4.1 0.424 (-4.8, 11.3)	13.9 ± 4.1 0.001 (5.9, 22.0)	10.7 ± 4.1 0.010 (2.6, 18.7)	
MDL 16 455A 180 mg vs Terfenadine 180 mg	5.2 ± 4.1 0.200 (-2.8, 13.3)	19.9 ± 4.1 0.000 (11.9, 28.0)	14.7 ± 4.1 0.000 (6.6, 22.7)	
MDL 16 455A vs Terfenadine	4.1 ± 2.9 0.159 (-1.6, 9.7)	14.4 ± 2.9 0.000 (8.7, 20.0)	10.3 ± 2.9 0.000 (4.6, 16.0)	
* P value is for a test of no difference from zero based on the fitted ANOVA model. † Positive values indicate greater increases with higher dose than lower dose or with terfenadine than MDL 16,455A. ‡ The average difference is based on the fitted means. § P value = 0.000 should be interpreted as P value less than 0.001.				
Supporting Data: Appendix C4.c: Analysis of QT _c			Page S8-V1.159-P137	

The graphic presentation of the fitted means data shows the separation of the Day 8 values for the terfenadine treatments. The graphic presentation of the daily arithmetic means shows the marked separation of the 180mg terfenadine curve and the lesser but similar trend of the 60mg terfenadine curve; but when examining this display of the arithmetic means, it must be kept in mind that only one ECG was obtained at the fourth hour after dosing on Days 3-7 while multiple ECGs were obtained at various times after dosing on Days 1, 2 and 8.

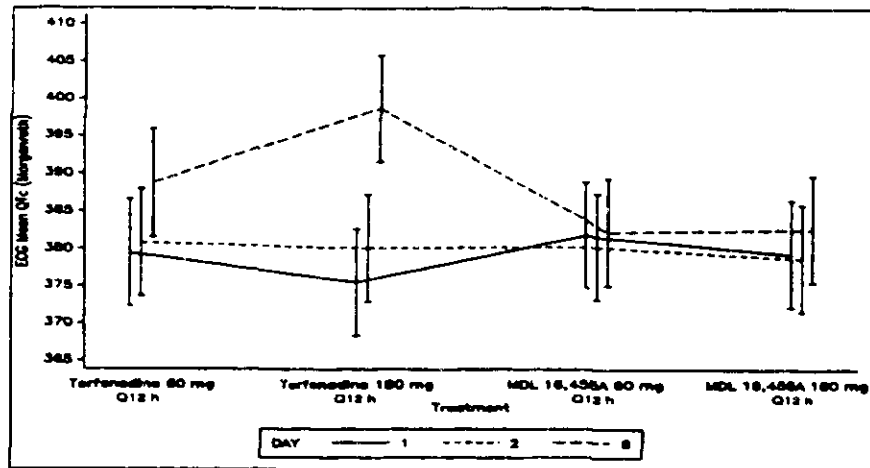


Figure 8-71. Fitted Means and 95% Confidence Intervals for Daily Mean Morganroth QT_c.

Supporting Data

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Daily Arithmetic Means

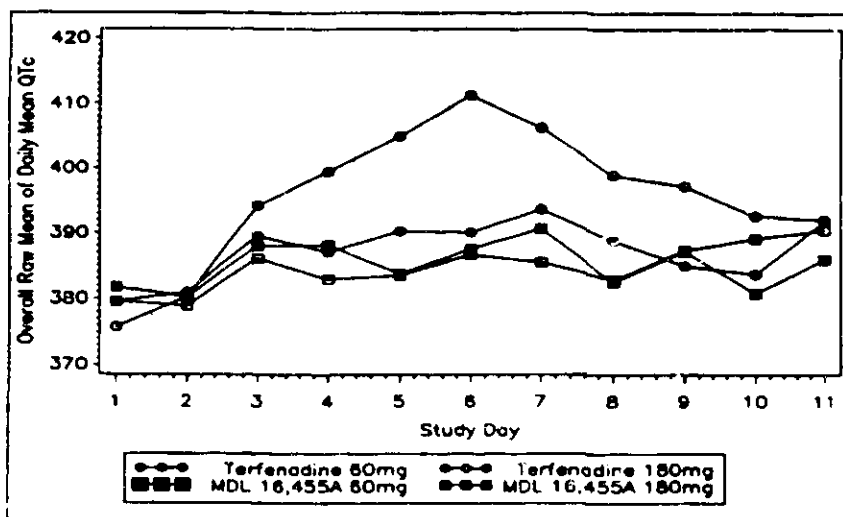


Figure 8-72. Daily Mean Morganroth QT_c by Day

Supporting Data

Appendix C4.c: Analysis of QT_c

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Focusing on the Day 8 minus Day 1 comparisons, results from the analysis of daily maximum QTc produces a pattern of statistical significance which is identical to that of the fitted daily means.

Table 8-163. QT _c Data - Daily Maximum (Morgenroth)				
Study Day	Fitted Means and Standard Errors P value* † 95% Confidence Interval			
	Terfenadine 80 mg Q12 h	Terfenadine 180 mg Q12 h	MDL 16,455A 80 mg Q12 h	MDL 16,455A 180 mg Q12 h
Day 1	392.9 ± 4.1	398.4 ± 4.1	397.1 ± 4.0	394.1 ± 4.1
Day 2	397.1 ± 4.1	398.6 ± 4.1	397.7 ± 4.0	395.3 ± 4.1
Day 8	405.1 ± 4.1	415.5 ± 4.1	394.7 ± 4.1	398.2 ± 4.1
	4.2 ± 3.9 0.290 (-3.4,11.8)	7.1 ± 3.9 0.095 (-0.5,14.8)	0.6 ± 3.9 0.879 (-6.9, 6.0)	1.2 ± 3.9 0.756 (-6.4, 8.8)
Day 2 minus Day 1	12.2 ± 3.9 0.002 (4.8,18.8)	26.0 ± 3.9 0.000 (18.4,33.7)	-2.3 ± 3.8 0.544 (-9.9, 5.2)	4.2 ± 3.9 0.281 (-3.4,11.8)
Day 8 minus Day 1	8.0 ± 3.9 0.040 (0.4,15.6)	16.9 ± 3.9 0.000 (11.3,26.5)	-2.9 ± 3.8 0.450 (-10.5, 4.7)	3.0 ± 3.9 0.443 (-4.6,10.6)
	Average Difference ‡ in Daily Means			
Comparison [§]	Day 2 minus Day 1 Mean ± Std Error P value † Confidence Interval	Day 8 minus Day 1 Mean ± Std Error P value † Confidence Interval	Day 8 minus Day 2 Mean ± Std Error P value † Confidence Interval	
MDL 16,455A 80 mg vs MDL 16,455A 180 mg	0.8 ± 5.4 0.908 (-10.0,11.3)	6.5 ± 5.5 0.234 (-4.2,17.3)	5.9 ± 5.5 0.262 (-4.9,16.6)	
Terfenadine 80 mg vs Terfenadine 180 mg	3.0 ± 5.5 0.599 (-7.8,13.7)	13.8 ± 5.8 0.012 (3.1,24.6)	10.9 ± 5.5 0.048 (0.1,21.7)	
MDL 16,455A 180 mg vs Terfenadine 180 mg	5.9 ± 5.5 0.278 (-4.8,16.7)	21.9 ± 5.5 0.000 (11.1,32.6)	15.9 ± 5.5 0.004 (5.1,26.7)	
MDL 16,455A vs Terfenadine	4.9 ± 3.8 0.216 (-2.8,12.4)	16.2 ± 3.9 0.000 (10.6,25.8)	13.4 ± 3.9 0.001 (5.8,21.0)	

* P value is for a test of no difference from zero based on the fitted ANOVA model.
 ** Positive values indicate greater increases with higher dose than lower dose or with terfenadine than MDL 16,455A.
 † The average difference is based on the fitted means.
 ‡ P value = 0.000 should be interpreted as P value less than 0.001.

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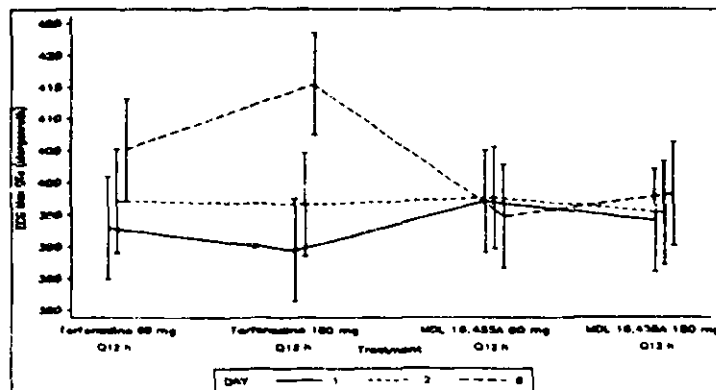


Figure 8-73. Fitted Means and 95% Confidence Intervals for Daily Maximum Morgenroth QT_c.

The following table presents QTc values greater than 440msec observed and reported by the sponsor. In examining the line listings it was noted that patient #008 had an additional outlier ECG on Day 8 on terfenadine 60mg and 5 other outlier ECGs during the days of active treatment with 180mg MDL-16,455A and one other outlier ECG during baseline on Day 1. Subject #024 also had 3 other outlier ECGs on Day 8 on 180mg terfenadine and one other on MDL-16,455A 60mg on each of Days 1, 2 and 7.

Subjects With Morganroth QTc Values Greater Than 440 msec				
Patient Number	Terfenadine 60mg	Terfenadine 180mg	MDL-16,455A 60mg	MDL-16,455A 180mg
0005	445	-	-	-
0008	458	443	440	462
0009	-	453	-	-
0015	-	442	-	-
0023	441	-	454	-
0024	-	460	448	-

Machine Read Database:

Focusing the on Day 8 minus Day 1 comparisons, the fitted daily QTc means from the machine read database show statistically significant increases from baseline (Day 1) by Day 8 for both terfenadine doses (60mg: 9.8 ± 2.1 msec; 180mg: 22.9 ± 2.1 msec) and for MDL-16,455A 180mg (4.3 ± 2.1 msec; $p=0.047$) but not for MDL-16,455A 60mg (2.2 ± 2.1 msec). Statistically significant increases were also seen for change from baseline between terfenadine 60mg and terfenadine 180mg (13.1 ± 3.0 msec) but not between MDL-16,455A 60mg and 180mg (2.1 ± 3.0 msec). A statistically significant increase was also seen between terfenadine 180mg and MDL-16,455A 180mg (18.7 ± 3.0 msec). Although the sponsor does not report a comparison for the 60mg doses, the numerical difference was 7.6 msec. Compared to the analyses of the Morganroth data for fitted daily QTc means, analyses of the machine read data produced the same pattern of statistical significance except that the machine read data showed statistical significance also for MDL-16,455A 180mg change from baseline (4.3 ± 2.1 msec; $p=0.047$).

Table 8-186. QTc Data - Daily Means (Machine-read ECG Data)				
Study Day	Fitted Means and Standard Errors			
	P value ‡			
	95% Confidence Interval			
	Terfenadine 60 mg Q12 h	Terfenadine 180 mg Q12 h	MDL 16 455A 60 mg Q12 h	MDL 16 455A 180 mg Q12 h
Day 1	372.5 ± 3.6	371.0 ± 3.6	374.6 ± 3.6	373.9 ± 3.6
Day 2	374.6 ± 3.6	373.9 ± 3.6	373.4 ± 3.6	379.2 ± 3.6
Day 8	382.3 ± 3.6	383.8 ± 3.6	377.0 ± 3.6	379.2 ± 3.6
Day 2 minus Day 1	2.1 ± 2.1 0.328 (-2.1, 6.3)	2.9 ± 2.1 0.178 (-1.3, 7.1)	-1.4 ± 2.1 0.808 (-5.5, 2.7)	-1.1 ± 2.1 0.881 (-5.4, 3.1)
Day 8 minus Day 1	9.8 ± 2.1 0.000 (5.6, 14.0)	22.8 ± 2.1 0.000 (18.7, 27.2)	2.2 ± 2.1 0.302 (-2.0, 6.4)	4.3 ± 2.1 0.047 (0.1, 8.4)
Day 8 minus Day 2	7.7 ± 2.1 0.000 (3.5, 11.9)	20.1 ± 2.1 0.000 (15.8, 24.3)	3.8 ± 2.1 0.082 (-0.6, 7.8)	5.4 ± 2.1 0.012 (1.2, 9.6)
Comparison**	Average Difference † in Daily Means			
	Day 2 minus Day 1 Mean ± Std Error P value ‡ Confidence Interval	Day 8 minus Day 1 Mean ± Std Error P value ‡ Confidence Interval	Day 8 minus Day 2 Mean ± Std Error P value ‡ Confidence Interval	
MDL 16 455A 60 mg vs. MDL 16 455A 180 mg	0.2 ± 3.0 0.938 (-5.6, 6.1)	2.1 ± 3.0 0.482 (-3.8, 6.0)	1.8 ± 3.0 0.545 (-4.1, 7.8)	
Terfenadine 60 mg vs. Terfenadine 180 mg	0.8 ± 3.0 0.799 (-5.1, 6.9)	13.1 ± 3.0 0.000 (7.2, 19.1)	12.3 ± 3.0 0.000 (6.4, 18.3)	
MDL 16 455A 180 mg vs. Terfenadine 180 mg	4.0 ± 3.0 0.181 (-1.9, 10.0)	18.7 ± 3.0 0.000 (12.7, 24.6)	14.6 ± 3.0 0.000 (8.7, 20.6)	
MDL 16 455A vs. Terfenadine	3.6 ± 2.1 0.078 (-0.4, 7.9)	13.1 ± 2.1 0.000 (9.0, 17.3)	9.4 ± 2.1 0.000 (5.2, 13.6)	

* P value is for a test of no difference from zero based on the fitted ANCOVA model.
 ** Positive values indicate greater increases with higher dose than lower dose or with terfenadine than MDL 16 455A.
 † The average difference is based on the fitted means.
 ‡ P value = 0.000 should be interpreted as P value less than 0.001.

Supporting Data:
 Appendix C4.c: Analysis of QTc

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The graphic presentation of the fitted means data from the machine read database also show the separation of the Day 8 terfenadine responses which appear comparable to that of the Morganroth data. The graphic presentation of the daily arithmetic means shows the marked separation of the 180mg terfenadine curve and the lesser but similar trend of the 60mg terfenadine curve.

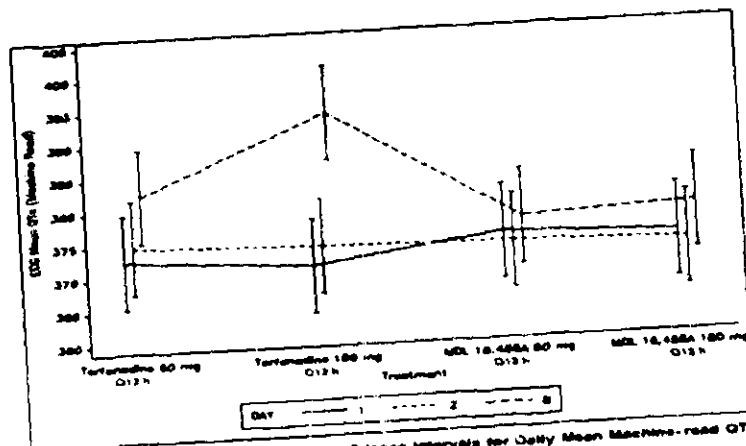


Figure 8-7d. Fitted Means and 95% Confidence Intervals for Daily Mean Machine-read QTc

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Daily Arithmetic Means

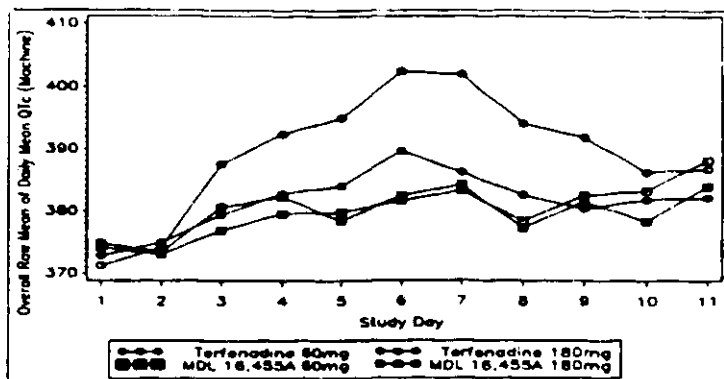


Figure 8-78. Daily Mean Machine-read QT_c by Day

Supporting Data Appendix C4.c: Analysis of QT_c Page SB-VI 159-P137

Focusing on the Day 8 minus Day 1 comparisons, results from the analysis of daily maximum QT_c produces a pattern of statistical significance which is identical to that of the machine read fitted daily means, except that the terfenadine 60mg dose loses statistical significance for change from baseline in daily maximum QT_c (5.7 ± 3.2 msec; $p=0.072$). Focusing on the Day 8 minus Day 1 comparisons, the machine read data, as did the Moranroth daily maximum QT_c data, shows statistical significance for the same treatment comparisons and for change from baseline for terfenadine 180mg; but the machine read data also shows statistical significance for the 180mg dose of MDL-16,455A (6.3 ± 3.2 msec; $p=0.050$) and does not show statistical significance for the 60mg dose of terfenadine.

Table 8-108. QT _c Data - Daily Maxima (Machine-read)				
Study Day	Fitted Means and Standard Errors			
	P value* ‡			
	95% Confidence Interval			
	Terfenadine 60 mg Q12 h	Terfenadine 180 mg Q12 h	MDL 16,455A 60 mg Q12 h	MDL 16,455A 180 mg Q12 h
Day 1	388.6 ± 4.0	390.6 ± 4.0	388.7 ± 3.9	388.6 ± 4.0
Day 2	390.2 ± 4.0	394.4 ± 4.0	394.6 ± 3.8	394.0 ± 4.0
Day 3	394.8 ± 4.0	404.4 ± 4.0	399.1 ± 4.0	392.1 ± 4.0
Day 2 minus Day 1	1.3 ± 3.2 0.672 (-4.9, 7.8)	4.4 ± 3.2 0.048 (0.1, 12.7)	-2.0 ± 3.1 0.612 (-8.2, 4.1)	0.2 ± 3.3 0.948 (-6.0, 6.5)
Day 8 minus Day 1	6.7 ± 3.2 0.072 (-0.5, 12.0)	24.4 ± 3.2 0.000 (18.1, 30.7)	-0.8 ± 3.2 0.648 (-8.5, 6)	6.3 ± 3.2 0.080 (0.0, 12.5)
Day 8 minus Day 2	4.4 ± 3.2 0.188 (-1.8, 10.7)	18.0 ± 3.2 0.000 (11.7, 24.3)	1.4 ± 3.2 0.690 (-4.6, 7.7)	6.0 ± 3.2 0.068 (-0.2, 12.3)
Comparison ^{††}	Average Differences [†] in Daily Means			
	Day 2 minus Day 1 Mean ± Std Error P value ‡ Confidence Interval	Day 8 minus Day 1 Mean ± Std Error P value ‡ Confidence Interval	Day 8 minus Day 2 Mean ± Std Error P value ‡ Confidence Interval	
MDL 16,455A 60 mg vs. MDL 16,455A 180 mg	2.3 ± 4.4 0.812 (-6.5, 11.0)	6.9 ± 4.5 0.127 (-2.0, 15.7)	4.6 ± 4.5 0.305 (-4.2, 13.4)	
Terfenadine 60 mg vs. Terfenadine 180 mg	5.3 ± 4.5 0.203 (-3.9, 13.3)	16.7 ± 4.5 0.000 (9.8, 27.5)	13.8 ± 4.5 0.003 (4.8, 22.5)	
MDL 16,455A 180 mg vs. Terfenadine 180 mg	6.2 ± 4.5 0.171 (-2.7, 13.0)	18.1 ± 4.5 0.000 (9.3, 27.0)	12.0 ± 4.5 0.008 (3.1, 20.8)	
MDL 16,455A vs. Terfenadine	4.8 ± 3.2 0.132 (-1.4, 11.0)	12.2 ± 3.2 0.000 (6.0, 18.5)	7.9 ± 3.2 0.020 (1.2, 13.7)	

* P value is for a test of no difference from zero based on the fitted ANOVA model.
 ** Positive values indicate greater increases with higher dose than lower dose or with terfenadine than MDL 16,455A.
 † The average difference is based on the fitted means.
 ‡ P value = 0.000 should be interpreted as P value less than 0.001.

Supporting Data Appendix C4.c: Analysis of QT_c Page SB-VI 159-P137

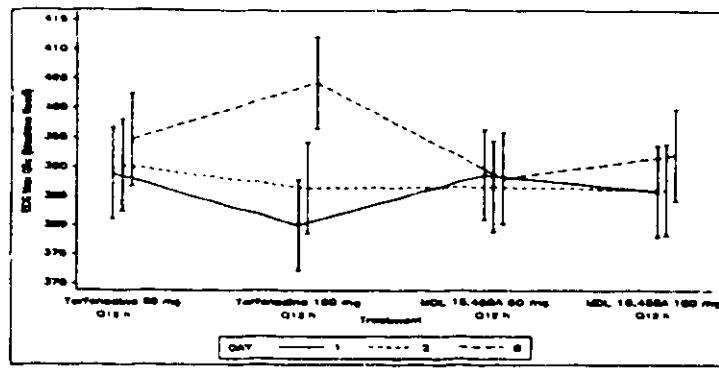


Figure 6-76. Pooled Means and 95% Confidence Intervals for Daily Maximum Machine-read QTc.

Supporting Data Appendix C-2: Analysis of QTc Page 88-VI 180-P137

The following table presents QTc values greater than 440msec observed and reported by the sponsor. In examining the line listings for outliers, subject #008 had two other outlier ECGs before Day 5 on MDL-16,455A 180mg and 2 other outlier ECGs on Days 7 and 8 on terfenadine 180mg.

Subjects With Machine Read QTc Values Greater Than 440 msec				
Patient Number	Terfenadine 60mg	Terfenadine 180mg	MDL-16,455A 60mg	MDL-16,455A 180mg
0008	446	443	-	464
0014	441	-	-	-
0023	450	-	-	-

Other Machine Read ECG Parameters:

The sponsor reports that mean heart rate increased slightly for both doses of MDL-16,455A and terfenadine on Days 2 and 8, mean QT interval increased by 180mg terfenadine but not appreciably with terfenadine 60mg, and slightly decreased by both MDL-16,455A doses. Mean PR and QRS intervals were not changed appreciably.

Results - Safety Measurements

Discontinuations: The sponsor reports that there were no serious adverse events and no deaths during this trial. Two patients were discontinued from the study due to adverse events. Subject #0002 discontinued from trial during Day 6 of period 1 while taking MDL 16,455A 60mg Q12h because of an erythematous rash which lasted 3 days and resolved without sequelae. Subject #0012 discontinued from trial during Day 7 of period 4 while taking MDL 16,455A 60mg Q12h because of a rash which he experienced during all 4 study periods and which increased in intensity from mild to moderate.

Adverse Events:

From the table below, it appears that nausea and headache were noted in equal numbers of patients taking terfenadine and MDL-16,455A, while abdominal pain occurring more often when taking MDL-16,455A and loose stools more often when taking terfenadine. Also noted but not included in the table that one subject experienced "palpitation" when taking terfenadine 180mg and one subject experienced "heart pounding" when taking terfenadine 60mg.

Number of Subjects With Adverse Events Which Occurred In 2 or More Subjects Per Treatment						
	Terfenadine 60mg Q12H	Terfenadine 180mg Q12H	MDL- 16,455A- 60mg Q12H	MDL- 16,455A- 180mg Q12H	Total Terfenadine	Total MDL-16,455A
Subjects With 1 or More AE	9	10	13	15	13	19
Nausea	2	2	2	3	4	5
Abdominal Pain		1	1	3	1	4
Diarrhea			1	1		2
Stools Loose	2	2		1	3	1
Headache	1	4	1	3	4	3
Light-headed Feeling	1		1	1	1	2
Rash Erythematous	2		3		2	3
Epistaxis			1	1		2
Sore Throat		1	1	1	1	2
Common Cold			2	1		3
Myalgia	1	1	1		2	1

Clinical Laboratory Assessments:

Since only two laboratory measurements were made, at screening and post trial, no comparisons between MDL-16,455A and terfenadine can be made. The sponsor reports that clinical laboratory values were unremarkable except for increases in SGOT (19.1 IU/l to 28.9 IU/l), SGPT (17.7 IU/l to 38.4 IU/l) and eosinophils ($0.105 \times 10^9/l$ to $0.208 \times 10^9/l$); but mean values poststudy were within the normal reference ranges for all three. The sponsor also reports that changes from normal to abnormal were noted for 5 subjects who had abnormal poststudy SGPT but all five values were less than 2 times the upper limit of normal (normal range - 10-49 - #3-97; #6-74; #13-87; #18-67; #22-62). Seven subjects had abnormal sodium levels at poststudy (normal range - 137-145 - #13-148; #14-146; #17-146; #18-147; #20-148; #22-136; #23-136). Three other subjects had abnormal poststudy values that were considered outlier values according to pre-defined criteria: #20 - direct bilirubin 0.76 (normal < 0.56); #21 - 35 bicarbonate (normal 20-30); #23 - 33 bicarbonate (normal 20-30).

Vital Signs:

The sponsor reports that no consistent trends were seen for all treatment groups and that there were no treatment related adverse reports of hypotension, hypertension, bradycardia or tachycardia.

Reviewer's Comments

Protocol PJPR0004 provides an important relative comparison between fexofenadine and terfenadine at two different dose levels, 60mg and 180mg, regarding pharmacokinetic estimates and pharmacodynamic parameters for wheal and flare inhibition and cardiac conduction. Unfortunately a placebo control was not included making it impossible to draw direct conclusions regarding the magnitude of effect relative to placebo. Nonetheless, data from another trial conducted by the sponsor with terfenadine at 180mg Q12H in normals and cardiac patients (Protocol #9918-1-C-176) showed an effect of similar magnitude (QTc increase from baseline of approximately 20-25 msec) lending credibility to the results from PJPR0004 which also demonstrated an effect of 23 msec from baseline for terfenadine 180mg Q12H. The substantial differences observed in effect on QTc prolongation between terfenadine and fexofenadine lends support for the safety of fexofenadine relative to terfenadine.

At the request of the Agency the sponsor provided by FAX on 3/4/96, the ECG time points actually used in computing daily QTc means. For this study report they were:

Days 1, 2 and 8: 0hr to 12hr after the 8AM dose

Days 3-7: 4hr after 8am dose

Day 9: 24hr after the final dose

Day 10: 48hr after the final dose

Day 11: 72hr after the final dose

Reviewer's Determinations

- 1) The AUC_{ss}(0-12 h) for fexofenadine following administration of fexofenadine was smaller (67% - 60mg; 75% - 180mg) than that observed following terfenadine administration
- 2) An 80mg dose of fexofenadine Q12H would result in an AUC_{ss}(0-12 h) for MDL-16,455 equivalent to a 60mg dose of terfenadine.
- 3) Following terfenadine or fexofenadine administration, the AUC_{ss}(0-12h), C_{max-ss} and C_{min-ss} for fexofenadine were dose proportional.
- 4) The T_{max} following fexofenadine (1-1.2h) was more rapid compared to terfenadine (2.3-4 h).
- 5) Steady state for fexofenadine is achieved by day 5 following both MDL-16,455A and terfenadine administration.
- 6) The half-life of fexofenadine is somewhat shorter following fexofenadine (11.8-14.0 h) administration compared to that following terfenadine administration (17.6-20.1 h).
- 7) Based on the Morganroth database and the machine read database, both terfenadine 60mg Q12H and 180mg Q12H prolonging QTc intervals at steady state by approximately 9msec and 22msec, respectively, from baseline while fexofenadine 60mg Q12H does not measurably prolong QTc intervals. Based on the machine read database, fexofenadine 180mg Q12H at steady state may be capable of prolonging QTc intervals by approximately 4msec. This observation will need to be confirmed or refuted by data from other studies. A lack of a placebo control and the lower plasma AUC_{ss} observed following fexofenadine administration, make it difficult to assess what impact time or bioequivalent plasma concentrations would have on the relative magnitudes of these pharmacodynamic observations.
- 8) The magnitude of wheal inhibition following dosing with the 180mg doses was greater than the 60mg doses in the range of 10.3% to 12.4%.
- 9) The mean maximum wheal inhibition ranged from -75% (fexofenadine 60mg) to -84% (terfenadine 180mg) across treatments.
- 10) Over the dosing interval at steady state, the trough wheal area inhibition was no less than 30% across treatments and the greatest degree of inhibition appeared to occur at approximately 6 hours.
- 11) Fexofenadine appears to be well tolerated by healthy adult male subjects.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: Protocol PJPR0007 from NDA 20-625

Protocol No. PJPR0007 - conducted from October 21, 1993 to February 19, 1994 in Miami, Florida

Title

" A Double-Blind, Randomized, Placebo-Controlled, 4-Period Crossover Pharmacodynamic And Safety Study Of MDL 16,455A In Normal Subjects."

Objectives

"To characterize the effect on QT intervals, if any, for normal subjects administered the following dosage regimens of MDL 16,455A: 40 mg BID, 200 mg BID, and 400 mg BID and placebo."

"To characterize the multiple dose plasma and urine pharmacokinetics of MDL 16,455A."

"To determine whether a relationship exists between MDL 16,455A plasma levels and changes in the QTc intervals, if observed."

Study Design

This study was a single center, double-blind, randomized, placebo-controlled, 4 period cross-over (11 days per period with 14 days washout) trial in 40 (20 male and 20 female) normal healthy volunteers between 18 and 60 years of age randomly assigned to treatment sequences. On Day 1, all subjects received placebo every twelve hours. On Day 2, MDL-16,455A or placebo were administered BID for 6 days (Days 2 to 7). On Day 8 a final single dose was administered. Serial ECGs and blood samples were obtained over Days 8, 9, 10 and 11 of each treatment period. The study subjects were divided and tested as two groups of 24 and 16 subjects per group. Serial ECGs and blood samples were obtained on Days 1, 2 and 8.

Treatments

MDL 16,455A was administered as an oral solution of MDL 16,455A in a propylene glycol-acetic acid (PGAA) vehicle from unit dose oral syringes will be filled at the clinic.

Placebo: 4 cc of a PGAA solution
MDL-16,455A 40mg: 4 cc (40 mg) of a 10 mg/ml MDL 16,455A in PGAA solution
MDL-16,455A 200mg: 4 cc (200 mg) of a 50 mg/ml MDL 16,455A in PGAA solution
MDL-16,455A 400mg: 4 cc (400 mg) of a 100 mg/ml MDL 16,455A in PGAA solution

Day 1 - Placebo: administered 8AM and 8PM
Days 2-7: administered 8AM and 8PM
Day 8 - final dose 8AM

Study Measurements**ECGs**

12-lead ECGs with a lead II rhythm strip were obtained at the following time points for each treatment period.

Screen Visit

Day 1:	0800, 0900, 1000, 1100, 1200, 1400, 1600, 2000
Day 2:	0800, 0900, 1000, 1100, 1200, 1400, 1600, 2000
Day 3-7:	0800, 1200, 1600
Day 8:	0800, 0900, 1000, 1100, 1200, 1400, 1600, 2000
Day 9:	0800, 2000
Day 10:	0800
Day 11:	0800

Plasma Samples for MDL-16.455A Concentration

Blood specimens were obtained at the following time points for each treatment period.

Day 2: 0800 hours just prior to dosing
 Day 6: 0800 trough
 Day 7: 0800 trough
 Day 8: 0800 trough, 0830, 0900, 0930, 1000, 1100, 1200, 1400, 1600, 2000 hours
 Day 9: 0200, 0800, 2000 hours
 Day 10: 0800 hours
 Day 11: 0800 hours

Safety Measurements

All subjects were monitored by lead II telemetry from Day 2 to Day 8. Vital signs were measured 2 times a day throughout the study. Reports of adverse events were collected. Clinical laboratory measurements were obtained at screening and at Days 1, 8 and 11 of each study period. A serum pregnancy test was performed on Day 1 and Day 11 of each treatment period for all females.

Subject Inclusion Criteria

- between 18 and 60 years of age;
- males and females, who are not pregnant, not lactating, or unable/unlikely to become pregnant (using contraception);
- non-smoker and non-user of smokeless tobacco (within the past 6 months);
- weight within 10% of the ideal range;
- no clinically significant abnormalities before study initiation for medical history, physical exam, clinical laboratory analyses, ECG, drug and HIV screen, and negative pregnancy test;

Subject Exclusion Criteria

- allergic reaction to a drug suggesting increased potential for an adverse hypersensitivity reaction to terfenadine or MDL 16,455A;
- pre-admission vital signs are not within the normal range;
- clinical laboratory evaluations considered clinically significant upon repeat evaluation;
- significant organ abnormality or disease;
- history of renal, hepatic, gastrointestinal, cardiovascular, or hematologic disease;
- a history of smoking or use of smokeless tobacco (within the last 6 months) or any history of alcohol or drug abuse (within the last 2 years);
- serious mental or physical illness within the past year;
- donated blood or plasma or participated in other drug studies within 30 days;
- treatment with prescription or nonprescription (OTC) medication within 14 days of study initiation;
- received any known hepatic or renal clearance altering agents (eg. erythromycin, cimetidine, barbiturates, phenothiazines, etc) within 30 days of study initiation;
- received ketoconazole or itraconazole within 3 months of study initiation;
- received astemizole (Hismanal) within 6 months prior to study initiation;
- QTc interval of greater than 440 msec recorded from a 12-lead ECG or with any underlying conditions known to prolong QTc;
- clinically significant cardiac abnormalities as determined from 24-hour Holter monitoring;
- chronic hypokalemia or potassium less than 3.5 mEq/L;
- investigational drug within 1 month before study initiation;
- positive HIV or Hepatitis B screen;
- positive qualitative drug screen (repeated prior to each treatment period);

Results - Patient Accounting

A total of 40 subjects (20 males and 20 females) were enrolled and 39 completed. One subject (#009037) was discontinued and hospitalized during Day 2 period 4 (placebo) due to pyloric stenosis (see discussion below). Data from all subjects was included in the pharmacokinetic analysis and ECG analysis except ECG data from period 4 for the subject who discontinued. The sponsor indicates on page 60 of the report that 6,850 ECGs were used in the analysis; 6880 ECGs (43 per period per subject) would have been collected if all planned ECGs were obtained. The sponsor has been asked to clarify the apparent ECG discrepancy since only 6,837 would have been used if dropout ECGs were not used.

Results - Pharmacodynamic Parameters - Cardiac Conduction

The sponsor reports the results of two analyses of QTC measurements as daily means and daily maxima. Both of these analyses are reported for 3 databases, one as measured by the ECG machine and two as measured by Dr Joel Morganroth referred to as "first Morganroth data" and "final Morganroth data." The sponsor explains the necessity for 2 complete readings of the ECGs by Dr Morganroth because of the observance of a significant carryover effect (p=0.0139) during the analysis of the database from the first reading which was not observed the analysis of the machine read database (p=0.2940) and which was reduced in the final database reading (p=0.1014). The sponsor expressed concern that significant carryover and significant trend across periods may confound treatment comparisons within subjects with individual treatment sequences. (See further discussion below)

Daily Means Analyses

The results of the three analyses for daily means were summarized in tabular format, reproduced below. The average of the 8 ECGs obtained on Days 1 and 8 was used for the primary analyses. Across all three analyses, no statistically significant differences are noted between placebo and any active treatment; but a decrease in statistical significance is noted for the comparisons between the 400mg dose and placebo (first: p=0.2519 vs final: p=0.7312). A reduction is also noted in the numerical size of treatment effect on QTc prolongation of the 400mg dose (mean msec change from base line compared to placebo: first: 3.2±2.8 vs final -0.7±2.2). The sponsor also provides a graphic presentations across periods of the daily mean QTc averaged across study treatments using the EGG time points common for Days 1-8 (0800, 1200, 1600 hrs) and using available EGG time points for Days 9-11 during which no treatments were administered. The increasing trend across treatments can be seen in the first Morganroth data, including the graph of placebo alone, but not in the machine or final Morganroth data. Analyses of all 3 databases shows statistical significance for period and day effects. Only the first Morganroth data shows statistical significance for carryover effect.

Table 8-214. Analysis of Daily Mean QT _c (First Morganroth Read Data)						
Treatment (BID)	N	Daily Mean QT _c (msec)				
		Mean† ± SE Baseline: Day 1	Mean† ± SE Day 2 (Day 2 - Day 1)	Mean† ± SE Day 8 (Day 8 - Day 1)		
Placebo	38*	388.4 ± 2.7	388.2 ± 2.7 (1.7 ± 2.0)	400.5 ± 2.7 (4.2 ± 2.0)		
40 mg	40	387.7 ± 2.7	387.5 ± 2.7 (-0.2 ± 2.0)	388.4 ± 2.7 (1.7 ± 2.0)		
200 mg	40	385.3 ± 2.7	387.0 ± 2.7 (1.7 ± 2.0)	400.2 ± 2.7 (4.8 ± 2.0)		
400 mg	40	386.3 ± 2.7	387.8 ± 2.7 (1.3 ± 2.0)	403.7 ± 2.7 (7.4 ± 2.0)		
Difference Between Treatments in Change from Baseline Mean QT _c (msec)						
Comparison	Mean ± SE	Day 2			Day 8	
		90% CI	P value†	Mean ± SE	90% CI	P value†
40 mg - Placebo	-2.0 ± 2.8	(-6.6, 2.7)	.4801	-2.5 ± 2.8	(-7.1, 2.2)	.3802
200 mg - Placebo	-0.04 ± 2.8	(-4.7, 4.6)	.9875	0.7 ± 2.8	(-3.9, 5.4)	.8006
400 mg - Placebo	-0.4 ± 2.8	(-5.1, 4.2)	.8748	3.2 ± 2.8	(-1.4, 7.9)	.2519
Model Factor		P Value†				
Period		<.0001				
Day		<.0001				
Treatment		.4480				
Day by Treatment Interaction		.5410				
Carryover		.0139				
Linear Trend Across Doses, at Day 8		.0791				
* Subject 008-037 was dropped from the study on Day 7 of Treatment Period 4 (placebo). Thus, N=38 for the placebo treatment group.						
† Adjusted treatment means and P values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.						
Supporting Data:						Page
Appendix F2, Summary 1: Least Mean and Daily Maximum QT _c , First Morganroth Data						S8-V1.174-P78
Appendix F3, Summary 1: Daily Mean QT _c , First Morganroth Data						S8-V1.174-P280
Appendix F4, Listing 1: All ECG Parameters, First Morganroth Data						S8-V1.175-P18

Table 8-218. Analysis of Daily Mean QT_c (Final Morgenroth Data)

Treatment (BID)	N	Daily Mean QT _c (msec)					
		Mean† ± SE Baseline: Day 1	Mean† ± SE Day 2 (Day 2 - Day 1)	Mean† ± SE Day 8 (Day 8 - Day 1)			
Placebo	38*	393.9 ± 2.8	395.3 ± 2.8 (1.4 ± 1.5)	398.5 ± 2.8 (4.6 ± 1.5) †			
40 mg	40	397.1 ± 2.8	395.0 ± 2.8 (-2.1 ± 1.5)	399.2 ± 2.8 (2.1 ± 1.5)			
200 mg	40	398.0 ± 2.8	397.6 ± 2.8 (-0.4 ± 1.5)	399.3 ± 2.8 (1.3 ± 1.5)			
400 mg	40	397.9 ± 2.8	397.7 ± 2.8 (-0.2 ± 1.5)	403.3 ± 2.8 (5.4 ± 1.5)			
Comparison		Difference Between Treatments in Change from Baseline Mean QT _c (msec)					
		Day 2 Mean ± SE	90% CI	P value†	Day 8 Mean ± SE	90% CI	P value†
40 mg - Placebo		-3.5 ± 2.2	(-7.1, 0.1)	.1056	-2.5 ± 2.2	(-6.1, 1.1)	.2518
200 mg - Placebo		0.2 ± 2.2	(-3.4, 3.8)	.9149	-0.8 ± 2.2	(-4.4, 2.8)	.7175
400 mg - Placebo		-1.7 ± 2.2	(-5.3, 1.9)	.4390	0.7 ± 2.2	(-2.8, 4.3)	.7312
Model Factor		P Value†					
Period		.0035					
Day		<.0001					
Treatment		.4290					
Day by Treatment Interaction		.4125					
Carryover		.1014					
Linear Trend Across Doses, at Day 8		.3547					
* Subject 009-037 was dropped from the study during Treatment Period 4 (placebo). Thus, N=38 for the placebo means.							
† Adjusted treatment means and P values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.							
Supporting Data:						Page	
Appendix F2, Summary 2: Daily Mean and Daily Maximum QT _c , Final Morgenroth Data						S8-V1.174-P94	
Appendix F3, Summary 2: Daily Mean QT _c , Final Morgenroth Data						S8-V1.174-P293	
Appendix F4, Listing 2: All ECG Parameters, Final Morgenroth Data						S8-V1.175-P158	

Table 8-218. Analysis of Daily Mean QT_c (Machine Data)

Treatment (BID)	N	Daily Mean QT _c (msec)					
		Mean† ± SE Baseline: Day 1	Mean† ± SE Day 2 (Day 2 - Day 1)	Mean† ± SE Day 8 (Day 8 - Day 1)			
Placebo	38*	398.7 ± 2.8	397.8 ± 2.8 (-1.1 ± 1.5)	391.3 ± 2.8 (-7.4 ± 1.5)			
40 mg	40	398.8 ± 2.8	398.7 ± 2.8 (-0.1 ± 1.5)	393.4 ± 2.8 (-5.4 ± 1.5)			
200 mg	40	398.5 ± 2.8	398.5 ± 2.8 (0.0 ± 1.5)	391.6 ± 2.8 (-6.9 ± 1.5)			
400 mg	40	398.9 ± 2.8	398.0 ± 2.8 (-0.9 ± 1.5)	393.7 ± 2.8 (-5.2 ± 1.5)			
Comparison		Difference Between Treatments in Change from Baseline Mean QT _c (msec)					
		Day 2 Mean ± SE	90% CI	P value†	Day 8 Mean ± SE	90% CI	P value†
40 mg - Placebo		1.2 ± 2.1	(-2.3, 4.6)	.5801	0.2 ± 2.1	(-3.2, 3.7)	.9197
200 mg - Placebo		2.1 ± 2.1	(-1.4, 5.5)	.3185	0.5 ± 2.1	(-2.9, 4.0)	.765†
400 mg - Placebo		1.1 ± 2.1	(-2.3, 4.6)	.5965	1.2 ± 2.1	(-2.3, 4.6)	.5711
Model Factor		P Value†					
Period		.0025					
Day		<.0001					
Treatment		.8384					
Day by Treatment Interaction		.9807					
Carryover		.2940					
Linear Trend Across Doses, at Day 8		.5456					
* Subject 009-037 was dropped from the study on Day 2 of Treatment Period 4 (placebo). Thus, N=38 for the placebo treatment group.							
† Adjusted treatment means and P values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.							
Supporting Data:						Page	
Appendix F2, Summary 3: Daily Mean and Daily Maximum QT _c , Machine Data						S8-V1.174-P112	
Appendix F3, Summary 5: Daily Mean QT _c , Machine Data						S8-V1.174-P293	
Appendix F4, Listing 10: All ECG Parameters, Machine Data						S8-V1.176-P10	

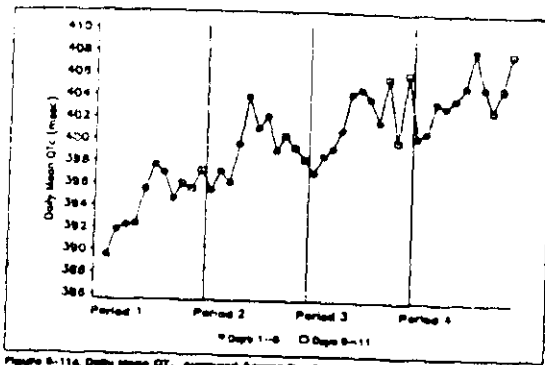


Figure 8-114. Daily Mean QTc, Averaged Across Treatments (First Morganroth Data)

Supporting Data	Page
Appendix P2, Summary 1: Daily Mean and Daily Maximum QTc, First Morganroth Data	88-VI-174-P76
Appendix P3, Summary 1: Daily Mean QTc, First Morganroth Data	88-VI-174-P80
Appendix P4, Listing 1: All ECG Parameters, First Morganroth Data	88-VI-173-P18

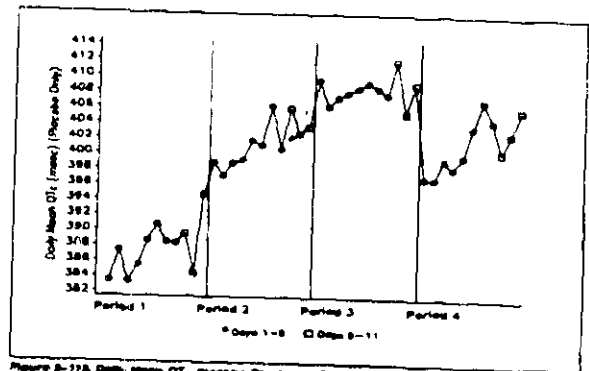


Figure 8-115. Daily Mean QTc, Morganroth Data Only (First Morganroth Data)

Supporting Data	Page
Appendix P2, Summary 1: Daily Mean and Daily Maximum QTc, First Morganroth Data	88-VI-174-P76
Appendix P3, Summary 1: Daily Mean QTc, First Morganroth Data	88-VI-174-P80
Appendix P4, Listing 1: All ECG Parameters, First Morganroth Data	88-VI-173-P18

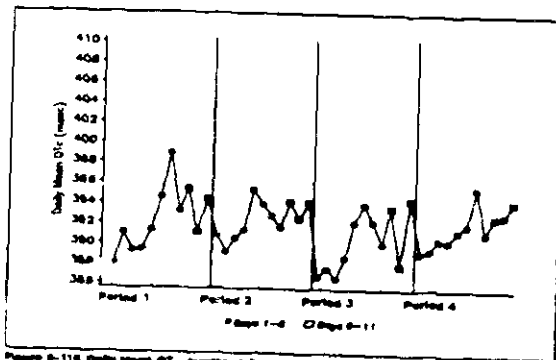


Figure 8-116. Daily Mean QTc, Averaged Across Treatments (Morganroth Data)

Supporting Data	Page
Appendix P2, Summary 2: Daily Mean and Daily Maximum QTc, Morganroth Data	88-VI-174-P112
Appendix P3, Summary 2: Daily Mean QTc, Morganroth Data	88-VI-174-P80
Appendix P4, Listing 1: All ECG Parameters, Morganroth Data	88-VI-173-P18

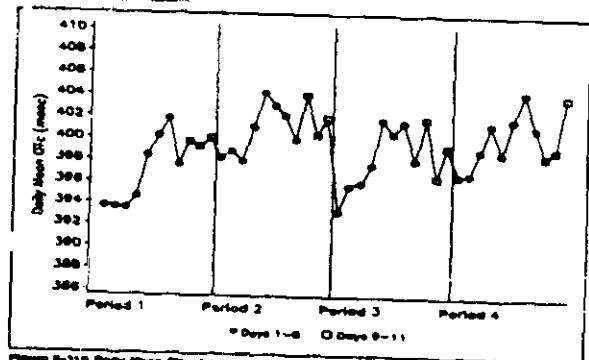


Figure 8-117. Daily Mean QTc, Averaged Across Treatments (Final Morganroth Data)

Supporting Data	Page
Appendix P2, Summary 2: Daily Mean and Daily Maximum QTc, Final Morganroth Data	88-VI-174-P86
Appendix P3, Summary 2: Daily Mean QTc, Final Morganroth Data	88-VI-174-P80
Appendix P4, Listing 1: All ECG Parameters, Final Morganroth Data	88-VI-173-P18

The sponsor speculates that three procedural deficiencies in processing the first Morganroth data may have been responsible for the trend and indicates these deficiencies were corrected for the final data.

- 1) Incomplete ECG Blinding - machine read parameters, subject number and initials, and ECG date and time were not covered before sending the ECGs to Dr Morganroth for interpretation and measurement and may have introduced bias since subject identification and ECG sequence could be discerned.
- 2) ECGs were processed by treatment period - ECGs from one treatment period were batched together and bias may have been introduced by recognition of ECG sequence within period. Additionally, interpretation and measurement procedures for a batch may have been slightly different for subsequent batches.
- 3) Multiple Digitizing Operators - no single staff member was assigned for digitizing all the ECGs for a subject and may have introduced operator variability. It is unclear why item #3 would introduce bias. The sponsor was asked to explain why this would introduce bias. The sponsor responded in a submission dated April 1, 1996 indicating that different techniques used by each operator combined with measurements performed in period order may have introduced variability. While this might be understood to introduce bias within a single period, this argument seems inconsistent since introduction of variability across periods would seem to be likely to reduce bias across periods.

The sponsor indicates that procedures were used for the final reading that should have avoided the above deficiencies. Unmarked ECGs from the study clinic were obtained, a new random code generated and ECGs blinded completely displaying only the protocol number and new sample random code. ECGs for one patient were shuffled and ECGs for each subject were measured by only one digitizing operator.

Daily Maxima Analyses

The sponsor summarizes the results from the 3 databases for daily QTc interval maxima. Results similar to those observed for the daily mean analyses are noted except maxima are more variable and confidence intervals are broader. No statistically significant differences are noted for any active treatment for change from baseline compared to placebo but the machine database for the 40mg dose approaches statistical significance at the p=0.0517 level. None of the analyses of maxima data show a carryover effect; but the first Morganroth data show both period and day effects; the machine data show a period effect; and the final Morganroth data show a day effect.

Table 8-215. Analysis of Daily Maximum QT _c (First Morganroth Data)						
Treatment (BID)	N	Daily Maximum QT _c (msec)				
		Mean† ± SE Baseline: Day 1	Mean† ± SE Day 2 (Day 2 - Day 1)		Mean† ± SE Day 8 (Day 8 - Day 1)	
Placebo	38*	418.5 ± 3.0	416.4 ± 3.1 (-0.1 ± 2.7)		418.0 ± 3.0 (2.5 ± 2.7)	
40 mg	40	417.1 ± 3.0	416.3 ± 3.1 (-0.8 ± 2.6)		417.1 ± 3.0 (-.04 ± 2.6)	
200 mg	40	416.4 ± 3.0	415.9 ± 3.1 (-0.5 ± 2.6)		418.5 ± 3.0 (3.1 ± 2.6)	
400 mg	40	415.1 ± 3.0	414.3 ± 3.1 (-0.8 ± 2.6)		421.9 ± 3.0 (6.8 ± 2.6)	
Difference Between Treatments in Change from Baseline Maximum QT _c (msec)						
Comparison	Mean ± SE	Day 2			Day 8	
		90% CI	P value†	Mean ± SE	90% CI	P value†
40 mg - Placebo	-0.7 ± 3.8	(-7.0, 5.5)	.8422	-2.5 ± 3.8	(-8.7, 3.7)	.4866
200 mg - Placebo	-0.4 ± 3.8	(-6.6, 5.6)	.9211	0.6 ± 3.8	(-5.6, 6.6)	.8732
400 mg - Placebo	-0.7 ± 3.8	(-6.9, 5.5)	.8615	4.3 ± 3.8	(-1.9, 10.5)	.2557
Model Factor		P Value†				
Period		<.0001				
Day		.0133				
Treatment		.3248				
Day by Treatment Interaction		.5934				
Carryover		.1195				
Linear Trend Across Doses, at Day 8		.1049				
* Subject 008-037 was dropped from the study on Day 2 of Treatment Period 4 (placebo). Thus, N=39 for the placebo treatment group.						
† Adjusted treatment means and P values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.						
Supporting Data:						Page
Appendix F2, Summary 1: Daily Mean and Daily Maximum QT _c , First Morganroth Data						S8-V1.174-P76
Appendix F3, Summary 3: Daily Maximum QT _c , First Morganroth Data						S8-V1.174-P200
Appendix F4, Listing 1: All ECG Parameters, First Morganroth Data						S8-V1.175-P16

Table 8-217. Analysis of Daily Maximum QT_c (Machine Data)

Treatment (SID)	N	Daily Maximum QT _c (msec)				
		Mean† ± SE Baseline: Day 1	Mean† ± SE Day 2 (Day 2 - Day 1)	Mean† ± SE Day 8 (Day 8 - Day 1)		
Placebo	39*	406.7 ± 3.4	405.4 ± 3.4 (-3.3 ± 3.3)	405.8 ± 3.4 (-2.9 ± 3.3)		
40 mg	40	407.9 ± 3.4	412.1 ± 3.4 (4.2 ± 3.3)	414.1 ± 3.4 (6.2 ± 3.3)		
200 mg	40	405.6 ± 3.4	408.2 ± 3.4 (2.6 ± 3.3)	408.7 ± 3.4 (3.2 ± 3.3)		
400 mg	40	407.4 ± 3.4	404.3 ± 3.4 (-2.5 ± 3.3)	409.3 ± 3.4 (1.9 ± 3.3)		
Difference Between Treatments in Change from Baseline Maximum QT _c (msec)						
Comparison	Day 2			Day 8		
	Mean ± SE	90% CI	P value†	Mean ± SE	90% CI	P value†
40 mg - Placebo	7.5 ± 4.6	(-0.2, 15.1)	.1074	9.0 ± 4.6	(1.4, 16.7)	.0517
200 mg - Placebo	5.9 ± 4.6	(-1.7, 13.6)	.2034	6.0 ± 4.6	(-1.8, 13.7)	.1929
400 mg - Placebo	0.9 ± 4.6	(-6.8, 8.5)	.8533	4.8 ± 4.6	(-2.8, 12.5)	.2987
Model Factor		P Value†				
Period		.0006				
Day		.3778				
Treatment		.8130				
Day by Treatment Interaction		.4482				
Carryover		.4842				
Linear Trend Across Doses, at Day 8		.7808				
* Subject 006-037 was dropped from the study on Day 2 of Treatment Period 4 (placebo). Thus, N=39 for the placebo treatment group.						
† Adjusted treatment means and P values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.						
Supporting Data:						Page
Appendix F2, Summary 3: Daily Mean and Daily Maximum QT _c , Machine Data						SB-VI.174-P112
Appendix F3, Summary 6: Daily Maximum QT _c , Machine Data						SB-VI.174-P298
Appendix F4, Listing 10: All ECG Parameters, Machine Data						SB-VI.176-P10

Table 8-218. Analysis of Daily Maximum QT_c (Final Morganroth Data)

Treatment (SID)	N	Daily Maximum QT _c (msec)				
		Mean† ± SE Baseline: Day 1	Mean† ± SE Day 2 (Day 2 - Day 1)	Mean† ± SE Day 8 (Day 8 - Day 1)		
Placebo	39*	414.1 ± 3.1	415.5 ± 3.1 (1.4 ± 2.3)	417.8 ± 3.1 (3.6 ± 2.3)		
40 mg	40	418.1 ± 3.1	414.1 ± 3.1 (-2.0 ± 2.3)	418.4 ± 3.1 (2.3 ± 2.3)		
200 mg	40	418.0 ± 3.1	418.2 ± 3.1 (0.1 ± 2.3)	418.8 ± 3.1 (0.8 ± 2.3)		
400 mg	40	418.9 ± 3.1	414.5 ± 3.1 (-2.4 ± 2.3)	421.8 ± 3.1 (4.8 ± 2.3)		
Difference Between Treatments in Change from Baseline Maximum QT _c (msec)						
Comparison	Day 2			Day 8		
	Mean ± SE	90% CI	P value†	Mean ± SE	90% CI	P value†
40 mg - Placebo	-3.4 ± 3.3	(-8.8, 2.0)	.2963	-1.3 ± 3.3	(-6.7, 4.1)	.6880
200 mg - Placebo	-1.3 ± 3.3	(-6.7, 4.1)	.8831	-3.0 ± 3.3	(-8.4, 2.4)	.3612
400 mg - Placebo	-3.8 ± 3.3	(-9.2, 1.6)	.2483	1.2 ± 3.3	(-4.2, 8.6)	.7039
Model Factor		P Value†				
Period		.7363				
Day		.0056				
Treatment		.1832				
Day by Treatment Interaction		.4708				
Carryover		.2022				
Linear Trend Across Doses, at Day 8		.6432				
* Subject 006-037 was dropped from the study on Day 2 of Treatment Period 4 (placebo). Thus, N=39 for the placebo treatment group.						
† Adjusted treatment means and P values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.						
Supporting Data:						Page
Appendix F2, Summary 2: Daily Mean and Daily Maximum QT _c , Final Morganroth Data						SB-VI.174-P94
Appendix F3, Summary 4: Daily Maximum QT _c , Final Morganroth Data						SB-VI.174-P290
Appendix F4, Listing 2: All ECG Parameters, Final Morganroth Data						SB-VI.175-P158

QTc Outlier Values

The sponsor defined outlier values as QTc >440msec and increase of > 10msec.

The following percent of patients had one or more outlier per treatment and the respective longest QTc per treatment: Placebo-35%(555msec); 40mg-30%(463msec); 200mg-35%(474msec), 400mg-40%(474msec). Of the subjects with outlier values 15 were females and 6 were males. Attached to the end of the review is a graph prepared by the review team statistician, Barbara Bono, of the trials QTc responses by gender. Note that females have approximately 15msec higher mean baseline and that the 400mg dose may have exerted a small QTc prolonging effect in females compared to males; primarily in the the clinical significance of this observation is uncertain.

Equivalence to Placebo

The sponsor indicates that according to predefined criteria, equivalence to placebo would be concluded if the 90% confidence interval, for change in daily mean QTc for the difference between each active treatment and placebo, fell entirely within the range of -12msec to 12msec. (Please see reviewer's comments below regarding this issue.)

Results - Pharmacokinetic Parameters

The sponsor summarized the pharmacokinetic results in tabular and graphic format, reproduced below. The sponsor reports that pre dose plasma concentrations were below the limit of quantification at the beginning of each period, indicating adequate washout; and trough analysis for Days 6, 7 and 8 indicated that steady state conditions were reached by the fifth day of dosing. Over the 10 fold increase in dose, there was a disproportionate increase in dose normalized AUC_{0-12 h} and C_{max,ss} but not in C_{min,ss}. Approximately 9.16% to 13.63% of the dose was excreted in the urine across treatments and renal clearance was dose independent. Across treatments, females had AUC_{0-12 h} 33%, C_{max,ss} 46% and A_e 33% greater than males. The sponsor states that no examination of the relationship between plasma concentrations and change in QTc were not conducted because of the lack of apparent treatment effect on QTc.

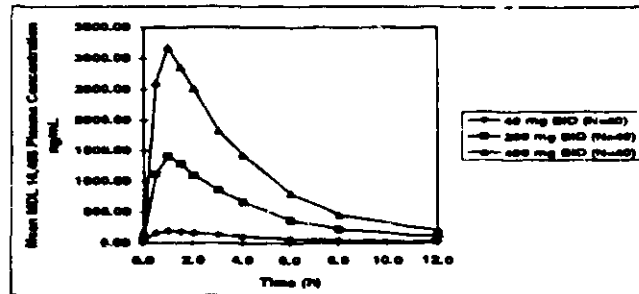


Figure 6-195. Mean MDL 16,466 Plasma Concentrations Over Time Following Administration of MDL 16,466A 40, 200, and 400 mg BID

Supporting Data: Appendix II: Individual MDL 16,466 Plasma Concentrations by Time Appendix III: Individual MDL 16,466 Plasma Concentration-Time Figures by Subject Page 20-VI.176-P187 20-VI.176-P188

Parameter	N	Mean	%CV	Adjusted Mean*	Pairwise Comparisons			
					Pair	Ratio (%)	95% CI	P value
AUC _{0-12 h} (ng/mL)	40	1028.39	33.25	973.08				
	200	8187.87	38.08	1189.88	200/40	124.20	(111.8,137.8)	<.001
	400	13877.75	33.88	1280.38	400/40	137.23	(123.7,152.3)	<.001
					400/200	110.48	(98.6,122.8)	.115
C _{max,ss} (ng/mL)	40	211.89	38.17	182.89				
	200	1818.00	48.86	277.22	200/40	143.87	(127.3,162.8)	<.001
	400	3884.88	38.18	312.39	400/40	182.11	(143.4,183.2)	<.001
					400/200	112.89	(98.7,127.4)	.108
C _{min,ss} (ng/mL)	40	18.83	37.78	17.87				
	200	87.02	32.42	18.98	200/40	82.09	(62.0,103.8)	.243
	400	188.89	38.81	15.17	400/40	84.38	(78.1,94.8)	.018
					400/200	91.83	(81.8,103.0)	.216
t _{max} (h)	40	1.08	44.18	0.98				
	200	1.08	38.77	0.98	200/40	101.32	(87.0,117.8)	.898
	400	1.04	38.41	0.98	400/40	88.28	(84.4,114.4)	.750
					400/200	97.00	(83.3,112.8)	.740
t _{1/2} (h)	40	18.00	88.08	13.80				
	200	14.40	32.87	13.74	200/40	88.87	(88.8,108.8)	.844
	400	18.11	41.30	14.33	400/40	103.11	(83.7,113.8)	.888
					400/200	104.28	(84.8,114.8)	.888
Cl _{CR,ss} (L/h)	40	48.78	88.78	38.87				
	200	34.33	37.25	32.18	200/40	80.51	(72.8,88.3)	<.001
	400	31.23	43.88	28.13	400/40	72.87	(68.7,80.8)	<.001
					400/200	80.51	(81.8,100.4)	.115

40 = MDL 16,466A 40 mg BID (N=40)
 200 = MDL 16,466A 200 mg BID (N=40)
 400 = MDL 16,466A 400 mg BID (N=40)
 * Adjusted mean and statistical comparisons are based on data normalized to the 40 mg dose for AUC_{0-12 h}, C_{max,ss} and C_{min,ss}.

Supporting Data: Appendix E2. Summary & Pharmacokinetic Parameters: Treatment Comparisons Appendix M. Individual MDL 16,466 Plasma Pharmacokinetic Parameters Page 20-VI.174-P20 20-VI.176-P228

Table 6-233. Mean MDL 16,466 Urine Pharmacokinetic Parameters and Treatment Comparisons

Parameter	Trt	Mean	%CV	Adjusted Mean*	Pairwise Comparisons			
					Pair	Ratio (%)	90% CI	P value
CL _R L/h	40	3.88	28.38	3.48				
	200	3.80	37.18	3.18	200/40	82.14	(80.9,104.9)	.298
	400	3.98	30.84	3.78	400/40	109.51	(86.2,123.8)	.300
					400/200	117.70	(103.3,134.3)	.042
A ₀ ng	40	3817.71	41.01	3221.8				
	200	21208.81	47.12	3728.8	300/40	115.74	(100.6,133.2)	.088
	400	80837.14	76.48	4723.2	400/40	148.82	(127.3,169.8)	<.001
					400/200	128.88	(109.9,148.1)	.007
% of Dose Excreted in Urine %	40	9.18	44.28					
	200	11.37	47.12					
	400	13.83	38.48					

40 = MDL 16,466A 40 mg BID (N=40)
 200 = MDL 16,466A 200 mg BID (N=40)
 400 = MDL 16,466A 400 mg BID (N=40)
 * Adjusted mean and statistical comparisons are based on data normalized to the 40 mg dose for A₀.

Supporting Data: Page
 Appendix E2, Summary 6: Pharmacokinetic Parameters Treatment Comparisons 28-V1,174-P30
 Appendix E3: Individual MDL 16,466 Urine Concentrations and Pharmacokinetic Parameters 28-V1,178-P33

Table 6-234. Mean MDL 16,466 Plasma and Urine Pharmacokinetic Parameters and Treatment Comparisons by Gender

Parameter	Trt	Gender	Mean	%CV	Adjusted Mean by Gender*	Pairwise Comparisons			
						Pair	Ratio (%)	90% CI	
AUC _{0-12h}} (0-12 h) h*ng/ml	40	F	1119.28	23.88					
		M	827.48	40.43					
	200	F	8883.20	37.88		1080.88	F/M 40	128.21	(108.5,188.8)
		M	8481.24	34.88		880.88	F/M 200	128.82	(107.3,187.2)
	400	F	18484.07	27.23		1818.38	F/M 400	140.88	(118.8,170.3)
		M	11701.44	38.01		1081.12			
	sexes	F			1188.88		F/M	128.08	(114.8,184.2)
		M			888.2				
C _{max}} ng/ml	40	F	248.04	28.34					
		M	177.78	47.38		231.88	F/M 40	143.78	(118.0,178.1)
	200	F	1781.22	48.17		230.87	F/M 200	142.18	(118.0,178.8)
		M	1284.78	38.47		238.48			
	400	F	2808.08	27.88		288.70	F/M 400	188.28	(123.8,180.1)
		M	2801.81	38.88		288.34			
	sexes	F			288.15		F/M	148.28	(128.2,171.8)
		M			211.28				
CL _{plasma} L/h	40	F	28.38	27.11					
		M	88.18	84.81					
	200	F	28.33	38.38					
		M	28.33	37.40					
	400	F	28.87	22.70					
		M	28.88	48.30					
	sexes	F							
		M							
CL _R L/h	40	F	3.82	18.11		3.37	F/M 40	108.78	(88.7,131.8)
		M	3.88	34.82		3.31			
	200	F	3.44	37.88		3.13	F/M 200	87.11	(78.8,118.8)
		M	3.88	37.42		3.21			
	400	F	3.84	28.88		3.80	F/M 400	108.88	(82.8,127.1)
		M	3.88	34.87		3.70			
	sexes	F			3.48		F/M	108.18	(88.8,117.8)
		M			3.42				
A ₀ ng	40	F	4087.38	38.88		3778.88	F/M 40	127.42	(108.7,173.7)
		M	2878.08	48.81		2748.08			
	200	F	22888.30	44.83		4148.88	F/M 200	123.82	(88.0,188.8)
		M	18818.82	80.83		3880.78			
	400	F	87488.30	28.84		4281.87	F/M 400	128.88	(108.8,177.8)
		M	44178.87	37.71		3888.88			
	sexes	F			4438.78		F/M	123.44	(113.1,187.8)
		M			3328.30				

40 = MDL 16,466A 40 mg BID (N=40)
 200 = MDL 16,466A 200 mg BID (N=40)
 400 = MDL 16,466A 400 mg BID (N=40)
 F = female
 M = male
 * Adjusted mean and statistical comparisons are based on data normalized to the 40 mg dose for AUC_{0-12h}}, C_{max}}, and A₀.

Supporting Data: Page
 Appendix E2, Summary 3: Pharmacokinetic Parameters: Male vs Female Comparisons 28-V1,174-P42
 Appendix E3: Individual MDL 16,466 Plasma Pharmacokinetic Parameters 28-V1,178-P38
 Appendix E5: Individual MDL 16,466 Urine Concentrations and Pharmacokinetic Parameters 28-V1,178-P33

Results - Safety Measurements

Discontinuations

The sponsor reports that no deaths occurred during this study. One subject (#099-037), a 55 year old Hispanic male, was discontinued during period 4 (placebo) and hospitalized due to pyloric stenosis which was judged by the investigator as severe and unlikely related to study medication. The sponsor reports that the patient reported to clinic for period 4 without complaint of adverse events. When Day 1 ECGs showed multiple QTc intervals greater than 440 msec, the investigator inquired about adverse experiences at which time the subject admitted to not eating and taking Zantac, Roloids and Alka-Seltzer for abdominal pain and vomiting over the past few days. On Day 2 the subject was discontinued from trial and was scheduled for evaluation by a gastroenterologist the next day. Day 1 laboratory results showed an abnormal electrolyte pattern and multiple Day 2 ECGs also showed QTc intervals greater than 440 msec. In the evening of Day 2 the subject experienced postural blood pressure changes and blood tinged vomitus and was hospitalized where he was found to have pyloric obstruction which improved with dilation. During hospitalization the subject admitted to having gastric and peptic ulcer disease at age 38 and a history of smoking and alcohol abuse which had not been reported to the investigative site at the time of screening.

Adverse Events

The table below was constructed from the sponsor's table of incidence of all adverse events. It is difficult to ascribe any of these events to active treatment.

Number of Subjects with Adverse Events Which Occurred In 2 or More Subjects On Active Treatment					
	Placebo	MDL-16,455A-40mg	MDL-16,455A-200mg	MDL-16,455A-400mg	MDL-16,455A Total
Number of Subjects With 1 or More AE	7	8	3	9	18
Infection Viral	1	1	0	2	3
URI Infection	0	0	1	1	2
Headache	1	1	0	1	2
Arthralgia	0	0	1	1	2

Clinical Laboratory Measurements

Clinical laboratory measurements were obtained on Days 1, 8 and 11 during each period of the trial. Day 1 values of each period were considered the baseline value for that period and Day 11 values were considered post baseline treatment values. The sponsor reports the mean pre and post treatment values excluding retest values for each period in Appendix K2 and noted that all post baseline mean values were within normal limits.

Twenty subjects had one or more outlier values according to the sponsor's pre-defined criteria. The majority of these were not considered to be clinically significant by the investigator for changes in cholesterol, A/G ratio, Hct, Hg, MCH, neutrophils and basophils; other values were related to the episode with subject #099-037 (i.e. creatinine, chloride, carbon dioxide, basophils) who was withdrawn

and subsequently found to have pyloric stenosis. With regard to lymphocytes, 2 subjects had changes which were not commented upon by the investigator (subject #009-028 on placebo: 1.46 to 0.68x10⁹/ul and subject #009-035 on 400mg: 0.63 to 0.03x10⁹/ul).

Two other subjects had outlier values which reflect liver status. No subject, including these 2 with outlier liver related values, was reported to have elevations of total bilirubin or direct bilirubin in the line listings.

--- Subject #009-002 had outlier elevations in SGPT on 40mg: 14 to 104 u/l and on 200mg: 13 to 107 u/l; and also had elevations of SGOT on these treatments which were not reported as outliers. Subject #009-002 also had elevations of GGT on placebo, 40mg and 200mg and alkaline phosphatase on 40mg which were not reported as outliers.

--- Subject #009-032 had elevations in SGOT, SGPT, GGT and alkaline phosphatase on all 4 treatments except no elevation in alkaline phosphatase on placebo. These elevations were reported as adverse events by the investigator and as possibly drug related. For this patient, only SGOT and SGPT met outlier criteria and are summarized in the table below.

Subject#009-032	SGOT	SGPT
Placebo		13 to 99 on 1/25/94 13 to 107 on 1/28/94
MDL-16,455A 40mg	25 to 114 on 11/30/93	23 to 178 on 11/30/93 23 to 132 on 12/3/93
MDL-16,455A 200mg	14 to 87 on 2/16/94	11 to 170 on 2/16/94
MDL-16,455A 400mg	15 to 94 on 12/21/93	16 to 135 on 12/21/93 16 to 186 on 12/24/93

Vital Signs

The sponsor reports that no consistent trends with increasing dose were observed for any vital sign. The numbers of patients who met outlier criteria for vital signs were similar across treatments (Placebo-11; MDL-16,455A 40mg-6; MDL-16,455A 200mg-11; MDL-16,455A 400mg-7).

Reviewer's Comments

Protocol PJPR0007 provides an important comparison between placebo and fexofenadine at 3 dose levels, 40mg, 200mg, and 400mg regarding pharmacokinetics and pharmacodynamic responses for QTc interval prolongation. No apparent effect on QTc interval prolongation was noted for each of the active treatments even at 400mg dose (C_{max,ss} = 3354 ng/ml) which is 6.7 fold higher than the proposed 60mg dose. The enrollment of 40 subjects is a desirable feature since trial in as few as 28 subjects (Protocol ##9918-1-C-176 submitted to NDA#18,942 for Seldane tablets), looking at 3 times the daily dose of terfenadine, was able to detect an approximately 20-25msec change from baseline. While these data provide a reasonable level of reassurance that the phenomenon should not occur at the 60mg dose level of fexofenadine (C_{max,ss} 299ng/ml from protocol PJPR0003) or at plasma concentrations substantially higher, the lack of statistical significance should not be used to support a statement that indicates that no effect occurs or can not occur because the trial may not have contained sufficient statistical power to detect a difference if in fact a difference does exist. **The statistical reviewer has been asked to comment the statistical power for this study.** By the same logic, a declaration of equivalence to placebo would be inappropriate for the same reason. However, the results

from this study do support a statement of fact, that no statistically significant or clinically significant increase in QTc interval was observed.

It is difficult to say with certainty that it is preferential to rely on the results of the reanalyzed ECG database, "final Morganroth data". While the observance of the carryover effect makes it more difficult to assess the results, a new baseline was established prior to each treatment period and change from baseline was the parameter of primary interest which should diminish the influence of numerical differences in baseline measurements. **The statistical reviewer has been asked to comment on the inclusion of carryover effect in the statistical model and the relative magnitude its inclusion imparts on the results.**

We note that the method of fexofenadine administration to study subjects in this study and other important studies was achieved by the extemporaneous preparation of a solution and dosage forms at the study site. Recognizing the potential for dosing error or dosing imprecision under such circumstances, the pharmacokinetic results showing dose related separation of the plasma-concentration-time curve suggests that any occurrence of these events were small in magnitude.

We noted that the subjects were studied as two smaller groups (i.e. 24 and 16). We also noted that all males were assigned odd subject numbers and all females were assigned even subject numbers. The sponsor was asked the purpose for these procedures. The sponsor replied in a submission dated April 1, 1996 saying the division of the subjects was necessary due to the limitations of the number of telemetry units; and that the study site personnel made the numerical assignments to simplify study procedures. The sponsor indicates that the randomization schedule was defined such that each subject had equal probability of receiving any one of the 24 possible treatment sequences and that assignment of males to odd subject numbers would not be expected to affect the randomness of treatment sequence assignment.

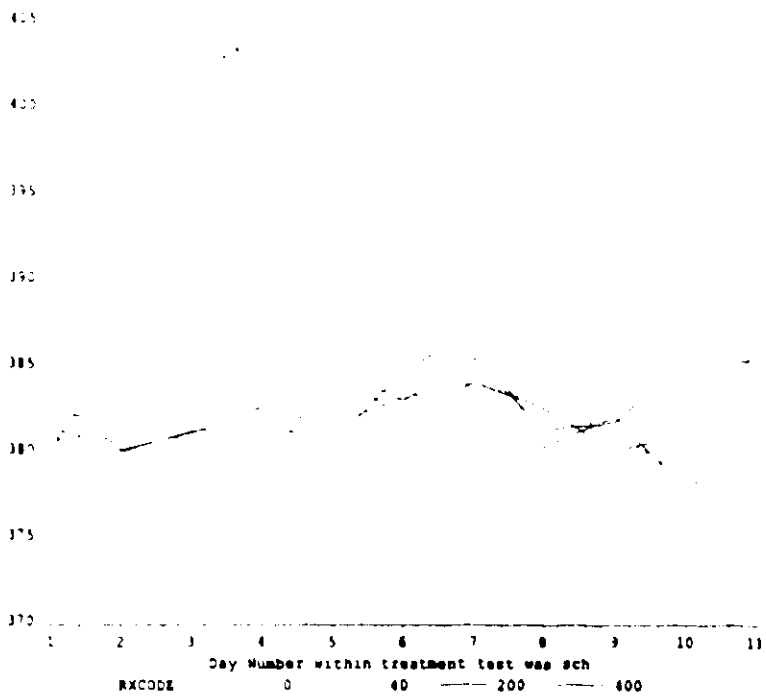
The sponsor was asked to provide by gender daily mean QTc and mean maxima QTc changes from baseline. The sponsor replied in a submission dated April 1, 1996. At baseline females had a higher mean QTc (across treatments including placebo: females 402-407 msec; males 385-391 msec). Day 8-Day 1 daily mean QTc change from baseline (across treatments including placebo: females 3.6-10.3 msec; males 0.37-1.04 msec) but this was not statistically significant $P > 0.8061$ for treatment by gender interaction. A similar pattern was observed for the mean maxima QTc.

The sponsor was asked to provide by gender analysis for correlation between plasma concentrations and QTc data. The sponsor replied in a submission dated April 1, 1996. The sponsor reports no significant positive correlation between fexofenadine concentration and QTc measurements for males or females, although a statistically significant ($p=0.01$) but weak negative correlation (-0.075) was observed for males for decrease from baseline in QTc and increased plasma concentration.

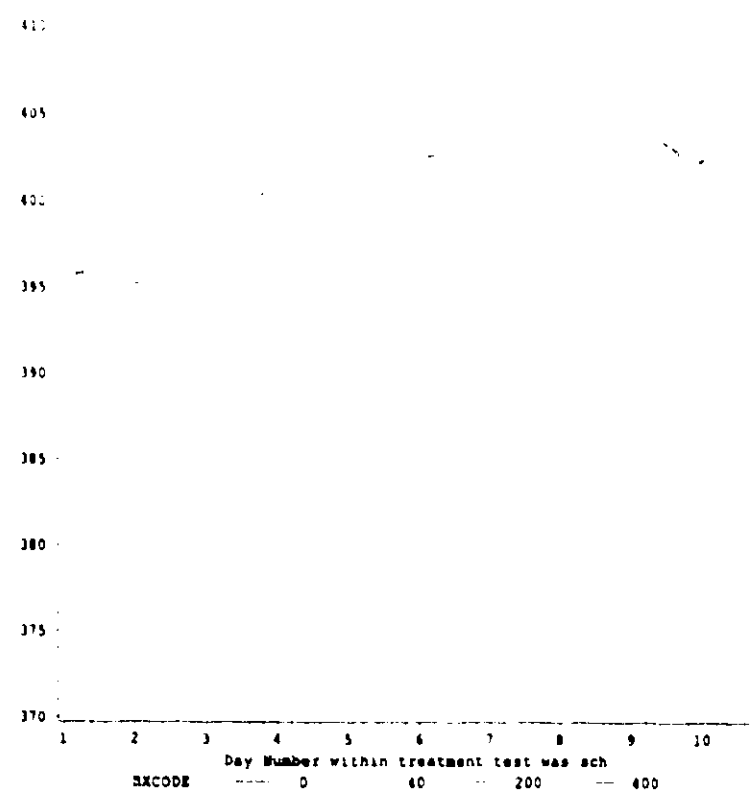
Reviewer's Determinations

- 1) Based on both Morganroth databases and the machine read database, no statistically significant difference was observed for change from baseline between any fexofenadine dose and placebo for either mean daily QTC or mean daily maxima QTC measurements. The largest observed difference between fexofenadine and placebo for change from baseline to Day 8 for mean daily QTC was 3.2 ± 2.8 msec. for the 400mg dose (first Morganroth data).
- 2) Fexofenadine appears to be well tolerated at doses of 40mg, 200mg, and 400mg Q12H for 8 days in healthy normal males and females.
- 3) The observance of liver enzyme elevations to outlier criteria in two subjects will need further comparison to the larger overall database.
- 4) There was a slight disproportionate increase in fexofenadine pharmacokinetic parameters over the 10 fold dosing range for: AUC_{ss(0-12h)}, C_{max,ss}, and A_e.
- 5) Across treatments, females had AUC_{ss} 33%, C_{max,ss} 46% and A_e 33% greater than males.
- 6) No examination of the relationship between plasma concentrations and change in QTC was conducted because of the apparent lack of treatment effect on QTC. The sponsor has been asked on March 13, 1996 to conduct such an examination, particularly for any possible differences in response by gender because of the pharmacokinetic differences between gender and the small apparently greater effect that the 400mg dose may be having in females compared to males that was observed on the attached graphs.
- 7) The sponsor indicates on page 60 of the report that 6,850 ECGs were used in the analysis; 6880 ECGs (43 per period per subject) would have been collected if all planned ECGs were obtained. The sponsor should be asked to clarify the apparent ECG discrepancy since only 6,837 would have been used if dropout ECGs were not used.

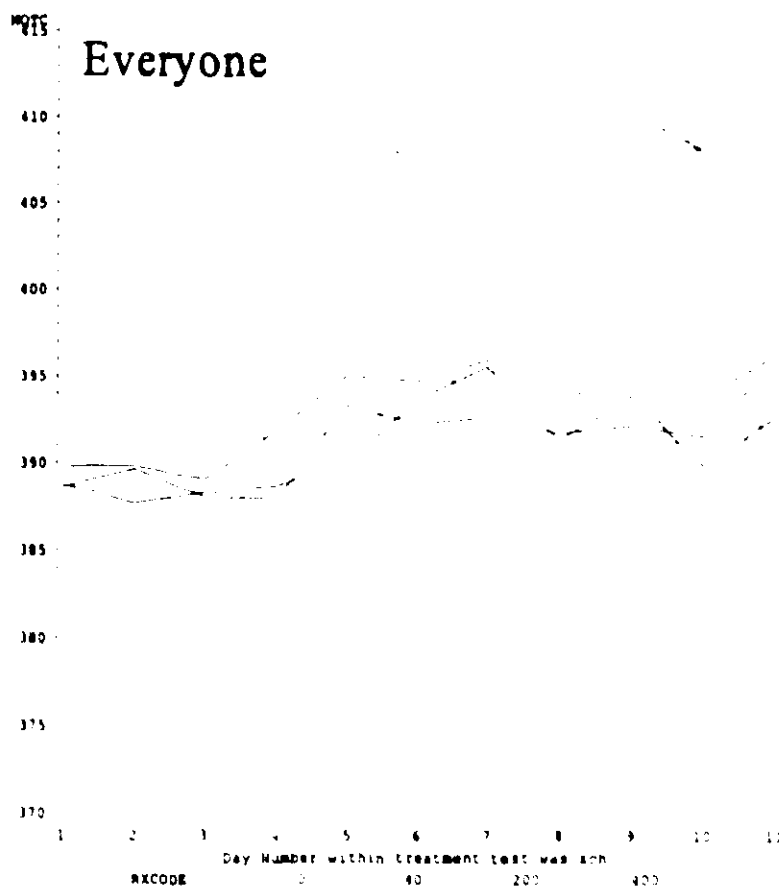
Males



Females



Everyone



Medical Officer Review

Reviewer: Michael J. Sevka, M.D.
Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**
Sponsor: Hoechst Marion Roussel, Inc.
Date NDA Submitted: July 31, 1995
Material Reviewed: Protocol PJPR0003 from NDA 20-625

Protocol No. PJPR0003 - conducted from June 1993 to November 1993 in Leeds, England

Title

"Subchronic Dose Tolerance Study of MDL-16,455A in Healthy Male Subjects"

Objectives

- (1) "establish the maximum tolerated multiple, oral dose of MDL 16,455A in order to define the human dose range";
- (2) "characterize the safety profile of multiple, oral doses of MDL 16,455A over the human dose range";
- (3) "characterize the multiple dose pharmacokinetics of MDL 16,455A over the human dose range";
- (4) "characterize the multiple dose pharmacodynamics of antihistaminic activity of MDL 16,455A over the human dose range using skin wheal and flare inhibition."

Study Design

This study was a double-blind (but sponsor unblinded), placebo controlled, parallel, randomized, dose escalating (8 dose levels), design conducted in 32 healthy males (4 per dose level) who were between 18 and 55 years of age. On Day 1 all subjects received a single dose of placebo. On Days 2 through 29, at each dose level three subjects received MDL-16,455A and one received placebo every 12 hours. On Day 30, each subject received their final dose at 8AM. Each dose level was assessed for safety and tolerance prior to dose escalation. Different subjects were enrolled for each dose level. All drug administrations and study procedures were conducted in a clinical facility.

Treatments

MDL-16,455A was administered from a stock oral solution prepared by a pharmacist who dissolved it in 1.5% glacial acetic acid in propylene glycol at the clinic. It had an expiration date set at 72 hours following preparation. Study treatments were administered by unit dose oral syringes filled at the clinic and followed by 240ml of water. Doses up to and including 520mg were administered as 4ml; the 690mg dose was administered as 6ml. Corresponding volumes of diluent were administered as placebo. Dose levels tested were: 20mg, 40mg, 80mg, 160mg, 260mg, 390mg, 520mg, and 690mg.

Study Measurements

ECGs:

Serial 12-lead electrocardiograms (ECGs) were obtained -

-- prior to and for 72 hours after the final dose on Day 30 (0, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72 hours);

-- prior to and for 12 hours after the morning dose on Days 2, 8, 15 and 22 (0, 1, 2, 3, 4, 6, 8, 12 hours);

-- prior to and for 18 hours after placebo treatment on Day 1 (0, 1, 2, 3, 4, 6, 8, 12 and 18 hours);

A single ECG was obtained at -

-- 3 hours after the morning dose on Days 3-7.

-- prior to and 3 hours after the morning dose on Days 9-14, 16-21 and 23-29.

Plasma Samples:

-- Serial blood samples were collected prior to and for 72 hours after the last dose on Day 30 (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours);

-- trough blood samples were collected prior to the morning dose on Days 6, 7, 8, 28 and 29 (pre-dose Day 30 sample is another trough);

-- a pre-dose (placebo) blood sample was obtained on Day 1.

Urine Samples:

Urine samples were collected from 0 - 12 hours around the morning treatment administration times on Days 1, 2 and 30.

Wheal and Flare Measurements:

Serial wheal and flare areas were measured for -

-- prior to and for 72 hours after the final dose on Day 30 (0, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72 hours);

-- prior to and for 12 hours after the morning dose on Days 2, 8 and 22 (0, 1, 2, 3, 4, 6, 8, 12 hours);

-- prior to and for 18 hours after treatment on Day 1 (0, 1, 2, 3, 4, 6, 8, 12 and 18 hours).

Safety Measurements:

All subjects were monitored by lead-II telemetry from Day 1 to Day 8. Vital signs were measured three times a day throughout the study. Clinical laboratory measurements were conducted on Days 1, 8, 15, 22 and 33. Reports of adverse events were collected.

Subject Inclusion Criteria

- healthy, nonsmoking males between the ages 18 and 55 years and not more than 15% from the ideal weight and age
- no clinically significant abnormalities before study initiation for the following: medical history, physical exam, clinical laboratory measurements, ECG, 24 hour Holter monitor, screens for hepatitis B, HIV and urine drug
- histamine wheal area must be approximately two times subject's own saline wheal area

Subject Exclusion Criteria

- potential for hypersensitivity to MDL 16,455A
- significant organ abnormality or disease
- treatment with either prescription or nonprescription (OTC) medication within 14 days of trial initiation
- hepatic or renal clearance altering agents (eg, erythromycin, cimetidine, barbiturates, phenothiazines, etc) within 30 days of study initiation
- ketoconazole or itraconazole within three months of study initiation
- astemizole (Hismanal®) within six months of study initiation
- QTc interval of greater than 440 msec or with any underlying conditions known to prolong the QTc
- a flare area greater than 2 cm² after intradermal injection with normal saline.
- donated blood or participated in another drug study within 30 days

Results - Patient Accounting

Thirty-two subjects were enrolled and 31 completed the study. One subject (#0019) who was on placebo was withdrawn by the investigator on Day 2 due to an abnormal ECG which were later deemed artifactual from electrode movement.

Results - Pharmacokinetic Parameters

A selected table and graphs from the submission are reproduced below which summarize the pharmacokinetic results from this study. AUC_{ss} generally increase with dose and suggest dose proportionality in the range of 20mg to 260mg. The sponsor also reports that the average cumulative percent of dose excreted in urine at steady state ranged from 5.5% to 17.6% over the dose range.

Table 8-111. MDL 16,455 Plasma Pharmacokinetic Parameters Following Administration of Multiple Oral Doses of MDL 16,455A								
Dose Q12 h (mg)		C _{max,ss} (ng/mL)	T _{max,ss} (h)	C _{min,ss} (ng/mL)	AUC _{ss} (h·ng/mL)	C _{max} /C _{min} Ratio	CL _{ss} (L/h)	Half-Life (h)
20	Mean	57.91	1.17	4.62	288.08	6.90 ^a	85.30	.6
	SD	34.43	0.78	8.00	188.86	-	55.23	-
	%CV	59.45	65.47	173.21	58.26	-	64.87	-
40	Mean	212.57	0.83	16.53	1036.89	14.23	41.73	.6
	SD	180.68	0.58	5.84	488.48	12.22	18.99	-
	%CV	73.18	69.28	34.14	47.12	85.88	45.51	-
80	Mean	327.03	1.33	32.73	1728.07	10.10	43.33	.6
	SD	41.74	0.29	4.18	112.04	1.62	2.71	-
	%CV	12.76	21.65	12.72	6.49	16.02	6.26	-
160	Mean	785.30	1.17	61.33	3529.99	12.52	43.44	10.53
	SD	303.32	0.29	7.46	724.21	3.48	6.72	7.31
	%CV	38.62	24.74	12.15	20.52	27.79	20.08	69.41
260	Mean	1588.97	1.00	88.87	6417.78	16.07	38.74	12.41
	SD	382.52	0.00	13.82	1618.31	2.78	11.70	8.81
	%CV	25.05	0.00	14.27	25.23	17.18	29.44	70.99
360	Mean	3389.13	1.00	180.47	14899.17	17.06	29.53	12.11
	SD	544.30	0.00	13.93	2891.86	2.08	5.56	2.33
	%CV	16.18	0.00	7.32	19.73	11.83	21.84	19.23
520	Mean	3074.83	1.00	204.07	12438.18	14.13	48.54	12.82
	SD	2306.88	0.00	115.80	7843.25	3.53	23.83	4.83
	%CV	74.88	0.00	56.81	61.48	24.99	48.31	36.13
680	Mean	4877.07	1.17	289.57	21708.33	17.51	31.83	8.80
	SD	880.87	0.29	151.77	7408.64	8.32	9.78	3.16
	%CV	20.97	24.74	50.88	34.13	36.08	30.87	35.93

^a C_{max}/C_{min} ratio reportable for one subject only.
^b Could not be accurately determine due to assay sensitivity.

Supporting Data: Appendix A1: Plasma Page 58-VI.143-P89

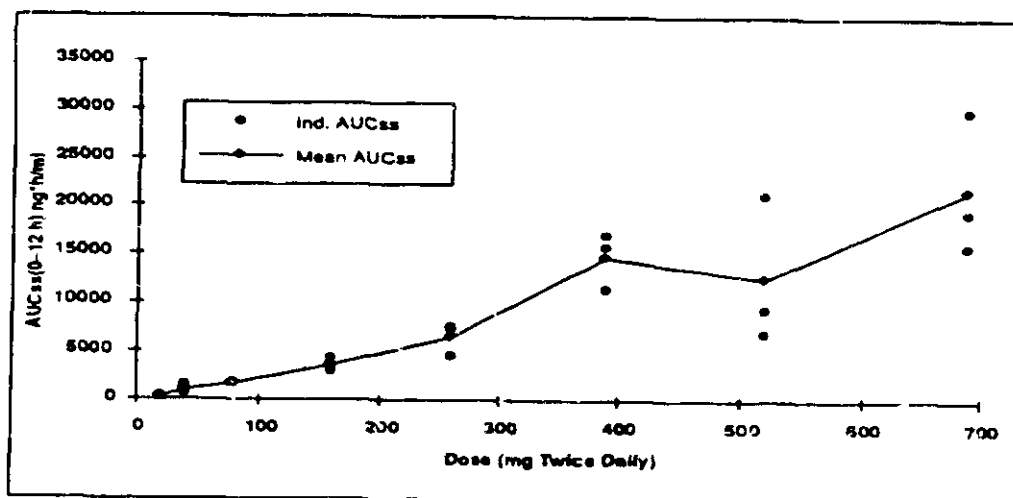


Figure 8-39. Individual and Mean AUC_{ss}(0-12 h) Versus MDL 16,455A Dose

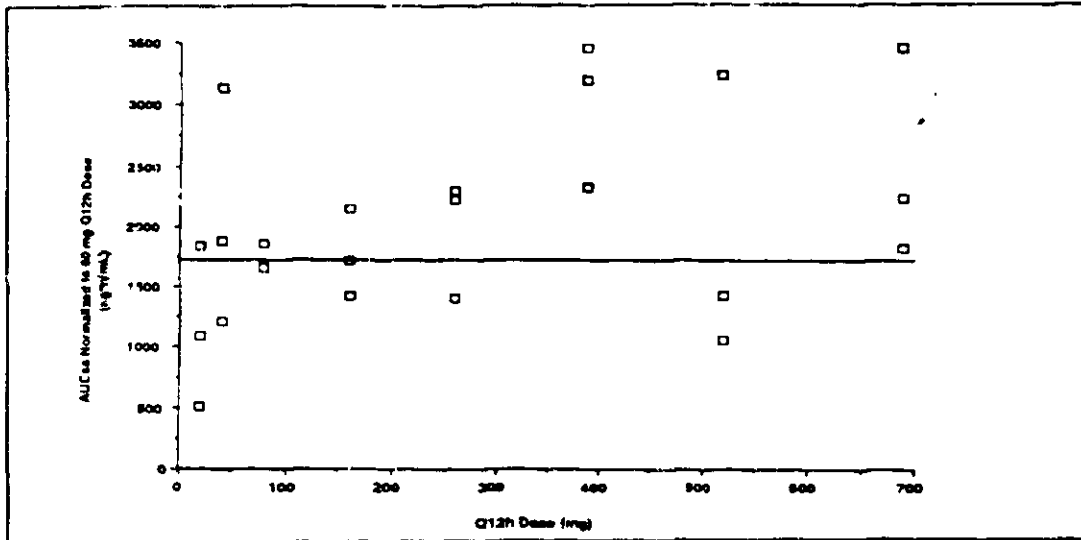


Figure 8-40. Individual MDL 16,455 AUC_{0-12h} Values Normalized to 80 mg Twice Daily

Supporting Data:
Appendix A1: Plasma

Page
S8-V1.143-P89

Results - Pharmacodynamic Parameters - Wheal

A selected table and graph from the submission are reproduced below which summarize the pharmacodynamic results for wheal from this study. The sponsor reports that at trough (i.e. 12 hours after the last dose) the mean percent change in wheal area from baseline was inhibited by 25% to 67% at doses 160mg or greater, but close examination of the table seems to indicate a range of 22% to 66%. Further examination of Table 8-114 at other doses such as 20mg to 80mg shows considerable variability of these data across doses and over the dosing interval. Although supportive of drug activity, these data do not quantify the effect well. Note: CHG1 refers to point-adjusted means - the percent difference between corresponding time points of the treatment day and Day 1 measurements.

Table 8-114. Mean Percent Change (CHG1) in Wheal Area From Baseline Measurements Following Twice Daily Administration of MDL 18,455A

CHG1(160-d1)									
Time (h)	Placebo (N=8)	20 mg (N=3)	40 mg (N=3)	80 mg (N=3)	160 mg (N=3)	280 mg (N=3)	380 mg (N=3)	520 mg (N=3)	880 mg (N=3)
0	-0.056	-14.488	-46.842	-18.908	-53.984	-22.037	-46.213	-61.747	-29.902
1	27.436	5.500	-48.383	-82.482	-54.818	-33.653	-89.714	-70.484	-59.448
2	34.001	-34.988	-58.422	-44.774	-7.088	17.438	-70.122	-33.361	-40.482
3	12.445	-24.291	-58.371	-33.027	-73.428	-38.227	-63.101	-80.745	-30.811
4	15.980	-18.808	-8.388	-42.480	-23.577	-1.828	-57.130	-53.324	-34.263
6	17.838	-8.388	-33.530	-34.467	-31.408	8.487	-53.730	-88.535	-49.878
8	44.985	-36.968	-32.867	-5.588	17.528	-38.102	-80.480	-50.583	-7.888
12	4.825	7.211	-20.338	-4.073	-38.071	-25.728	-71.008	-58.971	-58.482
CHG1(800-d1)									
Time (h)	Placebo (N=8)	20 mg (N=3)	40 mg (N=3)	80 mg (N=3)	160 mg (N=3)	280 mg (N=3)	380 mg (N=3)	520 mg (N=3)	880 mg (N=3)
0	5.318	0.210	-46.362	-3.908	-73.086	-42.412	-33.034	-87.281	-48.190
1	-27.218	1.403	-27.108	-42.378	-84.044	2.908	-28.881	-82.111	-88.814
2	48.108	-28.088	-34.077	-43.316	-82.738	37.188	-88.828	-86.007	-73.117
3	10.188	-23.827	-34.015	-51.131	-67.420	-38.320	-88.301	-28.888	-88.388
4	8.252	31.313	-14.088	-58.777	-67.384	-33.880	-88.871	-71.423	-88.441
6	20.237	53.875	-43.728	-58.448	-33.570	-18.848	-57.180	-38.838	-88.788
8	24.848	-18.441	88.874	-18.088	24.784	-22.288	-80.388	-73.288	-84.828
12	-8.118	-4.174	-38.081	-11.288	-88.832	-38.003	-44.887	-58.320	-48.888
18	-18.241	4.328	-41.808	0.708	-53.343	-18.520	-32.802	-38.182	-78.385
24	15.088	-54.981	-8.885	-30.883	-22.820	-29.333	-22.035	-38.247	-88.323

Supporting Data: Appendix A: Skin Wheal Area Page 58-V1.143-P187

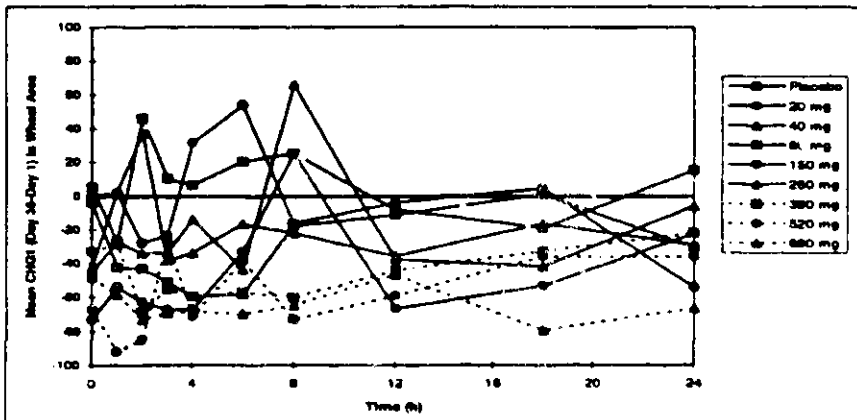


Figure 8-43. Mean Percent Change in Wheal Area on Day 30 From Baseline (Day 1) During Twice Daily Treatment with MDL 18,455A or Placebo: All Doses

Results - Pharmacodynamic Parameters - Cardiac Conduction

The sponsor reports the results of the analyses of QTc measurements as daily means of absolute values and as daily means of changes from baseline. These analyses are reported using the QTc values as read by Dr Joel Morganroth, an independent consultant, and as measured by the ECG machine. The sponsor indicates that the database generated by Dr Morganroth was constructed from blinded readings of ECG of intervals. These data were summarized in tabular and graphic form, reproduced below.

Morganroth Database:

Examination of these data shows that the absolute mean QTc was ≥ 400 msec only in 4 cells, at the 80mg on Days 1, 22 and 30 and for the 260mg level at Day 22 with the highest QTc value 405 msec on Day 30 for the 80mg level. Examination of these data also shows that the absolute mean QTc change was ≥ 10 msec only in 2 cells, at the 40mg on Days 22 (16.4msec) and 30 (14.2 msec). Although the sponsor provides a statistical significance value for comparison of all doses versus placebo, it is misleading to place confidence in this value since the numbers of subjects is relatively small per cell for detecting a statistically significant difference in a parameter such as QTc which shows broad variance. Nonetheless, the graphic display of the data shows that no apparent increase or trend in QTc interval increase can be observed compared to placebo over a broad range of doses from 20mg to 690mg. The observation of an apparent increase in the 80mg dose level can not be considered a real finding since it occurred on all days including baseline, suggesting that this is subject related rather than treatment related.

Dose (mg)	Day 1		Day 2		Day 8		Day 15		Day 22		Day 30	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Placebo (N=8)	384.6	4.5	377.9	5.1	379.9	5.2	384.9	5.6	382.1	5.4	382.3	4.9
20 (N=3)	382.8	9.4	377.3	9.2	378.5	8.7	384.5	9.2	379.1	10.7	388.9	10.2
40 (N=3)	379.7	11.0	375.4	7.9	383.0	10.1	375.4	15.1	388.1	12.4	383.9	12.9
80 (N=3)	402.0	1.1	385.2	0.8	398.7	2.5	388.2	4.6	400.8	5.5	405.0	4.9
160 (N=3)	385.7	5.0	384.7	5.4	389.9	5.1	391.3	5.5	397.9	10.8	386.8	2.7
260 (N=3)	386.8	3.0	380.8	4.1	386.4	2.8	391.6	6.3	400.0	5.3	386.1	3.5
380 (N=3)	374.0	17.0	369.5	13.6	382.2	10.8	373.1	5.3	379.3	4.5	378.5	3.0
520 (N=3)	387.9	11.7	384.3	9.1	379.0	7.4	391.4	9.6	395.9	14.0	384.6	8.8
690 (N=3)	381.9	2.5	383.2	2.3	380.2	5.3	384.5	3.3	390.6	3.0	385.9	6.6

Supporting Data: Appendix C4 e.3: Mean QTc Readings (Morganroth)

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Dose (mg)	Day 2		Day 8		Day 15		Day 22		Day 30	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Placebo (N=8)	-6.7	3.5	-4.7	2.8	0.1	3.5	-2.8	3.5	-2.6	4.5
20 (N=3)	-5.5	3.6	-4.3	2.7	1.7	1.8	-3.7	1.5	4.1	2.5
40 (N=3)	-4.3	4.0	3.2	5.2	-4.4	5.9	16.4	10.1	14.2	10.4
80 (N=3)	-6.8	1.3	-5.4	3.6	-3.9	5.8	-1.2	6.5	3.0	5.6
160 (N=3)	-1.1	3.8	4.2	1.2	5.6	1.8	12.2	5.9	1.1	4.2
260 (N=3)	-6.0	6.7	-0.4	5.8	-1.2	9.0	3.3	8.1	-0.7	6.4
360 (N=3)	-4.5	4.2	8.2	11.6	-0.2	15.7	5.3	17.0	4.5	17.5
520 (N=3)	-3.6	7.1	-8.9	6.3	3.5	5.9	6.0	5.8	6.8	3.1
660 (N=3)	1.3	1.3	-1.7	3.8	2.6	2.9	8.6	4.5	4.0	9.0

Dose Response P-value=0.3838

Comparison of All Doses Versus Placebo P-value=0.2630

Supporting Data: Page

Appendix C4.a.3: Mean QT_c Readings (Morganroth) S8-V1.146-P218

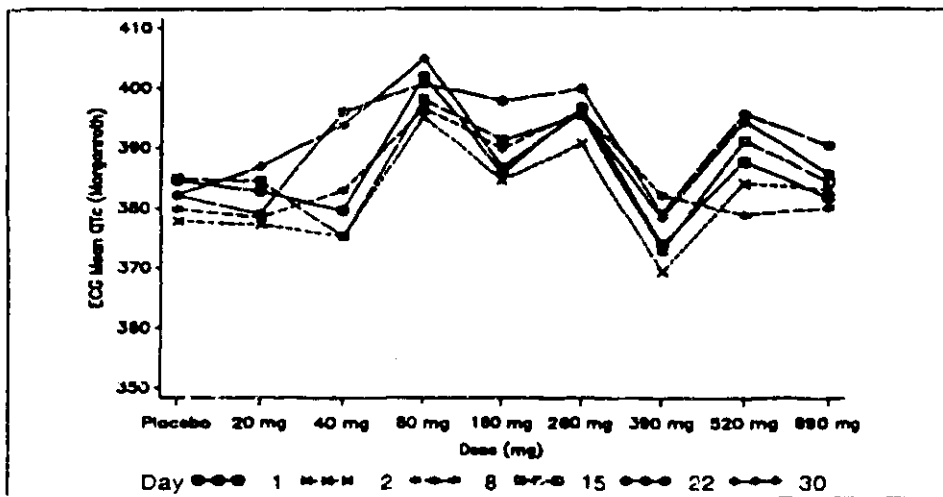


Figure 8-52. Mean QT_c (Morganroth Read) as a Function of Dose

Supporting Data:	Page
Appendix C4.a.1: Morganroth ECG Listing	S8-V1.146-P146
Appendix C4.a.2: Morganroth ECG Means and Standard Errors - QT _c	S8-V1.146-P209

Machine Read Database:

Examination of these data affirms the findings observed with the Morganroth data and shows that the absolute mean QTc was ≥ 400 msec only in 2 cells, at the 80mg on Days 22 and 30 with the highest QTc value 401.6msec on Day 30 for the 80mg level. Examination of these data also shows that the absolute mean QTc change was ≥ 10 msec only in 1 cell, at the 690mg on Day 22 (10.3msec). The same caution in interpreting the statistical significance value applies as it did for the Morganroth data. The graphic display of these data is similar to that of the Morganroth data.

Dose (mg)	Day 1		Day 2		Day 8		Day 15		Day 22		Day 30	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Placebo (N=8)	374.7	2.9	370.0	2.3	371.7	3.1	379.2	3.6	375.3	2.2	375.9	2.8
20 (N=3)	377.2	7.1	379.5	3.8	378.4	4.8	382.4	2.8	380.1	2.3	381.9	2.3
40 (N=3)	370.7	11.9	366.0	7.9	371.6	8.6	366.3	9.2	376.8	8.1	375.7	10.0
80 (N=3)	387.1	2.8	382.8	3.1	384.9	1.7	384.8	1.2	401.5	1.7	401.6	4.2
160 (N=3)	380.5	3.2	372.9	6.1	379.8	4.5	380.8	6.6	387.4	10.3	379.1	3.4
260 (N=3)	374.1	2.3	372.6	3.2	377.5	1.6	378.5	3.1	382.7	4.9	377.9	3.0
360 (N=3)	372.4	3.3	371.4	4.5	376.3	1.4	375.8	3.0	379.2	2.5	377.4	3.1
520 (N=3)	384.1	10.8	378.8	11.2	380.1	7.9	384.9	9.3	389.5	10.8	388.6	10.8
690 (N=3)	372.5	1.9	374.5	1.4	376.0	4.2	379.8	6.3	382.8	4.0	379.0	1.2

Supporting Data: Appendix C4.b.6: Mean QT_c Readings (Machine)

Page
S8-V1.146-P281

Table 8-130. QTc Mean Changes, Standard Errors (Machine)

Dose (mg)	Day 2		Day 8		Day 15		Day 22		Day 30	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Placebo (N=8)	-4.7	1.4	-3.0	2.5	3.1	2.8	-0.9	2.2	-0.2	1.7
20 (N=3)	2.4	3.4	1.2	3.7	5.2	5.2	2.9	5.5	4.7	4.8
40 (N=3)	-4.7	4.2	0.9	6.0	-4.4	7.2	6.1	3.9	4.3	5.9
80 (N=3)	-4.5	2.1	-2.2	4.0	-2.4	3.8	4.4	4.3	4.5	5.5
160 (N=3)	-7.6	4.8	-0.7	4.0	0.3	4.9	6.9	7.2	-1.4	0.7
260 (N=3)	-1.5	1.0	3.3	2.7	4.3	1.7	8.6	3.5	3.8	1.5
360 (N=3)	-1.0	1.5	3.9	3.6	3.4	2.9	6.8	4.1	5.0	5.5
520 (N=3)	-5.4	4.5	-4.0	4.2	0.8	3.6	5.4	2.2	4.5	0.9
890 (N=3)	1.9	2.5	3.5	5.0	7.2	7.8	10.3	4.8	6.5	0.7

Dose Response P-value=0.1063
 Comparison of All Doses Versus Placebo P-value=0.1030

Supporting Data: Page
 Appendix C4.b.8: Mean QTc Readings (Machine) S8-V1.146-P281

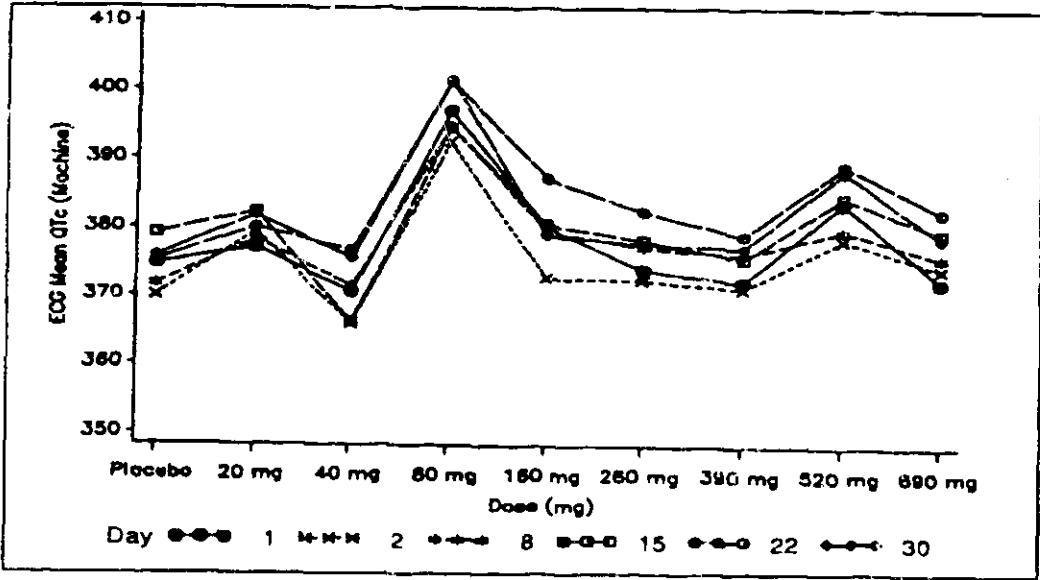


Figure 8-53. Mean QTc (Machine Read) as a Function of Dose

Clinical Laboratory Assessments:

Each subject had six laboratory measurements obtained over the course of the trial. The sponsor considered the first laboratory value drawn before the first dose as the pre-treatment measurement and the one drawn at Day 33 (3 days after the last dose) at the post-treatment measurement. The sponsor reports that the mean values were generally unremarkable except for SGPT (nl - 10-49 IU/L) with the 160mg dose group showing the largest change 16.3 IU/L to 40.0 IU/L. Examination of the tables in Appendix C.2.a.4 shows that 6 subjects (2- placebo; 1 each on 80mg, 160mg, 520mg, 690mg) had normal to abnormal changes in SGPT by the end of the trial with the highest absolute value of 77 IU/L for any day for these subjects and the largest change from baseline being 14 IU/L to 52 IU/L. Two other subjects met outlier criteria for SGPT (160mg - 25 to 126 IU/L; 260mg - 38 to 128 IU/L).

Also noted in the list of outlier values are bicarbonate (18 subjects - 2-placebo; 14 elevations, 4 reductions) and chloride (12 subjects - 2-placebo; all reductions). Although noted it is difficult to ascribe these changes to active treatment. The sponsor was asked on March 6, 1996 to address these observed changes. The sponsor responded by submission dated April 1, 1996 in which a table indicating the frequency of low chloride and high bicarbonate outliers was provided by fexofenadine dose. No obvious dose related effect could be observed with 12.5% placebo response for bicarbonate and 37.5% placebo response for chloride. The sponsor points out that the observed rates in PJPR0003 are inconsistent with outlier rates in other large placebo controlled trials and that it is unclear why the higher frequency was observed for PJPR0003.

Vital Signs:

The sponsor reports that no consistent trends with increasing dose were observed for any of the vital signs.

Reviewer's Comments

Although the number of subjects assigned to each dose level is small (i.e. 3), Protocol PJPR0003 provides important relative comparisons of fexofenadine across a broad range of doses (i.e. from 1/3 to 11 times the proposed dose) and supports the safety profile of fexofenadine.

At the request of the Agency the sponsor provided by FAX on 3/4/96, the ECGs time points actually used in computing daily QTc means. For this study report they were:

- Day 1: 0hr to 12hr;
- Day 2: 0hr to 12hr plus 18hr from Day 1;
- Days 8, 15 and 22: 0hr to 12hr;
- Day 30: 0hr on Day 30 to 72hr Day 33.

In this communication, the sponsor indicates that, for this study report, the Day 1 - 18hr value was incorrectly included in the computation for the Day 2 mean instead of the Day 1 mean. Similarly, the sponsor indicates that the Day 30 mean for this report incorrectly included values from Days 31-33. Additionally, the sponsor indicates that baseline ECG values from subject #19 (placebo), who was withdrawn, were used to calculate the baseline mean for this study report. In the integrated summary of safety the sponsor provides reanalysis of these data which corrects the three concerns described above. However the reanalysis provides only the mean QTc change from baseline for Morganroth data (Table 8-627; S8-V1.262-P289). I have compared the reanalyzed results to the results of the flawed analysis from Tables 8-127 and 8-128, reproduced in this review, and have found that the largest

increase in mean QTc change from baseline, across all doses for Days 8, 15, 22 and 30, was 3.3msec (1.1msec to 4.2msec) for the 160mg dose at Day 30. Although these changes in the results are small, a full reanalysis of the Morganroth data and machine read data including analyses of daily mean maxima data and outliers should be submitted to the NDA because this is an important safety issue which needs adequate safety support. The sponsor has been asked to submit these analyses to the NDA by telecon on March 15, 1996. The sponsor provided a response by submission dated April 1, 1996. Since only the results from data computed for Days 1 and 30 would be expected to change, examination of the Morganroth and machine read data do not change the determinations made from the data submitted in the original NDA.

Reviewer's Determinations

- 1) Fexofenadine administration for 29 days in doses ranging from 20mg Q12H to 690mg Q12H are well tolerated in healthy adult males, although headache may occur somewhat more frequently at doses above 260mg Q12H.
- 2) The results from this study do not suggest that fexofenadine prolongs QTc intervals in the doses administered during this trial.
- 3) Because of the importance of these safety data, it merits a reanalysis of the ECG data using optimal ECG time points for the calculation of the mean daily data.
- 4) Pharmacokinetic results show that the AUCs generally increases with dose and suggests dose proportionality in the range of 20mg to 260mg; the average cumulative per cent of dose excreted in urine at steady state ranges from 5.5% to 17.6%.
- 5) The observance of small elevations in SGPT values and a number of outlier values for bicarbonate and chloride will need confirmation in other trials.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Reviewed: **Protocol PJPR0018** - conducted from October 1994 to November 1994

Title

"Effect of Erythromycin on the Pharmacokinetics of MDL-16,455A."

Objectives

"The primary objective of the present study is to examine the pharmacokinetics of MDL-16,455A when administered alone and in combination with steady-state erythromycin administration."

Secondary Objectives:

1. "To examine the pharmacokinetics of erythromycin when administered alone and in combination with MDL-16,455A."
2. "To characterize the effects on QTc when MDL-16,455A is administered in combination with erythromycin. This effect will be compared to the interaction effect observed in previous terfenadine studies."

Study Design

The study was an open-label, randomized three-way complete crossover (9 days per period with at least 10 day washout) in 24 healthy non-smoking males, 18-45 years of age.

Study Treatments

- Treatment A: Multiple dose oral administration of 120 mg (2x60 mg capsule) MDL 16,455A Q12h under fasted conditions for 6.5 days (total of 13 doses).
- Treatment B: Multiple dose oral administration of 500 mg Q8h erythromycin for 6.33 days (total of 19 doses).
- Treatment C: Concomitant multiple dose oral administration of 120 mg (2x60 mg capsule) MDL 16,455A Q12h under fasted conditions for 6.5 days (total of 13 doses) and 500 mg erythromycin Q8h for 6.33 days (total of 19 doses).

Blood Sample Collection

Treatment A - predose and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours after MDL 16,455A administration on Day 7.

Treatment B - predose and at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose on Day 7.

For Treatment C -

---For MDL 16,455 analysis - predose and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours after MDL 16,455A administration on Day 7.

---For erythromycin analysis will be collected at 0, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after the morning dose of erythromycin on Day 7.

For trough levels -

--- Two separate for trough analysis on Days 5 and 6 before the morning dose for all treatments.

ECG Measurements

Day 0 (no drug dosing) and Day 7 (steady state) - 0700, 0900, 1100, 1300, 1500, 1900 hours

Day 8 and 9 at 0700 hours

Days 1-6 for treatment C only - at 0900, 1300 and 2100 hours - collected only for safety and not pharmacodynamic effect

Drug Administration

MDL-16455A: 0700hr and 1900hr on Days 1-7; final dose at 0700hr on Day 8

Erythromycin: 0700hr, 1700hr and 2300hr on Days 1-7

No Drug Administration on Day 0

Safety Measures

Pre- and post study laboratory blood tests and physical examinations

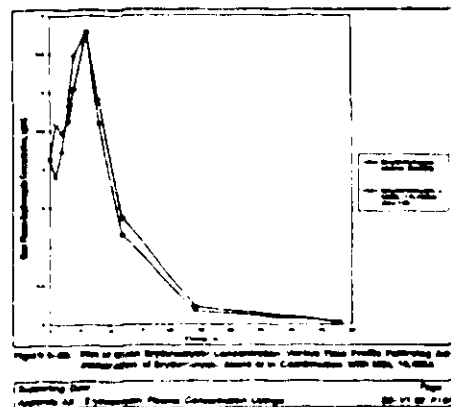
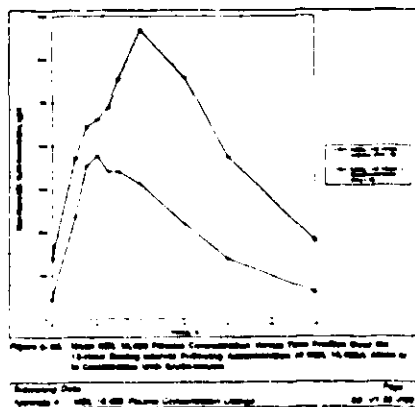
Results - Patient Accounting

- 24 enrolled
- 18 received Treatment A
- 20 received Treatment B
- 19 received Treatment C
- 18 completed the study

Two patients (subject #0005 on period 1 and subject #0021 on period 2 had abnormal ECGs on Day 0) were excluded from the study. Three subjects left for personal reasons and one other failed to report back to clinic.

Results - Pharmacokinetic Parameters

The sponsor summarizes the pharmacokinetic results in tabular and graphic form, reproduced below. From these results AUC_{0-12hr} and C_{max,ss} are noted to increase by 203% and 180%, respectively, when the two drugs are administered concomitantly. A graph of plasma erythromycin concentrations shows that erythromycin pharmacokinetics are not influenced by concomitant administration. As with ketoconazole the slopes from the graphic presentation do not appear to differ substantially. The sponsor suggests that the mechanism for the interaction would not be from an alteration in the elimination of MDL-16,455A.



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4 OF 7

Table 6-320. Mean Plasma Pharmacokinetic Parameters and Treatment Comparisons for MDL 16,455								
Parameter	Trmt	Mean	%CV	Adjusted Mean	Pairwise Comparison			
					Pair	Ratio (%)	90% CI	P Value
AUC _{0-12h} (h·ng/mL)	A	2421.72	28.02	2357.69	-	-	-	-
	C	8064.94	34.81	4786.12	C/A	203.58	(181.9,227.4)	<0.001
CL _{po}	A	50.36	34.15	47.45	-	-	-	-
L/h	C	24.75	35.12	23.33	C/A	48.17	(44.0,55.0)	<0.001
C _{max,ss} ng/mL	A	409.74	34.42	393.83	-	-	-	-
	C	743.89	32.89	710.52	C/A	180.37	(159.7,203.7)	<0.001
t _{max,ss} h	A	2.2	42.63	2.31	-	-	-	-
	C	3.7	30.90	3.51	C/A	174.71	(143.1,213.2)	<0.001

Treatment A=MDL 16,455A 120 mg Q12h
 Treatment C=MDL 16,455A 120 mg Q12h + Erythromycin 500 mg Q6h

Supporting Data: Page
 Appendix A3: MDL 16,455 Plasma Pharmacokinetic Parameter Listings 98-V1.62-P93
 Appendix B2: MDL 16,455 Pharmacokinetic Parameters: Treatment Comparisons 98-V1.62-P142

Results - Pharmacodynamic Parameters - QTc Measurements

The sponsor provides a summary of results of QTc analyses in tabular form, reproduced below. No statistically significant differences were noted for any comparison of change from Day 0 to Day 7 are noted. The combined treatment is noted to produce a mean increase from baseline of 1.6 ± 2.5 msec.

Table 6-320. Change From Baseline in Mean and Maximum QTc. Morganroth Read ECG Data					
Mean QTc					
Treatment	N ^a	Day 0 mean ± SE	Day 7 mean ± SE	Change from Day 0 to Day 7 mean ± SE	P value †
MDL 16,455A	19	382.7 ± 5.0	389.0 ± 5.6	-6.6 ± 3.3	.1793
Erythromycin	20	381.4 ± 4.9	383.6 ± 5.0	2.2 ± 2.4	.3839
MDL 16,455A + Erythromycin	19	381.0 ± 5.4	382.6 ± 5.6	1.6 ± 2.5	.8286
Maximum QTc					
Treatment	N ^a	Day 0 mean ± SE	Day 7 mean ± SE	Change from Day 0 to Day 7 mean ± SE	P value †
MDL 16,455A	18	412.7 ± 5.6	407.0 ± 5.8	-5.6 ± 4.1	.1848
Erythromycin	20	412.1 ± 4.7	414.8 ± 5.5	2.0 ± 4.4	.5776
MDL 16,455A + Erythromycin	19	414.3 ± 4.8	412.0 ± 5.8	-2.3 ± 4.1	.5810

^a N=24 subjects began the study, 6 subjects withdrew prior to completion.
[†] P value from t-test of change from Day 0 to Day 7 equals 0.

Supporting Data: Page
 Appendix C5: Electrocardiograms 98-V1.63-P1

The sponsor also provides a table comparing the results from this study to the results from 2 others in which terfenadine was administered concomitantly with erythromycin using a different multiple dose study design, but nonetheless showing a marked increase in average QTc mean (11.7 ± 4.8 msec; 25.2 ± 2.6 msec) when the combination was administered.

Table 6-327. Comparison of Terfenadine and MDL 16,455A in Change From Baseline in QTc, When Administered Concomitantly With Erythromycin

Protocol/Treatment	Average QTc Mean ± SE	95% Confidence Interval
9918-1-C-18J / Erythromycin Alone (N=12)	3.3 ± 3.9	(-5.3, 11.9)
Terfenadine Alone (N=12)	0.5 ± 4.1	(-6.5, 9.5)
Erythromycin Plus Terfenadine (N=12)	11.7 ± 4.8	(1.1, 22.2)
SEPR0022 / Erythromycin Alone (N=14)	6.3 ± 1.5	(3.1, 9.5)
Terfenadine (N=15)	0.6 ± 2.3	(-4.3, 5.5)
Erythromycin Plus Terfenadine (N=13)	25.2 ± 2.6	19.5, 30.9)
PJPR0018 / Erythromycin Alone (N=20)	2.2 ± 2.4	(-2.6, 7.2)
MDL 16,455A Alone (N=18)	-4.6 ± 3.3	(-11.6, 2.4)
Erythromycin Plus MDL 16,455A (N=19)	1.6 ± 2.6	(-3.7, 6.9)

Supporting Data: *Table 6-326. Change From Baseline in Mean and Maximum QTc. Morganroth Read ECG Data.* Page S6-V1.82-P50

The sponsor reports that 6 subjects had one or more outlier QTc. Outlier was defined as QTc > 440msec with > 10msec increase from baseline. One of these subjects had outlier value on MDL-16,455A alone and 5 subjects had outlier values on combination treatment and 4 subjects had outliers on erythromycin alone. The highest value noted is 459msec during combination treatment.

Table 6-328. Listing of Outlier QTc and/or Maximum Post Baseline Values in Each Treatment, for Patients with Outlier QTc Values

Subject PJST0047	Outlier and/or Maximum QTc Values (msec) During Each Treatment QTc Value (Day, Hour) Change From Baseline		
	MDL 16455A	Erythromycin	MDL 16455A + Erythromycin
0013	437.3 (Day 8, Hour 24) 20.0	440.7* (Day 7, Hour 4) 24.3	444.0* (Day 9, Hour 48) 16.4
0016	419.2 (Day 7, Hour 6) -3.7	421.3 (Day 8, Hour 24) 16.9	444.2* (Day 7, Hour 12) 45.9
0017	437.7 (Day 7, Hour 6) 33.5	442.1* (Day 7, Hour 6) 45.6	424.3 (Day 8, Hour 24) 26.8
0018	441.4* (Day 7, Hour 6) 26.0	441.6* (Day 7, Hour 6) 21.4 447.9* (Day 7, Hour 12) 27.7	459.4* (Day 7, Hour 6) 41.9
0023	414.7 (Day 7, Hour 12) 5.4	439.2 (Day 7, Hour 3) 20.4	449.3* (Day 9, Hour 48) 53.2
0024	423.5 (Day 7, Hour 12) 42.5	448.5* (Day 7, Hour 6) 61.3 444.0* (Day 7, Hour 12) 56.7	442.0* (Day 7, Hour 12) 37.7

* Indicates outlier QTc values (greater than 440 msec with an increase from baseline of greater than 10 msec).

Supporting Data: *Appendix C5: Electrocardiograms* Page S6-V1.83-P1

Results - Adverse Events

The sponsor reports there were no deaths or dropouts due to adverse events during this study. The sponsor reports the following events which occurred in more than one subject: Monocytosis in 2 on erythromycin alone; diarrhea in 2 on erythromycin alone; and nausea in 2 on combination treatment.

Reviewer's Comment

As for ketoconazole, an obvious pharmacokinetic interaction was observed from the results of this study, no explanation is offered to account for this phenomenon.

At the request of the Agency the sponsor provided by FAX on 3/4/96, the ECG time points actually used in computing daily QTc means. For this study report they were:

Days 0 and 7: 0hr to 8hr after the 0700hr dose
ECGs performed at other times were for monitoring safety.

The sponsor was asked to explain the selection of the hours during Days 0 and 7 for computing ECG means. The sponsor responded by submission on April 1, 1996 indicating that 0hr to 8hr was selected because it was the dosing interval for erythromycin.

Reviewer's Determinations

- 1) A significant pharmacokinetic drug interaction occurs during concomitant administration of fexofenadine and erythromycin resulting in markedly elevated fexofenadine plasma concentrations and noted by AUC_{ss} and C_{max,ss}.
- 2) Erythromycin pharmacokinetics do not appear to be influenced by concomitancy with fexofenadine.
- 3) No statistically significant difference was noted for QTc prolongation as measured by change from baseline in mean and maxima QTc measurements.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: **Fexofenadine (MDL-16,455A-16,455A) 60mg Capsules**

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Reviewed: **Protocol PJPR0028** - conducted from October 1994 to November 1994

Title

"Effect of Ketoconazole on the Pharmacokinetics of MDL-16,455A."

Objectives

"The primary objective of the present study is to examine the pharmacokinetics of MDL-16,455A when administered alone and in combination with steady-state ketoconazole administration."

Secondary Objectives:

1. "To examine the pharmacokinetics of ketoconazole when administered alone and in combination with MDL-16,455A."
2. "To characterize the effect on QTc when MDL-16,455A is administered in combination with ketoconazole. This effect will be compared to the interaction effect observed in previous terfenadine studies."

Study Design

The study was an open-label, randomized three-way complete crossover (9 days per period with at least 10 day washout) in 24 healthy non-smoking males, 18-45 years of age.

Study Treatments

- Treatment A: Multiple dose oral administration of 120 mg (2x60 mg capsule) MDL-16,455A Q12h under fasted conditions for 6.5 days (total of 13 doses).
- Treatment B: Multiple dose oral administration of 400 mg QD ketoconazole for 7 days (total of 7 doses).
- Treatment C: Concomitant multiple dose oral administration of 120 mg (2x60 mg capsule) MDL-16,455A Q12h under fasted conditions for 6.5 days (total of 13 doses) and 400 mg ketoconazole QD for 7 days (total of 7 doses).

ECG Measurements

Day 0 (no drug dosing) and Day 7 (steady state) - 0700, 0900, 1100, 1300, 1500, 1900 hours

Day 8 and 9 at 0700 hours

Days 1-6 for treatment C only - at 0900, 1300 and 2100 hours - collected only for safety and not pharmacodynamic effect

Drug Administration

MDL-16455A: 0700hr and 1900hr on Days 1-7; final dose at 0700hr on Day 8

Ketoconazole: 0700hr and 1900hr on Days 1-7

No Drug Administration on Day 0

Blood Sample Collection

Treatment A - predose and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours after MDL-16,455A administration on Day 7 for MDL-16,455A concentration.

Treatment B - predose and at 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose on Day 7 for ketoconazole concentration.

Treatment C -

For MDL-16,455A concentration - predose and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours after MDL-16,455A administration on Day 7 .

For ketoconazole concentration - predose, 1, 2, 4, 6, 8, 12, 24, and 48 hours after the morning dose of ketoconazole on Day 7.

For trough levels -

-- Two separate samples for trough analysis on Days 5 and 6 before the morning dose for all treatments.

Safety Measures

Pre- and post study laboratory blood tests and physical examinations

Results - Patient Accounting

24 enrolled

24 received Treatment A

24 received Treatment B

23 received Treatment C

22 completed the study

Two patients were discontinued: subject # 0011 for flu symptoms on Day 4 of Period 3, Treatment A; and subject #0016 prior to Treatment C for a positive urine drug screen.

Results - Pharmacokinetic Parameters

The sponsor summarizes the pharmacokinetic results in tabular and graphic form, reproduced below. From these results AUC_{ss}(0-12hr) and C_{max,ss} are noted to increase by 259% and 230%, respectively, when the two drugs are administered concomitantly. A graph of plasma ketoconazole concentrations shows that ketoconazole pharmacokinetics are not are not influenced by concomitant administration. It is not clear why the sponsor does not provide an estimate for the half-lives since blood samples were collected for 48 hours, but comments that the slopes from the graphic presentation do not appear to differ substantially. From this observation the sponsor suggests that the mechanism for the interaction would not be from an alteration in the elimination of MDL-16,455A.

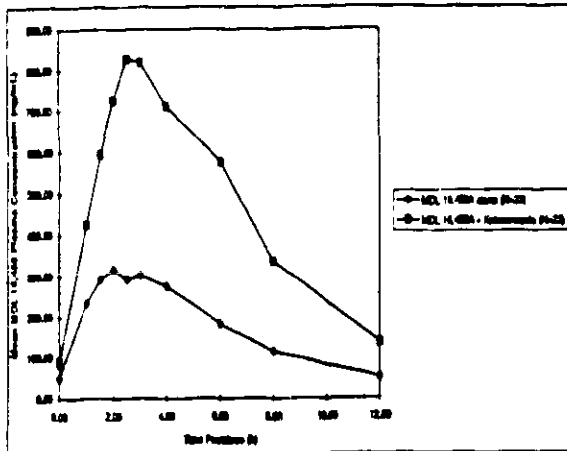


Figure 6-104. Mean MDL 18,455 Plasma Concentrations Over the 12-Hour Dosing Interval Following Administration of MDL 18,455 Alone or MDL 18,455 in Combination with Ketoconazole.

Supporting Data: Page
 Appendix A1: Plasma, MDL 18,455 SB-V1.06-P03

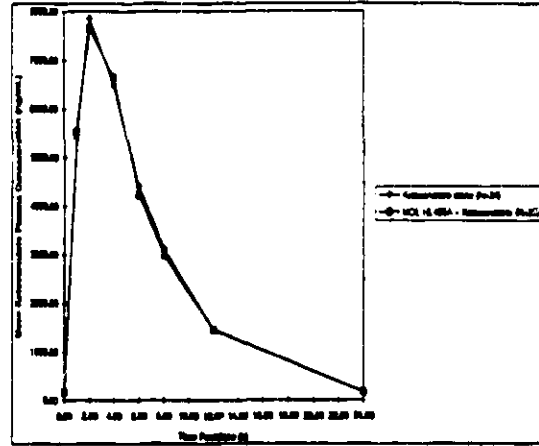


Figure 6-105. Mean Ketoconazole Plasma Concentrations Over the 24-Hour Dosing Interval Following Administration of Ketoconazole Alone or MDL 18,455 in Combination with Ketoconazole.

Supporting Data: Page
 Appendix A2: Plasma, Ketoconazole SB-V1.06-P102

Table 6-350. Mean Steady-State Plasma Pharmacokinetic Parameters and Treatment Comparisons for MDL 18,455

Parameter	T _{1/2}	Mean	%CV	Adjusted Mean	Pairwise Comparison			
					Pair	Ratio (%)	90% CI	P value
AUC _{0-12 h}	A	2089.67	33.33	2065.38	-	-	-	-
h _{mg/mL}	C	8647.24	24.88	5329.83	C/A	268.31	(231.4, 290.6)	<0.001
CL _{po}	A	67.84	28.22	54.43	-	-	-	-
L _h	C	21.51	27.18	20.88	C/A	38.88	(34.4, 43.2)	<0.001
C _{max,ss}	A	388.41	40.82	378.55	-	-	-	-
ng/mL	C	813.9	29.54	826.23	C/A	228.88	(183.3, 273.3)	<0.001
t _{max,ss}	A	2.43	52.85	2.12	-	-	-	-
h	C	2.78	43.98	2.52	C/A	118.88	(84.5, 148.7)	0.207
C _{min,ss}	A	43.78	48.12	-	-	-	-	-
ng/mL	C	86.07	48.38	-	-	-	-	-

Treatment A=MDL 18,455A 120 mg Q12 h
 Treatment C=MDL 18,455A 120 mg Q12 h + Ketoconazole 400 mg QD

Supporting Data: Page
 Appendix A1: Plasma, MDL 18,455 SB-V1.06-P03
 Appendix B3: MDL 18,455 Pharmacokinetic Parameters, Details of Treatment Comparisons SB-V1.06-P142

Results - Pharmacodynamic Parameters - QTc Measurements

The sponsor provides a summary of results of QTc analyses in tabular form, reproduced below. No statistically significant differences are noted for any comparison of change from Day 0 to Day 7 except for decrease in mean QTc change for MDL-16,455A when administered alone (-4.7 ± 2.2 msec; $p=0.0455$). The combination is noted to produce a mean increase of 3.1 ± 2.3 msec ($p=0.1812$).

Mean QTc					
Treatment	N*	Day 0 mean $\pm$ se	Day 7 mean $\pm$ se	Change from Day 0 to Day 7 mean $\pm$ se	P Value†
MDL 16,455A	23	398.9 $\pm$ 3.1	394.3 $\pm$ 2.7	-4.7 $\pm$ 2.2	.0465
Ketoconazole	24	396.9 $\pm$ 3.3	395.0 $\pm$ 2.7	-2.0 $\pm$ 2.3	.3960
MDL 16,455A + Ketoconazole	23	395.9 $\pm$ 2.9	399.0 $\pm$ 3.2	3.1 $\pm$ 2.3	.1812
Maximum QTc					
Treatment	N*	Day 0 mean $\pm$ se	Day 7 mean $\pm$ se	Change from Day 0 to Day 7 mean $\pm$ se	P Value†
MDL 16,455A	23	423.8 $\pm$ 3.9	420.5 $\pm$ 3.9	-3.3 $\pm$ 4.4	.4861
Ketoconazole	24	419.9 $\pm$ 4.1	417.1 $\pm$ 2.6	-2.8 $\pm$ 4.2	.5194
MDL 16,455A + Ketoconazole	23	417.2 $\pm$ 3.6	425.2 $\pm$ 3.6	8.0 $\pm$ 4.0	.0597

* N=24 subjects at the beginning of the study, 2 subjects withdrew prior to completion.
 † P Value from t test that the change from day 0 to day 7 is equal to zero.

Supporting Data:
 Appendix C5: Electrocardiograms

Page
S6-V1.87-P1

The sponsor also provides a table comparing the results from this study to another in which terfenadine was administered concomitantly with ketoconazole using a very different study design, but nonetheless showing a marked increase in average QTc mean (29.1 ± 5.5 msec) when the combination was administered.

Protocol / Treatment	Average QTc Mean $\pm$ SE	95% Confidence Interval
9918-1-C-188/ Ketoconazole Alone* (N=11)	2.6 $\pm$ 3.0	(-4.1, 9.3)
Terfenadine Alone* (N=5)	-1.5 $\pm$ 10.2	(-29.9, 26.9)
Ketoconazole† Plus Terfenadine† (N=11)	29.1 $\pm$ 5.5	(16.8, 41.4)
PJPR0028/ Ketoconazole Alone* (N=24)	-2.0 $\pm$ 2.3	(-6.8, 2.8)
MDL 16,455A Alone* (N=23)	-4.7 $\pm$ 2.2	(-9.2, -0.05)
Ketoconazole* Plus MDL 16,455A* (N=23)	3.1 $\pm$ 2.3	(-1.7, 7.9)

* Steady State
 † Single-Dose

Supporting Data:
 Table 6-355. Change from Baseline in Mean and Maximum QTc. Morganroth-Read ECG Data

Page
S6-V1.86-P45

The sponsor reports that 9 subjects had one or more outlier QTc. Outlier was defined as QTc > 440 msec with > 10 msec increase from baseline. Six of these subjects had outlier values on MDL-16,455A alone and 6 subjects had outlier values on combination treatment while none of these subjects had outliers during ketoconazole treatment. The highest value noted is 474 msec.

Subject PJST0172-	Outlier and/or Maximum QTc Values (msec) During Each Treatment QTc Value (Day, Hour) Change From Baseline		
	MDL 16455A	Ketoconazole	MDL 16455A + Ketoconazole
002	442.8* (Day 7, Hour 4) 35.9	422.8 (Day 9, Hour 48) 23.5	441.9* (Day 8, Hour 24) 51.1
008	451.4* (Day 7, Hour 0) 65.2	421.2 (Day 7, Hour 6) 36.4	420.6 (Day 8, Hour 24) 34.7
012	428.7 (Day 7, Hour 8) 16.8	425.0 (Day 9, Hour 48) 15.2	441.0* (Day 7, Hour 8) 37.8
013	434.5 (Day 7, Hour 0) 40.8	400.3 (Day 7, Hour 2) 2.4	450.0* (Day 9, Hour 48) 53.3
015	444.4* (Day 7, Hour 8) 48.5	422.2 (Day 7, Hour 12) 16.0	443.5* (Day 7, Hour 8) 36.8
021	456.1* (Day 9, Hour 48) 35.2	439.3 (Day 7, Hour 2) 22.8	460.2* (Day 7, Hour 8) 44.5 474.5* (Day 7, Hour 12) 58.8

Results - Adverse Events

The sponsor reports there were no deaths during this study. On dropout (subject #0011) was due to an adverse event - influenza-like symptoms. The sponsor reports the following events which occurred in more than one subject: nausea in 3 on ketoconazole alone; headache in 2 on ketoconazole alone; and influenza-like symptoms in 2 on MDL-16,455A alone.

Reviewer's Comment

While an obvious pharmacokinetic interaction was observed from the results of this study, no mechanism is postulated by the sponsor to account for this phenomenon.

At the request of the Agency the sponsor provided by FAX on 3/4/96, the ECG time points actually used in computing daily QTc means. For this study report they were:

Days 0 and 7: 0hr to 12hr after the 0700hr dose
ECGs performed at other times were for monitoring safety.

The sponsor was asked to explain the selection of the hours during Days 0 and 7 for computing ECG means. The sponsor responded by submission on April 1, 1996 indicating that 0hr to 12hr was selected because it was the dosing interval for ketoconazole.

Reviewer's Determinations

- 1) A significant pharmacokinetic drug interaction occurs during concomitant administration of fexofenadine and ketoconazole resulting in markedly elevated fexofenadine plasma concentrations as noted by AUC_{ss} and C_{max,ss}.
- 2) Ketoconazole pharmacokinetics do not appear to be influenced by concomitancy with fexofenadine.
- 3) No statistically significant difference was noted for QTc prolongation as measured by change from baseline in mean and maxima QTc measurements. The observance of outlier QTc values in subjects only when on fexofenadine or fexofenadine in combination with ketoconazole and no outlier values in the same individuals on ketoconazole alone, may subtly suggest a very weak potential for fexofenadine to prolong QTc intervals.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: Fexofenadine (MDL-16,455A) 60mg Capsules

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Reviewed: 4 Month Safety Update Submitted November 30, 1995 from NDA 20-625

Introduction

The four month safety update for this NDA consists of two interim clinical study reports, which include approximately 3 months of drug exposure information, for PJPR0027 (one year safety study in normal subjects) and PJPR0031 (6 month safety study in normal subjects), and a final pharmacokinetic study report for PJPR0021 (pharmacokinetics in patients with hepatic impairment). The results from PJPR0027 and PJPR0031 were not integrated with the results from the controlled clinical trials in patients because these two trials were conducted in normal volunteers and for much longer exposure times whereas the controlled clinical trials were conducted in patients with seasonal allergic rhinitis (SAR) with exposure times of 2 weeks. Since studies PJPR0027 and PJPR0031 are ongoing studies, treatment assignment was not completely unblinded, and the treatment groups were identified using codes "A" for placebo and "B" for fexofenadine 240mg, with the intent to maintain complete blinding for patients, investigative site personnel and the sponsor's monitoring personnel. This four month safety update also contains a list (Table 9-2 on page 9) of additional serious adverse events not reported in the clinical study reports for the 3 protocols above because these events were noted after the cutoff date for preparing the study reports but they needed to be reported (eg, events from ongoing studies).

Protocol PJPR0027

The sponsor reports the following information for this study. This study compares one year safety/tolerance of fexofenadine 240mg QD to Placebo QD in normal healthy subjects using a double-blind, randomized, parallel group, multi-center (14 sites) study design with a total planned enrollment of approximately 400 subjects who are either gender and 12-65 years of age and not taking any proscribed medications. After screening, subjects will have 13 follow-up clinic visits at approximately 30 day intervals. As of June 30, 1995, 477 (237-placebo; 240-fexofenadine) subjects were randomized and exposed to treatments, with 467 (234-placebo; 233-fexofenadine) subjects having one postbaseline adverse assessment, qualifying them as safety evaluable. Duration of double-blind for Treatment A - 74.0 ± 24.9 days and Treatment B - 71.2 ± 27.7 days; and percent compliance Treatment A - $98.6\% \pm 7.5$ and Treatment B - $97.3\% \pm 6.3$.

Reasons for Early Discontinuation in Randomized Subjects		
	Treatment A (N=237)	Treatment B (N=240)
Elected to discontinue	5.1%	9.2%
Adverse event	3.8%	4.6%
Lost to follow-up	1.3%	5.0%
Other	1.3%	3.8%
Use of prohibited medication	1.3%	1.7%
Reason not known at analysis time	0.4%	0.0%
Total	9.3%	15.8%

Incidence of All Adverse Events >1% in Either Treatment		
	Treatment A (N=234)	Treatment B (N=233)
Headache	22.6%	17.2%
Pain	3.4%	2.6%
Fatigue	1.7%	0.4%
Dizziness	0.9%	1.7%
Insomnia	0.4%	1.7%
Hypertonia	0.4%	1.3%
Upper Resp. Tract Infection	6.4%	6.0%
Sinusitis	3.8%	2.6%
Throat Irritation	3.4%	3.9%
Upper Resp. Congestion	1.3%	4.7%
Tooth Disorder	4.7%	2.1%
Dyspepsia	3.8%	3.4%
Nausea	3.4%	3.4%
Gastroenteritis	3.0%	3.0%
Diarrhea	2.6%	0.4%
Vomiting	1.3%	0.9%
Back Pain	6.4%	5.2%
Myalgia	4.7%	4.7%
Arthralgia	2.1%	3.9%
Myopathy	1.7%	1.7%
Arthrosis	1.3%	0.0%
Infection Viral	9.0%	13.3%
Influenza-Like Symptoms	2.1%	0.9%
Dysmenorrhea	1.3%	1.3%
Injury Accidental	3.4%	1.3%
Leukopenia	1.3%	.9%
Malaise	0.4%	1.7%
Dry Mouth	1.3%	0.4%

No deaths, life-threatening events, disabilities, congenital anomalies, cancers or overdoses were reported. One patient (#198-005 -46 year old female) was hospitalized after suffering 2 bouts of hematemesis after 13 days on Treatment A. Endoscopy showed six papillar lesions in the stomach with possible erosions which healed following treatment. Follow-up endoscopy revealed normal mucosa. It is difficult to ascribe causality to fexofenadine from reading the narratives describing the events for subjects discontinued from the trial due to an adverse event.

There were no statistically significant changes from baseline between treatment groups for mean clinical laboratory data except eosinophils ($P=0.007$) (Treatment A = $-0.038 \times 10^3/\mu\text{L}$; Treatment B = $-0.016 \times 10^3/\mu\text{L}$) which does not appear to be clinically significant. Results from sift and outlier tables were generally unremarkable except for a small percentage of subjects in both treatment groups for WBC shifts (Treatment A : 9.1% down, 4.8% up; Treatment B : 10.8% down, 3.6% up); WBC outlier (Treatment A : 1.8% low, 0.4% high; Treatment B : 2.7% low, 0.0% high).

There were no statistically significant differences between treatments in change from baseline for vital signs or ECG measurements (QTc, QT, QRS, PR, HR). The number of subjects with post baseline outlier values for QTc was similar between treatments (Treatment A : 4.7%; Treatment B : 2.3%).

Protocol PJPR0031

The sponsor reports the following information for this study. This study compares 6 month safety/tolerance of fexofenadine 60mg BID to Placebo BID in normal healthy subjects using a double-blind, randomized, parallel group, multi-center (15 sites) study design with a total planned enrollment of approximately 400 subjects who are either gender and 12-65 years of age and not taking any proscribed medications. After screening, subjects will have 7 follow-up clinic visits at approximately 30 day intervals. As of June 15, 1995, 433 (215-placebo; 218-fexofenadine) subjects were randomized and exposed to treatments, with 423 (209-placebo; 214-fexofenadine) subjects having one postbaseline adverse assessment, qualifying them as safety evaluable. Duration of double-blind for Treatment A - 83.4 ± 21.5 days and Treatment B - 82.8 ± 19.9 days; and percent compliance Treatment A - $96.5\% \pm 6.8$ and Treatment B - $96.8\% \pm 5.3$.

Reasons for Early Discontinuation in Randomized Subjects		
	Treatment A (N=237)	Treatment B (N=240)
Elected to discontinue	6.0%	6.4%
Adverse event	3.7%	3.7%
Lost to follow-up	1.9%	2.3%
Other	1.4%	0.0%
Use of prohibited medication	0.5%	0.5%
Reason not known at analysis time	1.4%	0.5%
Total	10.7%	10.6%

Incidence of All Adverse Events > 1% in Either Treatment		
	Treatment A (N=234)	Treatment B (N=233)
Headache	12.9%	11.2%
Pain	3.8%	5.1%
Fatigue	1.4%	0.5%
Migraine Headache	1.0%	0.5%
Infection Viral	12.4%	12.1%
Influenza-Like Symptoms	1.4%	0.9%
Candidiasis	1.0%	0.5%
Infection	1.0%	0.0%
Otitis Media	1.0%	0.0%
Throat Irritation	3.8%	6.1%
Upper Resp. Tract Infection	3.8%	4.2%
Throat Irritation	3.4%	3.9%
Sinusitis	2.9%	0.5%
Upper Resp. Congestion	2.4%	2.3%
Rhinitis	1.0%	0.0%
Coughing	0.0%	1.4%
Myalgia	2.4%	5.1%
Back Pain	2.4%	3.7%
Bone Disorder	2.4%	0.5%
Arthralgia	1.9%	0.9%
Arthrosis	1.9%	0.9%
Chest Pain	1.4%	0.9%
Nausea	2.4%	0.9%
Dyspepsia	1.9%	2.3%
Vomiting	1.4%	0.9%
Tooth Disorder	1.0%	2.8%
Diarrhea	1.0%	0.9%
Gastroenteritis	0.5%	1.4%
Leukopenia	3.8%	3.3%
Granulocytopenia	1.0%	0.9%
Phosphatase Alkaline Increased	1.0%	0.0%

Incidence of All Adverse Events >1% in Either Treatment (continued)		
Hypertension	0.0%	1.4%
Exanthema	1.4%	0.9%
Rash	1.0%	0.9%
Injury Accidental	2.4%	1.9%
Conjunctivitis	1.4%	0.5%
SGPT Increased	1.0%	0.9%
Polycythemia	1.4%	0.0%
Earache	1.0%	1.4%
Purpura	1.0%	0.9%

No life-threatening events, disabilities, congenital anomalies, or overdoses were reported. One patient (#180-019 - 54 year old male) was hospitalized after suffering 2 a cerebrovascular accident after 14 days on Treatment A and later suffered cardiopulmonary arrest and died. Another patient (#185-006 - 23 year old female) discontinued treatment after 75.5 days on Treatment B because of a malignant melanoma of the left calf. The lesion was present at baseline but the decision to biopsy was made because of change in lesion size. It is difficult to ascribe causality to fexofenadine from reading the narratives describing the events for subjects discontinued from the trial due to an adverse event.

There were no statistically significant changes from baseline between treatment groups for mean clinical laboratory data except platelets ($P=0.048$; Treatment A = $-3.878 \times 10^3/\mu\text{L}$; Treatment B = $-10.36 \times 10^3/\mu\text{L}$) and monocytes ($P=0.005$; Treatment A = $-0.007 \times 10^3/\mu\text{L}$; Treatment B = $0.024 \times 10^3/\mu\text{L}$) which do not appear to be clinically significant. Results from sift and outlier tables were generally unremarkable except for a small percentage of subjects in both treatment groups for WBC shifts (Treatment A : 7.9% down, 8.4% up; Treatment B : 9.5% down, 5.5% up); WBC outlier (Treatment A : 7.4% low, 0.0% high; Treatment B : 5.0% low, 0.5% high).

There were no statistically significant differences between treatments in change from baseline for vital signs or ECG measurements (QTc, QT, QRS, PR, HR). The number of subjects with post baseline outlier values for QTc (QTc >440msec and increase >10msec) was similar between treatments (Treatment A : 6.1%; Treatment B : 4.9%).

Serious Adverse Events Reported in Table 9-2

The results from this table are summarized below. No narratives have been submitted for these events but are anticipated when the final study reports are submitted to the NDA.

Additional Serious Adverse Events						
Protocol	Patient	Age	Sex	Treatment	Event	Serious Criteria
PJPR0027	204-028	27	M	Placebo	Suicide	Death
PJPR0027	194-019	24	M	Fexofenadine 240mg QD	Infectious Mononucleosis	Hospitalization
PJPR0027	198-007	59	M	Fexofenadine 240mg QD	Bilateral Arm Numbness Exertional Chest Pain	Hospitalization
PJPR0027	206-015	35	F	Placebo	Severe Abdominal Pain Fever	Hospitalization
PJPR0031	186-025	31	M	Fexofenadine 60mg BID	Delusions	Hospitalization
PJPR0019	084-008	21	M	N/A	Angioedema Urticaria	Hospitalization
PJPR0019	117-003	60	F	N/A	Angioedema	Hospitalization
PJPR0019	117-006	45	F	N/A	Fibromyomata	Hospitalization
N/A. = Not Available						

Protocol PJPR0021

This 4 month safety update provides the final pharmacokinetic study results from this trial in patients with hepatic impairment. Originally, 20 subjects were planned for enrollment but due to difficulty in patient accrual, the sponsor terminated the trial after 17 patients completed the study. This report includes the results of 3 additional subjects. The results from the first 14 subjects were reported in the original NDA submission but the results from these 17 subjects have been reviewed by the biopharmaceutics reviewer, Brad Gillespie.

Reviewer's Determinations

The results from this 4 month safety update do not alter the safety determinations made during the review of the integrated summary of safety.

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Reviewed: NDA 20-625 - DSI Auditing and Other Auditing Activities

The Division of Scientific Investigations (DSI) conducted a routine inspection as part of the FDA's Bioresearch Monitoring Program of five investigative centers and one contract research organization, Premier Research Worldwide (PRW), which processed ECG reading for most of the important safety trials for this NDA. Results from the audit of 4 investigative sites and the contract research organization were available by April 23, 1996. The results for the inspection indicate that no substantive violations were observed at any of these study centers. Photocopies are attached of the letters to the investigators indicating field classification of NAI (No Action Indicated) and of the summary of findings for the audit for PRW. The results from the audit of investigator site, #PJST0021 - Dr Frank Hample, is pending.

During the conduct of audits by DSI, a discrepancy was noted between the assigned treatment listed in the line listings and the CRF for one patient at one site. Follow-up by the sponsor indicated that 10 subjects were inadvertently unblinded incorrectly in preparation for data analysis. Please refer to the medical officer's review for Protocol# PJPR0009 for a detailed discussion regarding the results of the audit and subsequent responses by the sponsor and Agency.

During the review of this NDA, the Division of Pulmonary Products conducted some other auditing procedures. For patients who discontinued trial early because of an adverse event, the sponsor was asked to provide photocopies from the CRF for the adverse event page which identified the adverse event, the termination page which indicated the primary reason for discontinuation and documented discontinuation after exposure to study drug, and the line-listing tabulations for this information. The information for these items on the photocopies of the CRF were compared to the line listings and the comments in the narratives which described the discontinuations. No substantive discrepancies were noted for this information for patients who were discontinued early from the 4 major efficacy trials (PJPR0009/10/23/24).

Additionally for the 4 major efficacy trials, line listings for symptom scores were examined for patients who were listed in the line listings as having been randomized to treatment but were not considered intent-to-treat. For none of these randomized but not intent-to treat patients were there any symptom score data listings found in the symptom score line listings of the NDA, suggesting that no post-randomization symptom score data was available for these subjects that was not included in the database used for intent-to-treat efficacy analyses.

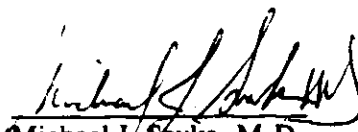
Additionally, ECGs were audited. The sponsor was asked to identify subjects with the highest measured fexofenadine plasma concentrations from specific protocols and to submit the ECG obtained at or near the time of blood sampling. ECGs from 10 subjects were submitted for protocols PJPR0003/ 07/ 23/ 24; and ECGs from 5 subjects were submitted for protocols PJPR0018/ 28. Recognizing the limitations of photocopied ECGs, the QT interval for each ECG was examined and compared to that recorded by Dr Morganroth. No obvious large discrepancy was noted nor significant morphologic

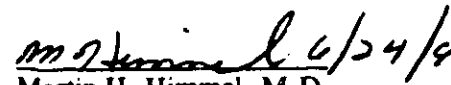
change seen. The plasma concentrations ranged from 722 ng/ml to 7359 ng/ml with all but 9 over 1000 ng/ml.

NDA 20-625

SIGN-OFF - Final Safety Update

PRODUCT: FEXOFENADINE CAPSULES 60MG
SPONSOR: HOECHST MARION ROUSSEL, INC
ORINGINAL NDA SUBMITTED: JULY 31, 1995

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JUN 24 1996

NDA 20-625 - Final Safety Update

Page 1 of 20

Medical Officer Review

Reviewer: Michael J. Sevka, M.D.

Product: **Fexofenadine (MDL-16,455A) 60mg Capsules**

Sponsor: Hoechst Marion Roussel, Inc.

Date NDA Submitted: July 31, 1995

Material Examined: A) Minor Amendments Since Original NDA Submission

Material Reviewed: B) Final Safety Update Submitted June 4, 1996 for NDA 20-625

C) NDA Issues Remaining Open

A) Minor Amendments Since Original NDA Submission To June 20, 1996

General Correspondence - 11/02/95 - Missing pages of patient listings for PJPR0003 - NDA section S6-V1.146-P206-207.

Minor Amendment - 11/30/95 - 4-Month Safety Update (See separate M.O. review).

Minor Amendment - 12/08/95

- a) by-week analyses of efficacy assessments for individual symptom scores and composite scores for the 4 pivotal studies;
- b) analyses of responder rates;
- c) affirmation that Table 8-418 for Protocol PJPR0024 and Table 8-365 for Protocol PJPR0023 are Intent-To-Treat population.

Minor Amendment - 12/13/95

For the four pivotal safety and efficacy trials:

- a) summary of patient compliance with symptom diary assessments;
- b) explanation how missing diary data were handled for analyses;
- c) by-center summaries of demographic and baseline symptom scores;
- d) analyses of primary efficacy response by dose for each investigative site.

Minor Amendment - 12/21/95 - Description of the general ECG handling procedures for all clinical trials.

Minor Amendment - 12/22/95

- a) statistical "p" values for responder rates submitted 12/8/95;
- b) affirmation that no patients were unblinded during conduct of the 4 pivotal trials;
- c) QTc analysis by gender for PJPR0023 and PJPR0024;
- d) summary of doses and exposure duration for key ECG safety studies;
- e) scatter plots of QTc values vs fexofenadine plasma concentrations for selected ECG studies;
- f) identification of patients with highest fexofenadine plasma concentrations for selected ECG studies;
- g) clarification of incomplete blinding with first Morganroth ECG reading for Protocol PJPR0007.

Minor Amendment - 01/19/96 - Description and explanation of unblinding discrepancies for Protocol PJPR0009.

General Correspondence - 01/26/96 - Patient listings of those randomized but not intent-to-treat for the four pivotal trials.

Minor Amendment - 02/09/96 - Photocopies of ECG rhythm strips for patients with the highest fexofenadine plasma concentrations for selected ECG safety studies.

Minor Amendment - 02/12/96 - Additional information regarding unblinding discrepancies for Protocol PJPR0009.

Minor Amendment - 02/21/96

- a) explanation for lower plasma concentrations observed in the 60mg treatment group compared to those in the 40mg treatment group for pivotal clinical trials PJPR0009/10;
- b) description of packaging procedures for medication supplies for trials PJPR0009/10 .

Minor Amendment - 02/27/96 - Description of peak plasma concentration variability for Protocol PJPR0009.

Minor Amendment - 03/04/96 - Additional analyses of primary efficacy parameters in subgroups of patients defined by demographic factors for the 4 pivotal efficacy and safety trials.

Minor Amendment - 03/25/96 - Pollen count units of measure for the 4 pivotal trials.

Minor Amendment - 04/01/96

- a) explanation of carryover and period effects for first Morganroth-generated ECG readings in Protocol PJPR0007 and lack of such effects for Protocols PJPR0003/04;
- b) submission of compliance estimates for ECG assessments across ECG safety studies;
- c) explanation for use of differing ECG assessment times between the ketoconazole and erythromycin interaction studies;
- d) description of telemetry data handling for important ECG safety trials;
- e) submission of narratives and CRF pages (termination, termination tabulation, adverse event, adverse event tabulation) for patients who discontinued prematurely due to an adverse event and also narratives for patients with possible preexisting cardiovascular problems in PJPR0018/28;
- f) comment on small changes in bicarbonate and chloride clinical laboratory values observed in Protocol PJPR0003;
- g) clarification why study patients in Protocol PJPR0007 were divided into 2 groups during the study execution;
- h) clarification of the impact on randomization in Protocol PJPR0007 of all male assignments to odd numbers and female to even numbers;
- i) provide by gender analysis for Protocol PJPR0007 of daily mean QTc and mean maximum QTc changes from baseline;
- j) provide by gender analysis for Protocol PJPR0007 for correlation between plasma fexofenadine concentrations (and other pharmacokinetic parameters) and QTc data;
- k) provide reanalysis of QTc data for Protocol PJPR0003 using ECGs from the same time points for Day 30 as baseline;
- l) clarification regarding possible typographical errors for 2 patients listed as having outlier phosphate or bilirubin values;
- m) clarification of the count for safety-evaluable population for Protocol PJPR0010 being off by one patient;
- n) provide an analysis of QTc data comparing 60mg fexofenadine versus 60mg terfenadine for Protocol PJPR0004.

Minor Amendment - 04/23/96

- a) resubmission of summaries of patient compliance with diary entries;
- b) submission of all adverse events by dose for the 4 pivotal efficacy and safety trials, combined into a single table;
- c) tabular listing studies to be included in the final safety update and tabular listing of on-going clinical trials.

Minor Amendment - 05/02/96

- a) description of medication compliance computation for the 4 pivotal clinical trials;
- b) clarification of patient accounting for Protocol PJPR0010;
- c) clarification of the reason for the number of dropouts in Protocol PJPR0017, onset of action study in an environment exposure unit.

Minor Amendment - 05/10/96 - Submission of adverse events rates and outlier clinical laboratory data for subgroups defined by age (<16; >16-60; >60 years).

Minor Amendment - 06/04/96 - Final Safety Update (See separate M. O. review)

Minor Amendment - 06/18/96 - Case report forms for patients who were reported to have experienced syncope as an adverse event.

General Correspondence - 06/18/96 -

- a) clarification that data presented in the appendices of the final safety update (06/04/96) contain a duplication of information located in the tabulations, which were not submitted in updated format for the final safety update;
- b) clarification that final safety update would be limited to provision of adverse event information and not include updated summary data for ECGs or clinical laboratory data.

Minor Amendment Provided as telefax - 06/21/96 - Correct case report form for subject #206-010 in Protocol PJPR0027, that should have been submitted in minor amendment dated 06/18/96 which provides information on subjects experiencing syncope; and also includes available ECG information for 4 patients from Protocol PJPR0027 which reported experiencing syncope.

B) Final Safety Update**Introduction**

The final safety update for this NDA consists of the following items:

- A) Second interim report - Protocol PJPR0027 (1 year safety study in normal subjects - 240mg QD);
- B) Final report - Protocol PJPR0031 (6 month safety study in normal subjects-60mg BID);
- C) Final report - Protocol PJPR0045 (Bioequivalence of 180 mg tablet formulations);
- D) Table of ongoing studies;
- E) Global list and narratives for serious adverse events from ongoing studies (excluding those reported in the individual reports noted above for PJPR0027, PJPR0031, and PJPR0045), occurring since March 31, 1995 (cut-off period of the NDA). The list and narratives include the serious adverse event reports which were also reported in the 4 month safety update.

The results from PJPR0027 and PJPR0031 were not integrated with the results from the controlled clinical trials in patients because these two trials were conducted in normal volunteers and for much longer exposure times whereas the controlled clinical trials were conducted in patients with seasonal allergic rhinitis (SAR) with exposure times of 2 weeks.

Protocol PJPR0027

This study compares one year safety/tolerance of fexofenadine 240mg QD to Placebo QD in normal healthy subjects using a double-blind, randomized, parallel group, multi-center (14 sites) study design with a total planned enrollment of approximately 400 subjects who are either gender and 12-65 years of age and not taking any proscribed medications. After screening, subjects will have 13 follow-up clinic visits at approximately 30 day intervals. Since study PJPR0027 is ongoing, treatment assignment was not completely unblinded, and the treatment groups were identified using codes "A" for placebo and "B" for fexofenadine 240mg, with the intent to maintain complete blinding for patients, investigative site personnel and the sponsor's monitoring personnel.

The data cut-off date for this interim report was January 31, 1996. The report focuses on adverse event data and does not contain updated analyses of clinical laboratory data or ECG data. The sponsor reports the following information for this study. There were 477 (237-placebo; 240-fexofenadine) subjects randomized and exposed to treatments and 467 (234-placebo; 233-fexofenadine) subjects having one postbaseline adverse assessment, qualifying them as safety evaluable. Duration of double-blind for placebo - 200.3 ± 67.4 days and fexofenadine - 192.5 ± 81.7 days.

Incidence of All Adverse Events >1% in The Fexofenadine Group and Greater In The Fexofenadine Group Compared To Placebo		
<i>System Organ Class/Preferred Term</i>	<i>Placebo (QD) (N=234) N (%)</i>	<i>Fexofenadine (240mg QD) (N=233) N (%)</i>
Dizziness	3 (1.3%)	6 (2.6%)
Insomnia	2 (0.9%)	9 (3.9%)
Hypertonia	2 (0.9%)	3 (1.3%)
Migraine Headache	1 (0.4%)	3 (1.3%)
Syncope	1 (0.4%)	3 (1.3%)
Upper Respiratory Tract Infection	31 (13.2%)	42 (18.0%)
Bronchitis	2 (0.9%)	5 (2.1%)
Coughing	2 (0.9%)	3 (1.3%)
Lower Respiratory Congestion	0 (0.0%)	3 (1.3%)
Influenza-Like Symptoms	6 (2.6%)	8 (3.4%)
Infection Fungal	3 (1.3%)	5 (2.1%)
Back Pain	25 (10.7%)	28 (12.0%)
Arthralgia	11 (4.7%)	16 (6.9%)
Myopathy	8 (3.4%)	9 (3.9%)
Chest Pain	3 (1.3%)	4 (1.7%)
Dyspepsia	13 (5.6%)	18 (7.7%)
Nausea	9 (3.8%)	10 (4.3%)
Abdominal Pain	4 (1.7%)	10 (4.3%)
Hyperlipemia	5 (2.1%)	8 (3.4%)
Hypoglycemia	2 (0.9%)	4 (1.7%)
Rash Erythematous	2 (0.9%)	4 (1.7%)
Premenstrual Symptoms	1 (0.4%)	3 (1.3%)
Urinary Tract Infection	4 (1.7%)	6 (2.6%)
Cystitis	0 (0.0%)	3 (1.3%)
Malaise	2 (0.9%)	8 (3.4%)
Anemia	1 (0.4%)	4 (1.7%)
Conjunctivitis	2 (0.9%)	3 (1.3%)
Allergic Reaction	0 (0.0%)	3 (1.3%)
A subject may have experienced more than one adverse event; therefore, subject counts for Preferred Terms may not equal the sum of subject counts for System Organ Classes or the Total Occurrence Rate.		
<i>Supporting Data:</i>		<i>Page</i>
<i>Appendix C2, Summary 1: Incidence of All Adverse Events</i>		276
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<i>Appendix C3, Listing 2: All Adverse Events by Subject</i>		518

Serious Adverse Events

The sponsor reports no serious adverse events, defined as immediate risk of death, disability, congenital anomaly, cancer, or overdose. However, I have noted from examination of the case report forms (CRFs) for patients discontinuing treatment due to an adverse event, that the sponsor has not recognized a report of one 50 year old male subject (PJST02040013) who was discovered to have a

high grade astrocytoma, 4 days after treatment discontinuation. It was rated as unlikely related to study drug by the investigator. This subject is reported to have discontinued treatment after 16 days of fexofenadine exposure (81% medication compliance estimate) due to headache and acute eustachian tube dysfunction. Although it is difficult to ascribe any causality of the astrocytoma to fexofenadine exposure, the report will be noted.

Deaths - One death was reported for a 29 year old male (#204-028) who committed suicide by gunshot after 177 days of taking Treatment A (placebo). The subject is reported to have had no history of psychiatric disease.

Hospitalizations - Six hospitalizations were reported - placebo = 3, fexofenadine = 3. The sponsor reports the following regarding the three subjects treated with fexofenadine. After reading the complete narrative for these subjects, it is difficult to ascribe causality of the event to fexofenadine. Study drug was reported to have been reintroduced for all three subjects and CFRs were not submitted.

- (PJST0194-0019; 23 year old male) was hospitalized with mononucleosis after 239 days of study treatment. Study drug was reintroduced;

- (PJST0198-0007; 59 year old male) was hospitalized after 98 days of study treatment for chest pain on exertion with bilateral numbness. Two exercise stress tests showed ST depression but cardiac catheterization showed normal vessels. Study drug was reintroduced.

- (PJST0201-0034; 30 year old female) was hospitalized after 253 days of study treatment and going to an emergency room complaining of heartburn. She was diagnosed with gallstones and underwent cholecystectomy.

Pregnancies - Pregnancy was reported in 7 subjects - placebo = 4, fexofenadine = 3. For the subjects treated with fexofenadine, follow-up is ongoing for one and the pregnancy was terminated by induced abortion for another. For the remaining subject, pregnancy was confirmed after the 23rd day of treatment (estimated exposure of 18 days), a child was born with a shallow hip socket, of which the sponsor reports the subject has a family history. The CFR was not submitted by the sponsor for examination. Although it is difficult to ascribe causality of the event to fexofenadine, the report will be noted.

Dropouts Due To Adverse Events - Dropouts due to adverse events were comparable between treatments - placebo = 14, fexofenadine = 12). After reading the narratives for all 26 of these subjects, it is difficult to ascribe causality of the events to fexofenadine. For these 26 subjects, I have examined the CFRs for the adverse event reported in the narrative as cause for discontinuation and found no discrepancies.

Cardiac Arrhythmias

Occurrence of cardiac arrhythmias was similar between treatments - placebo = 9, fexofenadine = 6. Of these only one for each treatment group discontinued study participation due to arrhythmia - placebo (#207-034); fexofenadine (#200-021). The sponsor presents available data on these subjects in tabular format, reproduced below. After examining this table, and the narrative and CFR for the one fexofenadine treated patient which discontinued treatment, it is difficult to ascribe causality of these events to fexofenadine.

Subjects with Cardiac Arrhythmia or Conduction Disturbance Adverse Events							
Site-Subject	Age/Sex	Treatment At Onset	Adverse Event Preferred Term (Verbatim description when different from preferred term)	Event Severity	Relationship to Treatment	Outcome	Other Information/Comments

Protocol PJPR0031

This study compares 6 month safety/tolerance of fexofenadine 60mg BID to Placebo BID in normal healthy subjects using a double-blind, randomized, parallel group, multi-center (15 sites) study design with a total planned enrollment of approximately 400 subjects who are either gender and 12-65 years of age and not taking any proscribed medications. After screening, subjects will have 7 follow-up clinic visits at approximately 30 day intervals. The results reported here are from the sponsor's final report. In the 4 month safety update only an interim report was available since the trial was ongoing at that time.

The sponsor reports that 436 (216-placebo; 220-fexofenadine) subjects were randomized and exposed to treatments, with 428 (211-placebo; 217-fexofenadine) subjects having one postbaseline adverse assessment, qualifying them as safety evaluable. Reproduced below is the sponsor's table displaying the reasons for early discontinuation.

Reasons for Early Discontinuation in Subjects Randomized to Double-Blind Study Medication			
<i>Reason</i>	<i>Placebo (BID) (N=216) N (%)</i>	<i>60 mg MDL 16,455A (BID) (N=220) N (%)</i>	<i>Total (N=436) N (%)</i>
Adverse Event	16 (7.4%)	9 (4.1%)	25 (5.7%)
Elected to Discontinue	22 (10.2%)	22 (10.0%)	44 (10.1%)
Subject did not return. Lost to Follow-up	11 (5.1%)	11 (5.0%)	22 (5.0%)
Use of Prohibited Medication	5 (2.3%)	4 (1.8%)	9 (2.1%)
Other	9 (4.2%)	3 (1.4%)	12 (2.8%)
Total*	42 (19.4%)	41 (18.6%)	83 (19.0%)
* Subjects may have had more than one reason for discontinuing the study; therefore, subject counts for early discontinuation may not equal the total number of subjects having early discontinuation.			
<i>Supporting Data:</i>			<i>Page</i>
<i>Appendix F1. Summary 5: Summary of Reasons for Early Discontinuation - Randomized Subjects</i>			1132
<i>Appendix F2. Listing 2: Reasons for Early Discontinuation in Subjects Randomized to Double-Blind Study Medication</i>			1163

Analyses of baseline demographics for exposed subjects showed no statistically significant differences between treatments for gender, age, age categories, race, weight, and height.

Duration of double-blind treatment exposure was, placebo - 157.4 ± 39.2 days and fexofenadine - 155.9 ± 41.0 days; and percent compliance, placebo - $97.0\% \pm 5.9$ and fexofenadine - $96.8\% \pm 5.2$.

Incidence of All Adverse Events >1% In The Fexofenadine Group and Greater In The Fexofenadine Group Compared To Placebo		
<i>System Organ Class/Preferred Term</i>	<i>Placebo (BID) (N=211) N (%)</i>	<i>60 mg MDL 16,455A (BID) (N=217) N (%)</i>
Upper Respiratory Tract Infection	20 (9.5%)	22 (10.1%)
Bronchitis	2 (0.9%)	3 (1.4%)
Rhinorrhea	1 (0.5%)	5 (2.3%)
Pain	9 (4.3%)	17 (7.8%)
Back Pain	12 (5.7%)	15 (6.9%)
Myalgia	11 (5.2%)	14 (6.5%)
Arthralgia	6 (2.8%)	7 (3.2%)
Diarrhea	2 (0.9%)	4 (1.8%)
Gastroenteritis	2 (0.9%)	4 (1.8%)
Abdominal Pain	1 (0.5%)	3 (1.4%)
Eosinophilia	1 (0.5%)	3 (1.4%)
Hyperlipemia	4 (1.9%)	6 (2.8%)
Fever	3 (1.4%)	4 (1.8%)
Erythema	3 (1.4%)	4 (1.8%)
Anemia	2 (0.9%)	6 (2.8%)
SGPT Increased	3 (1.4%)	5 (2.3%)
Earache	2 (0.9%)	4 (1.8%)
A subject may have experienced more than one adverse event; therefore, subject counts for Preferred Terms may not equal the sum of subject counts for System Organ Classes or the Total Occurrence Rate.		
<i>Supporting Data:</i>		<i>Page</i>
<i>Appendix J2, Summary 1: Incidence of All Adverse Events</i>		<i>1691</i>
<i>Appendix J3, Listing 1: All Adverse Events Reported by System Organ Class</i>		<i>1766</i>
<i>Appendix J3, Listing 2: All Adverse Events by Subject</i>		<i>1873</i>

Serious Adverse Events

No life-threatening events, disabilities, congenital anomalies, or overdoses were reported.

Deaths - One patient (#180-019 - 54 year old male) was hospitalized after suffering a cerebrovascular accident after 14 days on placebo and later suffered cardiopulmonary arrest and died.

Hospitalizations - In addition to the hospitalization of the patient that died, another patient (#186-025 - 31 year old male) was hospitalized, after treatment with fexofenadine 60mg twice daily for approximately 5 months, for a psychotic, paranoid, delusional episode of 8 day duration. This patient was the subject of a 10-Day adverse reaction report (2/13/96 - serial #075) to the IND through the sponsor from the investigator. This report indicates that he was treated with haloperidol, lithium and lorazepam and improved and was discharged. His medical history includes bipolar disorder.

Cancer - Another patient (#185-006 - 23 year old female) discontinued treatment after 75.5 days on fexofenadine because of a malignant melanoma of the left calf. The lesion was present at baseline but the decision to biopsy was made because of change in lesion size.

Dropouts Due To Adverse Events - Dropouts due to adverse events were more frequent in the placebo group - placebo = 16, fexofenadine = 9. After reading the narratives for all 25 of these subjects, it is difficult to ascribe causality of the events to fexofenadine. For the 9 subjects who were on fexofenadine treatment, I have examined the CFRs for the adverse event reported in the narrative as cause for discontinuation and found no discrepancies.

Pregnancies - Pregnancy was reported in 3 subjects - placebo = 2, fexofenadine = 1. For the subject exposed to fexofenadine, pregnancy was confirmed during the 4th month of treatment (estimated exposure of 14 days). The sponsor reports that a healthy female child was born.

Cardiac Arrhythmias

Occurrence of cardiac arrhythmias was similar between treatments - placebo = 2, fexofenadine = 2. Of these neither in the fexofenadine treated group discontinued study participation due to arrhythmia. The sponsor presents available data on these subjects in tabular format, reproduced below. After examining this table, it is difficult to ascribe causality to fexofenadine.

Subjects with Cardiac Arrhythmia or Conduction Disturbance Adverse Events							
Site-Subject	Age/Sex	Treatment At Onset	Adverse Event Preferred Term (Verbatim Description When Different from Preferred Term)	Event Severity	Relationship To Treatment	Outcome	Other Information/Comments
191-026							
184-020							
180-019							

Subjects with Cardiac Arrhythmia or Conduction Disturbance Adverse Events							
Site-Subject	Age/Sex	Treatment At Onset	Adverse Event Preferred Term (Verbatim Description When Different from Preferred Term)	Event Severity	Relationship To Treatment	Outcome	Other Information/Comments
193-027							
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Appendix J3, Listing 1: All Adverse Events Reported by System/ Organ Class							1766
Appendix J3, Listing 2: All Adverse Events by Subject							1873

Clinical Laboratory Data

The sponsor reports that there were no statistically significant changes from baseline between treatment groups for mean clinical laboratory data except platelet count (P=0.048; placebo = $-11.30 \times 10^3/uL$; fexofenadine = $-16.81 \times 10^3/uL$), which does not appear to be clinically significant. Results from shift and outlier tables were generally unremarkable.

ECG Results/ Vital Signs

The sponsor reports no statistically significant differences between treatments in change from baseline for vital signs or ECG measurements (QTc, QT, QRS, PR, HR). The number of subjects with post baseline outlier values for QTc (QTc > 440msec and increase > 10msec) was similar between treatments : placebo - 18 (8.6%); fexofenadine - 16 (7.4%).

Protocol PJPR0045

This single-dose six-period crossover trial was conducted to establish the bioequivalence of 180mg fexofenadine HCl tablet formulations. The sponsor reports no serious adverse events.

Serious Adverse Events Reported From Other Ongoing Trials

The sponsor provides a comprehensive table of 18 ongoing clinical trials, worldwide. From these trials the sponsor reports 5 serious adverse events which have occurred between the time of the NDA cut-off date of March 31, 1995 and May 15, 1996. The sponsor's table is reproduced below. One additional patient (#0388-0008) is the subject of a 10-Day ADR report to the IND (May 29, 1996 - serial #080). This report indicates that the subject was taking fexofenadine 120mg twice daily for about 6 days prior to the event, and that his atrial fibrillation was converted to sinus rhythm with one dose of digoxin. His medical work-up appears normal thus far. QTc on the date of the event following conversion is reported as 405 msec when in sinus tachycardia and 395 msec on the following day when he was in normal sinus rhythm. From this limited information it is difficult to ascribe causality of any of these events to fexofenadine.

List of Serious Adverse Events from Other Ongoing Studies with Fexofenadine Hydrochloride									
Protocol	Patient No.	Age	Sex	Unblinded Treatment	Adverse Event Preferred Term	Severity	Study Drug Relationship	Outcome	Serious Criteria
PJPR0019	0117-0003								a-
PJPR0019	0117-0006								
PJPR0032	0222-0008								
PJPR0032	0429-0013								
PJPR0053	0388-0008								

NOS = Not Otherwise Specified

C) Open NDA Issues

1) Division of Scientific Investigation (DSI) Inspection

All requested inspections of investigational sites had been completed except that for Dr Frank Hampel, site #21 for Protocol PJPR0009. The results for the inspection are now available and indicate that no substantive violations were observed. A photocopy is attached (Attachment A) of the letter to the investigator indicating field classification of NAI (No Action Indicated). This study site is noted in other parts of the NDA as having been the site where incorrect unblinding of treatment assignment for 6 subjects occurred. This discovery was the result of the use of a form generated by the statistical reviewer, Barbara Bono, for this NDA for the Pulmonary Division, for DSI use to directly match SAS data to patient records at the study site. A photocopy of the form for subject #021064 is attached (Attachment A) and documents the inspector's findings. All other data points selected for audit for this patient and the other patients selected for audit were verified as correct. These forms, although generated for other investigational sites, were not used by the DSI investigators. The reader is referred to the medical officer review of protocol PJPR0009 which discusses the issue of incorrect unblinding and its resolution in greater detail.

2) Consult To Cardio-Renal Pharmacologist Regarding Canadian Arrhythmia Study - "Testing for Antihistamine-Induced Cardiac Arrhythmias." by G. N. Beatch, Ph.D. of the Canadian Health Protection Branch.

In the Overview of Safety, there is discussion of the results from a study in a rabbit model of ventricular arrhythmias. Additional comment was sought from John Koerner, Ph.D. in the Division of Cardio-Renal Drugs because of his past experience using the same and other animal models used to evaluate arrhythmogenic potential of drugs. His comments, dated May 13, 1996, are attached (Attachment B) with out a photocopy of the original study report (copy of the original study report added to the Division File with arrival date of March 28, 1996). Dr Koerner points out several observations regarding the results of the study :

"terfenadine did not significantly increase the incidence of polymorphic ventricular tachycardia (VT) in this model, suggesting that the sensitivity of the ...model is limited or that the doses were inadequate to elicit this arrhythmia;"

"although nonsignificant increase in monomorphic tachycardia incidence was observed....with intravenous fexofenadine these monomorphic tachycardia....did not fill the criteria for torsades;"

"....any suggestion of a relationship of fexofenadine to induction of monomorphic tachycardia could not be established due to the small sample size."

Given the uncertain significance of these findings and their relevance to the clinical experience, the findings of this study should not change the conclusions previously reached regarding the safety profile of fexofenadine, particularly since the human experience thus far does not indicate a propensity for fexofenadine to prolong QTc intervals at the clinical dose.

3) Reanalysis of QTc Data From Protocol PJPR0003

Since the sponsor initially analyzed these data including times points out to 72 hours past the last dose for the Day 30 analysis, which would include data when serum concentrations were declining, the sponsor was asked to reanalyze the data without those time points. The sponsor provided, on April 1, 1996, the

reanalysis for Morganroth read and machine read data for mean daily QTc data and added an analysis for mean maxima QTc. The results for the reanalyses for both the Morganroth-generated data and machine-generated data were virtually unchanged by the exclusion of the extra time points:

Largest change from baseline for Day 30 (1st analysis vs reanalysis, respectively)-

Morganroth: +14.2msec (40mg) vs +15.7msec (40mg);

Machine: +6.5msec (690mg) vs +8.6msec (690mg).

The added analyses for QTc maxima were not previously conducted using the extra time points; but comparison of the Morganroth and machine data for the analyses provided in this submission show the following largest and smallest changes from baseline for Day 30, respectively (largest vs smallest, respectively):

Morganroth: +19.8 msec (40mg); -6.8 msec (Placebo);

Machine: +13.3 msec (690mg); -9.7msec (160mg).

No obvious dose response can be detected for the mean QTc or maxima analyses.

These reanalyses do not change conclusions reached during the initial review of the results for protocol PJPR0003.

4) Protocol PJPR0007 -

A) Gender Effects On QTc Response

On April 1, 1996 the sponsor provided a response to the Agency's request for an examination of the data between genders. The sponsor conducted analyses for mean QTc and maxima QTc. The sponsor reports that there were no statistically significant differences in treatment effects between genders on Day 2 or Day 8. However, females in general had numerically longer QTc intervals and change from baseline (including placebo) than males.

Gender By Treatment Interaction Significance Levels		
	Day 2	Day 8
Mean QTc	0.3562	0.8061
Maxima QTc	0.3684	0.4432

The sponsor also provided analyses for relationships between QTc by gender and fexofenadine plasma concentrations and reported significance levels for Spearman correlation coefficients for the following variables: Day 8 mean QTc vs AUC; Day 8 maximum QTc vs Cmax,ss; Day 8 change from baseline mean QTc vs AUC; Day 8 change from baseline maxima QTc vs AUC; serial QTc vs plasma concentration and serial change from baseline QTc vs plasma concentration. The sponsor reports no statistically significant positive correlation between fexofenadine concentration and QTc for either gender. The smallest reported significance level is p=0.1197 for Day 8 change from baseline mean QTc vs AUC.

B) Statistical Power and Carryover Effect

During the initial review of the results from this protocol the statistical reviewer was asked to comment on the magnitude of statistical power to detect differences in change from baseline in QTc responses and to comment on the possibility of carryover effect from period to period. The statistical reviewer, Barbara

Bono, in her two addenda, dated June 3 and 18, 1996, to her original review for the NDA, indicates the following:

a) power estimate of approximately 71% (Morganroth) and 62% (machine-generated) for change from baseline in QTc which yielded no statistically significant difference among any two of the dose groups with the largest difference being 3.24msec between 40mg and 400mg groups (Morganroth) and 1.44msec between placebo and 400mg groups (machine-generated).

b) the results of analyses conducted by the sponsor and the statistical reviewer indicate no carryover effect from period to period.

5) Syncope Reports As Adverse Events

It was noted in the final safety report that 4 episodes (3 for active treatment and 1 for placebo) of syncope were reported. The sponsor was asked to provide the CRFs for all patients reported in the NDA to have experienced an adverse event reported as syncope. The sponsor's response was received June 19, 1996 (CRFs for 5 patients) and June 21, 1996 by telefax (CRF for sixth patient and ECG information for patients in PJPR0027). For three subjects the episode of syncope occurred during blood drawing - #046-013 on fexofenadine (PJPR0015), #167-037 on fexofenadine (PJPR0024), #199-014 on placebo (PJPR0027). The remaining 3 subjects were all in PJPR0027 and were all taking fexofenadine - #196-009, #201-099, and #206-010.

For subject #196-009, the QTc was 389msec on the day of the event (QTc = 401msec at screening; 409 at study end); and the event did not reoccur despite reintroduction of study medication for 4 additional months until completion of study with 97-101% medication compliance reported for the 4 remaining visits.

For subject #201-099, additional events were not reported despite continuation of study medication for 6 additional months until completion of study with 93-104% medication compliance reported for the 6 remaining visits; the patient reportedly was found by the police in her car unable to remember anything. She had started Prozac the same day, and reportedly had the event work-up by her physician but no diagnosis made; and did not release her medical records. The subject's QTc was 401msec at screening, 405msec about one month after the episode, and 381msec at study end.

Subject #206-010, discontinued from trial after 4 days participation because of syncope (dizziness) which he experienced 15 minutes after each dose of study medication and which lasted 3 hours. QTc at baseline screening was 421msec and 405msec at exit visit 12 days later. It is difficult to clearly ascribe causality of any of the reported syncopal episodes to fexofenadine.

Reviewer's Determinations Regarding The Final Safety Update and Open NDA Issues

The results from this final safety update and open NDA issues do not alter the safety or efficacy determinations made during initial review of this NDA. However, note is made of a report of a congenital anomaly, shallow hip socket, (PJST0205-002) and a separate report of astrocytoma (PJST02040-013) in study PJPR0027.

STATISTICAL REVIEW AND EVALUATION STABILITY STUDY

NDA#: 20-625
Applicant: Hoechst Marion Roussel, Inc.
Name of Drug: Allegra (Fexofenadine Hydrochloride or Fexofenadine)
Indication: Treatment of patients with seasonal allergic rhinitis
Documents Reviewed: June 3, 1996 Electronic data and documentation
Statistical Reviewer: B. Bono, M.S.
Chemist: C. Bertha, Ph.D.
Key words: linear regression, intercept, slope, 95% confidence interval, assay, water content, total degradation, degradation product

Summary of Review

- The sponsor proposes a 24 month expiry date based on 18-months of data.
- This review focuses on the clear blister packages, and the 30- and 3000-count bottles.
- The data support a 24 month expiry date for clear, blister packages, 30-count and 3000-count bottles.

I. Background

Hoechst Marion Roussel has submitted 18 month stability data (25 degrees Celsius and 60% relative humidity) on drum, foil, foil blisters, 30-, 100-, 500- and 3000-count HDPE bottles, clear and opaque PVC/PVDC blisters. It should be noted that the clear PVC/PVDC blisters and the 30-, 100-, 500- and 3000-count HDPE bottles are the only packaging types to be used with the United States marketed drug product. The applicant proposed a 24 month expiration period for all of these packages. The reviewing chemist, Craig Bertha, Ph.D., HFD-570, has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data for the clear blister packages and the 30- and 3000-count bottles for each of the following variables using the specifications listed below:

1. Assay (Potency)
2. Water Content
3. Total degradation
4. MDL 102,038 degradation product

II. Reviewer's Analyses

The statistical procedures described in the FDA Guidelines (February 1987) were applied to the stability data provided by the sponsor.

Poolability tests indicate that in the analyses of Assay, Total Degradation and 102,038 Degradation Product, the data cannot be pooled to calculate common intercepts; and in the analysis of 102,038 Degradation Product in the 30-count bottles, the data cannot be pooled to calculate a common slope (Table 1). Hence, different regression lines are fitted to the three different batches for all of the factors except water content (Table 2).

Table 1: Poolability Test Results

Factor	Packaging		
	Clear Blister	30-Count Bottles	3000-Count Bottles
Assay			
Water Content			-
Total Degradation			-
102,038 degradation			

2 Pages

Purged

III. Conclusions

The proposed 24 month expiration date for clear blister packages, and 30- and 3000-count bottles is supported by the 18 month data the sponsor submitted. This is based on the specification limits of assay, water content, total degradation and the formation of the MDL 102,038 degradant. However, the results are based on data extrapolation beyond the range of storage time actually observed. The sponsor should be requested to continue to collect data up to 24 months and reanalyze the data when new data become available.

Barbara A. Bono

Barbara A. Bono

Concur: Dr. Wilson
Dr. Lin

EW 7/9/96
K. L. 7/9/96

cc.

Orig. NDA 20-625

HFD-570 / Division File

HFD-570 / GStrange

HFD-570 / CBertha

HFD-570 / GPoochikian

HFD-570 / Y-YChiu

HFD-570 / MSevka

HFD-715 / Division File, Chron

HFD-715 / ENevius, SWilson, KLin, BBono

bb/NDA/20625/STAT/95-07-31.CON

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA #: 20-625 **Date:** JUN 29 1996
Applicant: Marion Merrell Dow, Inc. / Hoechst Marion Roussel, Inc.
Name of Drug: Allegra (Fexofenadine hydrochloride or Fexofenadine)
Indication: Treatment of patients with seasonal allergic rhinitis (SAR)
Documents Reviewed:
July 31, 1995 Volumes 1.1, 185 - 311
Aug 15, 1995 Replacement Volume 219
September, 1995 Computer Assisted New Drug Application (CANDA)
Sept 5, 1995 Supporting Statistical Analysis Programs, Datasets and Documentation
Sept 27, 1995 Electronic Data (Adverse Events, ECG, Laboratory Tests)
Jan 19, 1996 Amendment describing problem with treatment codes of six patients
Statistical Reviewer: B. Bono, M.S. (HFD-715)
Medical Input: M. Sevka, M.D. (HFD-570)
Key Words: ANCOVA, Step-Down Procedure, Closed Procedure, linear-dose response, contrasts, interaction effects

Summary of Review

- The applicant submitted four large studies (Study 9, n=962; Study 10, n=995; Study 23, n=545, Study 24, n=570) to support the claim that fexofenadine is safe and effective in reducing the symptoms of seasonal allergic rhinitis. A five-point rating scale was used to assess each of the following symptoms: sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes. The reduction in TSS (defined as the average change between baseline and treatment period) ranged from -0.76 to -1.33 units for placebo and -0.91 to -2.55 units for active drug.
- Results from Studies 10, 23 and 24 support the conclusion that there was a statistically significant difference in reduction of total symptom score between fexofenadine and placebo.
- Studies 10 and 24 had statistically significant treatment interaction effects.
- Results from Study 9 were not consistent with those from Studies 10, 23 and 24.
- There was no apparent increase in efficacy with increasing dose above the 60 mg dose in any of the studies.

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I. Background Information

A. Introduction

The applicant has submitted four placebo-controlled multiple-dose clinical studies (9, 10, 23, and 24) to support the claim that fexofenadine is safe and effective, and two cardiac studies (03,07) to support the claim that fexofenadine does not prolong QTc intervals. (Treatment effects were not found to be statistically significant in the two cardiac studies. Study 7 is reviewed in two addenda to this review, dated June 3 and 18, 1996.) Studies 10, 23 and 24 support the claim that fexofenadine is effective. The results from Studies 10, 23 and 24 were robust. The applicant is proposing to market the 60 mg dose. One onset of action study was submitted to support the claim that the 60 mg dose starts acting at 60 to 80 minutes after dosing. This review focuses on Studies 9, 10, 23 and 24.

B. Summary of Studies

1. Objectives

The objectives of the studies were to determine the safety and efficacy profile of fexofenadine at varying doses BID as compared to placebo in the treatment of seasonal allergic rhinitis (SAR).

2. Designs

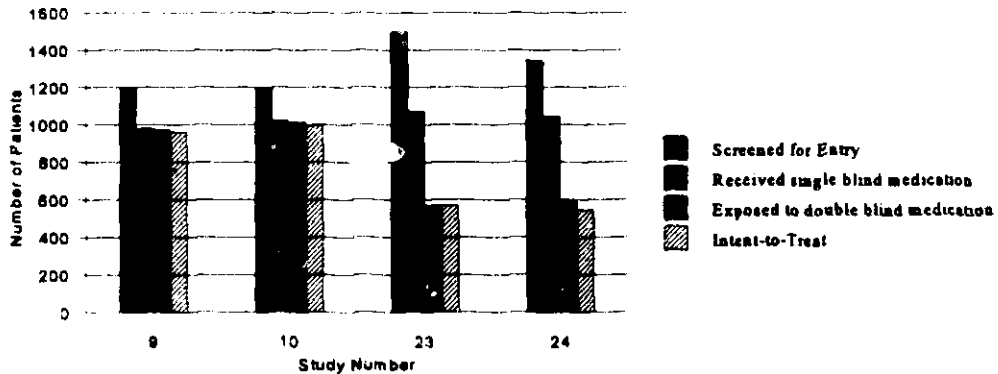
The studies were placebo-controlled, double-blind, randomized, parallel designs in patients with SAR (Table 1). Spring studies 9 and 10 were identical in design; fall studies 23 and 24 were identical in design. A single-blind placebo lead-in period (to measure baseline symptoms) was followed by a 2-week double-blind treatment period, with a total of 4 visits: Screen (which was combined with Entry in Study 10 in some cases), Entry, Interim, and Final, or Early Discontinuation. A bar chart of patient entrance and exit for all four studies is shown below (Figure 1). Patients took the treatment medication twice a day at 7 AM and 7 PM in all the studies.

An interim analysis was performed in Studies 9 and 10 to plan the design of Studies 23 and 24. The wide range of baseline values present in Studies 9 and 10 (0-15 units) influenced the design of Studies 23 and 24. Patients in Studies 23 and 24 were randomized to treatment after the single-blind baseline period and eligible to continue if the symptom scores were within a narrower range (5-12 units) than those in Studies 9 and 10.

Table 1: Study Designs

Study	Design
09 n=962	A placebo-controlled, double-blind, randomized, parallel design spring study in patients with SAR. A 2-day single-blind placebo lead-in period was followed by a 2-week double-blind treatment period. Patients were randomized before the placebo period to either placebo, 20 mg, 40 mg, 60 mg or 80 mg fexofenadine.
10 n=995	A placebo-controlled, double-blind, randomized, parallel design spring study in patients with SAR. A 2-day single-blind placebo lead-in period was followed by a 2-week double-blind treatment period. Patients were randomized before the placebo period to either placebo, 20 mg, 40 mg, 60 mg, or 80 mg fexofenadine.
23 n=545	A placebo-controlled, double-blind, randomized, parallel design fall study in patients with SAR. A 3-day single-blind placebo lead-in period was followed by a 2-week double-blind treatment period. Patients who responded to placebo were discontinued from the study. The remaining patients were then randomized (after the placebo period) to either placebo, 60 mg, 120 mg, or 240 mg fexofenadine using a stratified randomization scheme based on their baseline TSS levels.
24 n=570	A placebo-controlled, double-blind, randomized, parallel design fall study in patients with SAR. A 3-day single-blind placebo lead-in period was followed by a 2-week double-blind treatment period. Patients who responded to placebo were discontinued from the study. The remaining patients were then randomized (after the placebo period) to either placebo, 40 mg, 60 mg, 120 mg fexofenadine using a stratified randomization scheme based on their baseline TSS levels.

Figure 1: Summary Chart of Patient Activity



3. Efficacy Variables

Efficacy was based on assessments of the severity of the following individual allergy symptoms: sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes. A 5-point subjective rating scale was used. The total symptom score (TSS) for any observation time was the sum of the individual symptom scores. Nasal congestion was also assessed, but its severity rating was not included in TSS, as relief of nasal congestion was not expected using an H1-antagonist.

The primary efficacy variables were defined as the **average change between baseline and treatment period** for daily Bedtime Reflective TSS in Studies 9 and 10, and daily 7 PM Reflective TSS in Studies 23 and 24 (Tables 2a and 2b). Baseline was calculated as the average of the placebo lead-in 7 PM Reflective scores. (In Studies 23 and 24, the first day of the placebo lead-in period was not used as per protocol.) In all the studies, as per protocol, the first day of the double blind period was not used in calculating the average of the treatment period. If any of the individual symptoms used in calculating the TSS were missing then that TSS evaluation was also coded as missing. If any day of the treatment period had a missing value for TSS, the average TSS over the period was calculated using the recorded values. These details were outlined in the protocol.

Table 2a: Baseline Values

Baseline Symptoms	Spring Studies			Fall Studies		
	Bedtime 12-hour Reflective			7 PM 12-hour Reflective		
	9	10	Pooled	23	24	Pooled
Sneezing						
Mean ± SD	1.7 ± 0.8	1.3 ± 0.9	1.2 ± 0.8	2.0 ± 0.7	2.0 ± 0.7	2.0 ± 0.7
Range	0.0-4.0	0.0-3.5	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0
Rhinorrhea						
Mean ± SD	1.4 ± 0.9	1.5 ± 0.9	1.5 ± 0.9	2.4 ± 0.5	2.3 ± 0.5	2.4 ± 0.5
Range	0.0-3.5	0.0-4.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0
Itchy Nose, Palate +/-or Throat						
Mean ± SD	1.4 ± 0.9	1.5 ± 0.9	1.4 ± 0.9	2.2 ± 0.6	2.2 ± 0.6	2.2 ± 0.6
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0
Itchy, Watery, Red Eyes						
Mean ± SD	1.4 ± 0.9	1.5 ± 1.0	1.5 ± 0.9	2.2 ± 0.7	2.1 ± 0.7	2.1 ± 0.7
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0
TSS						
Mean ± SD	5.3 ± 2.6	5.7 ± 2.9	5.5 ± 2.7	8.9 ± 1.8	8.7 ± 1.7	8.8 ± 1.7
Range	0.0-13	0.0-15	0.0-15	4.3-12	5.0-12	4.3-12

Individual symptoms were rated by the investigator at the Entry Visit. The same individual symptoms were assessed and recorded by the patient in a diary at various times throughout the day as specified in each protocol. Assessments were either reflective, based on the severity of the individual symptoms for the previous 12 hours, or instantaneous, based on the severity of the individual symptoms for the previous 1 hour (Table 3). Since the patients took the medication at 7AM and 7PM, the instantaneous assessments at 7AM and 7PM were indications of the efficacy of fexofenadine at the end of the dosing intervals. At the Final Visit, in addition to rating the individual symptoms, the investigator rated the overall effectiveness of the study medication using a 5-point scale (complete relief, marked relief, moderate relief, slight relief, or no relief), and asked the patient if he/she would wish to take the study medication again.

Table 2b: Summary of Efficacy Parameters

	Spring Studies (9 and 10)	Fall Studies (23 and 24)
Primary Efficacy	Change in patient's average 12-hour reflective bedtime TSS	Change in patient's average 12-hour reflective 7 PM TSS
Secondary Efficacy	• Patient's assessment of: 1. Change in bedtime TSS for all days during the double-blind period 2. Change in average bedtime individual symptoms (sneezing; rhinorrhea; itchy nose, palate, and/or throat; itchy, watery, red eyes; nasal congestion) 3. Change in average noon TSS (reflective) 4. Change in average morning predose TSS (reflective) 5. Willingness to take study medication again. - Physician's assessment of: 1. Change in TSS (Entry and Final Visit) 2. Change in individual symptoms • Physician's evaluation of overall effectiveness- patient's were categorized as either a responder (complete, marked or moderate relief of symptoms) or a non-responder (slight or no relief of symptoms).	• Patient's assessment of: 1. Change in 7 PM reflective TSS over time (changes after each day, average of week 1, and average of week 2 of double-blind dosing period) 2. Change in average 7 AM reflective TSS 3. Change in average 7 PM instantaneous TSS 4. Change in average 7 AM instantaneous TSS 5. Change in average bedtime instantaneous TSS 6. Change in average 7 PM reflective individual symptoms (sneezing; rhinorrhea; itchy nose, palate, and/or throat; itchy, watery, red eyes; nasal congestion) • Physician's evaluation of overall effectiveness- patient's were categorized as either a responder (complete, marked or moderate relief of symptoms) or a non-responder (slight or no relief of symptoms).

**Table 3: Patient Symptom Assessments Collected in Studies 9, 10, 23 and 24
(Treatment was taken twice a day at 7AM and 7PM)**

Spring Studies (9 and 10)			Fall Studies (23 and 24)		
Assessment	Type	Reflective/ Instantaneous*	Assessment	Type	Reflective/ Instantaneous*
Noon	Peak	Reflective	7 AM	Trough	Reflective
Bedtime	Peak	Reflective	7 AM	Trough	Instantaneous
Morning Predose†	Trough	Reflective	7 PM	Trough	Reflective
			7 PM	Trough	Instantaneous
			Bedtime	Peak	Instantaneous

* Reflective (patient assesses symptoms over previous 12 hours)
Instantaneous (patient assesses symptoms over previous hour)

† Morning predose symptom assessment was collected at only the interim and final visits in the Spring studies.

The intent-to-treat (ITT) population was defined as any patient who takes the drug and comes back for at least one assessment of the primary efficacy variable (i.e.: Bedtime Reflective in Studies 9 and 10; 7 PM Reflective in Studies 23 and 24). This is the population the sponsor used for the primary analyses in all the placebo-controlled studies.

4. Statistical Concerns

- The "Closed Procedure" or "Step-Down Procedure" was used in all four trials submitted by the sponsor to make dose comparisons.¹ This procedure protects the overall Type I error rate by previously specifying the multiple comparisons which will be studied and the order in which the comparisons will be made. Each comparison could be assessed if the preceding comparison was statistically significant. In each study the protocol stated that the sequence of comparisons would start with the highest dose versus placebo and follow to the lowest dose versus placebo.
- In all the studies the sponsor tested the linear trend of the doses of the drug using an equation that inappropriately included the placebo group. For each study, a linear trend of the doses without placebo is tested in the discussion section (IIB).
- The protocol-specified analyses were analyses of variance with treatment and investigator as factors in Studies 9 and 10; and treatment, investigator and a dichotomous baseline score (High, Low) as factors in Studies 23 and 24. The primary efficacy variable in all the studies was analyzed using an analysis of covariance model with treatment, investigator and a continuous covariate baseline TSS, as predictor variables.
- Interaction effects of treatment with baseline and investigator were tested at the same time. If

¹Hochberg Y, Tamhane, AC. *Multiple Comparisons Procedures*. 1st ed. New York, NY: John Wiley & Sons, Inc.; 1987, pp 53-71.

either interaction effect was significant, it was included in the model. Studies 10 and 24 had a significant treatment-by-baseline interaction effect that posed problems with interpretation of the results. This is examined in the discussion section (II-C). Study 10 has a significant treatment-by-investigator interaction effect.

- The potential impact of missing daily diary entries are addressed in detail in the discussion section (II-D).
- Compliance was very high in all the studies ranging from 99-100% per the sponsor's reports. An explanation of how the sponsor measured compliance and descriptive statistics are found in the discussion section (II-E).

5. Adverse Events

Safety evaluations included clinical laboratory panels, physical examinations, and adverse event reporting.

There was no obvious relationship between dose of fexofenadine and number of patients reporting adverse events in any of the four placebo-controlled clinical studies (Table 4).

Table 4: Summary Table of Incidence of Adverse Events for all the studies

	Percentage of patients with 1 or more adverse events							Total Active
	Placebo	20 mg	40 mg	60 mg	80 mg	120 mg	240 mg	
Study 9	38.0	32.3	34.2	34.2	29.0			32.4
Study 10	33.5	29.3	28.9	35.1	23.0			29.1
Study 23	45.1			30.5		26.4	31.0	29.3
Study 24	33.8		36.6	37.2		34.0		35.9

C. Summary of Sponsor's Analyses

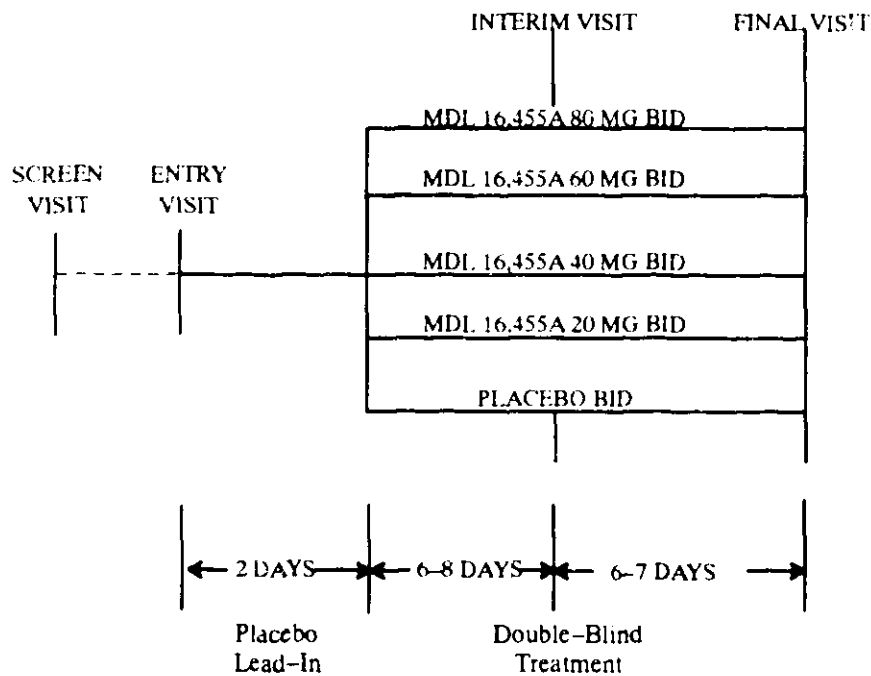
1. Study PJPR0009 - Spring Study - 20 mg, 40 mg, 60 mg, 80 mg

Note: There were six patients in this report who had the incorrect treatment recorded in the original Clinical Study Report. Refer to Dr. Michael Sevka's clinical review for details. All analyses originally submitted by the sponsor were performed using the incorrect treatment for the six patients. The primary efficacy intent-to-treat analysis and the protocol correct analysis were re-submitted by the sponsor using the correct treatment codes for the six patients. These results are reported here. The sponsor will submit a revised Clinical Study Report. The revised Clinical Study Report was not available for this review. The Week 1 and Week 2 analyses, the subgroup analyses, the individual symptom analyses and all other secondary analyses and the adverse event frequencies presented in this review were obtained from the original Clinical Study Report of Study 9.

a. Study Design

A two-day single-blind period was followed by a two-week double-blind period (Figure 2). Patients reflectively assessed and recorded individual symptoms at noon and bedtime (1-3 hours after the 7 PM dose). They reflectively assessed and recorded individual symptoms before their morning dose at the interim and final visits.

Figure 2: Study Design



*MDL 16,455A refers to Fexofenadine.

b. Interim Analysis

An interim analysis was performed in order to plan the design of subsequent studies. Based on results of the interim analysis, the α -levels for the interim and final analyses were calculated to be 0.0026 and 0.0490 respectively.

c. Statistical Methods

An analysis of covariance (ANCOVA) model was used to analyze the primary efficacy variable—change in bedtime reflective TSS. The protocol-specified analysis was an analysis of variance with investigative site and treatment as factors. Baseline TSS was found to be an important predictor

of the magnitude of reduction in TSS, thus the sponsor changed the primary efficacy analysis to an ANCOVA to include baseline as a continuous covariate. The results of the protocol-specified analysis were reviewed and were found to be similar. Only the ANCOVA will be presented in this review.

d. Results

Patient Accounting and Demographics

Nine hundred eighty-two (982) patients were randomized to receive treatment. Seven patients discontinued the study prior to receiving double-blind medication. The remaining 975 patients were exposed to double-blind treatment. Nine hundred sixty-two (962) of these patients had both baseline and post baseline bedtime symptom assessments; and 919 of these patients completed the study.

Summaries of patient demographics can be found in Appendix A. The treatment groups were similar with respect to baseline demographic characteristics and symptom scores.

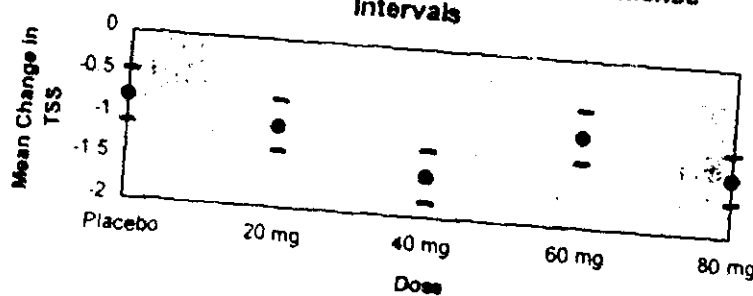
Primary Efficacy Variable and Analysis

Means and the associated standard deviations and 95% confidence intervals of the change in the bedtime reflective TSS are reported in Table 5 and plotted in Figure 3. Least squares means and associated standard errors from the primary efficacy analysis model are also reported in Table 5.

Table 5. Study 9: Means and Least Squares Means of Primary Efficacy Variable

Treatment (BID)	N	Change from Baseline Bedtime Reflective TSS		
		Mean ± SD	95% Confidence intervals	Least Squares Mean ± SE
Placebo	190	-0.76 ± 2.23	(-1.08, -0.44)	-0.69 ± 0.14
20 mg	194	-1.02 ± 2.12	(-1.32, -0.72)	-1.03 ± 0.13
40 mg	195	-1.51 ± 2.21	(-1.82, -1.20)	-1.43 ± 0.13
60 mg	191	-0.91 ± 2.23	(-1.22, -0.59)	-0.97 ± 0.14
80 mg	192	-1.30 ± 2.03	(-1.59, -1.01)	-1.32 ± 0.13

Figure 3: Study 9 Means and 95% Confidence Intervals



From the primary analysis model, the overall F test rejected the null that the means of all the doses (including placebo) were equal (p = .0007, Table 6). The mean TSS change from baseline of the 80 mg dose was statistically significantly different than that of placebo, however the 60 mg dose

was not. Because the sponsor used the "Step-Down Procedure" (discussed above), the comparisons of the other two doses could not be tested. Baseline was also statistically significant ($p = .0001$), indicating that patients with higher baseline TSS were likely to show a larger reduction in TSS, regardless of treatment. Investigator was found to be statistically significant ($p = .0003$), indicating that patients at different investigative sites were likely to show different reductions in TSS, regardless of treatment. Treatment by baseline interaction and treatment by investigator interaction were included in the model one by one and also together and were not found to be significant.

Although a linear trend in dose is significant ($p = .0045$) when the placebo group is included in the contrast vector, the significance does not remain when the placebo group is excluded. This is explained in detail in the discussion section (II-B).

6. Study 9: Intent-to-Treat Analysis of Change in Bedtime Reflective TSS (N = 962)

ANCOVA Model Covariates		P value *
Overall Treatment Differences		.0007
Baseline TSS		.0001
Investigator		.0003
Dose Response (Linear Trend)		.0045
Treatment Comparison	Mean ± Standard Error * of difference in means (Active minus Placebo)	
20 mg fexofenadine vs Placebo	-0.34 ± 0.19	.0767
40 mg fexofenadine vs Placebo	-0.74 ± 0.19	.0001
60 mg fexofenadine vs Placebo	-0.28 ± 0.19	.1471
80 mg fexofenadine vs Placebo	-0.63 ± 0.19	.0009
* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline and treatment		

Secondary Efficacy Variables and Analyses

Patient Assessments

The results from weekly analyses of the bedtime reflective TSS were similar (Table 7).

Table 7: P-values for comparisons with Placebo

Dose	Week 1	Week 2
20 mg vs Placebo	.0561	.1431
40 mg vs Placebo	.0001	.0021
60 mg vs. Placebo	.0691	.5211
80 mg vs. Placebo	.0018	.0063

Subgroup analyses by weight categories, by age categories, by gender and by race show that there are no significant interactions with treatment.

Individual analyses of covariance were done for each bedtime reflective symptom. Comparisons between each dose group and placebo were made for every symptom. The 40 and 80 mg doses reached significance for every symptom except nasal congestion. The 20 and 60 mg doses reached significance for sneezing only.

None of the dose groups were statistically significantly different from placebo in terms of the Patient's Willingness to Take Study Medication Again.

Physician Assessments

The physician's assessment of TSS and the individual symptoms was analyzed using an ANCOVA with baseline TSS, investigator and treatment as predictor variables. All dose groups were statistically significantly superior to placebo with respect to TSS. The 60 mg and 80 mg dose groups reached statistical significance over placebo for sneezing and rhinorrhea. With respect to itchy nose, palate and/or throat, the 40 mg and 60 mg dose groups were significantly different than placebo. Only the 40 mg dose group reached statistical significance over placebo for itchy, water, red eyes. No dose groups showed statistically significant improvement over placebo in the relief of nasal congestion.

Results of the Physician's Evaluation of Overall Effectiveness showed that only the 20 mg and 40 mg dose groups were statistically significantly superior to placebo.

Adverse Events

When considering all adverse events that occurred while patients were receiving double-blind study medication, 32.4% (253/780) of the patients receiving fexofenadine and 38.0% (73/192) of the patients receiving placebo experienced one or more adverse events. There was no obvious relationship between dose of fexofenadine and number of patients reporting adverse events. The System Organ Class within which most adverse events were reported in patients treated with fexofenadine was the Central and Peripheral Nervous System. The most commonly reported adverse event in patients receiving fexofenadine or placebo was headache. Headache was reported in 10.1% (79/780) of the patients receiving fexofenadine and 9.4% (18/192) of the patients receiving placebo.

2. Study PJPR0010 - Spring Study - 20 mg, 40 mg, 60 mg, 80 mg

a. Study Design (identical to Study 9)

A 2-day single-blind period was followed by a 2-week double-blind period. Patients reflectively assessed and recorded individual symptoms at noon and bedtime (1-3 hours after the 7 PM dose). They reflectively assessed and recorded individual symptoms before their morning dose at the interim and final visits.

b. Interim Analysis

An interim analysis was performed in order to plan the design of subsequent studies. Based on the results of the interim analysis, the α -levels for the interim and final analyses were calculated to be .0013 and .0495 respectively.

c. Statistical Methods (identical to Study 9)

An analysis of covariance (ANCOVA) model was used to analyze the primary efficacy variable change in bedtime reflective TSS. The protocol-specified analysis was an analysis of variance with investigative site and treatment as factors. Baseline TSS was found to be an important predictor of the magnitude of reduction in TSS, thus the sponsor changed the primary efficacy analysis to an ANCOVA to include baseline as a continuous covariate. The results of the protocol correct analysis were reviewed and were found to be similar. Only the ANCOVA will be presented in this review.

d. Results

Patient Accounting and Demographics

One thousand twenty-one patients were randomized to treatment. Nine patients discontinued the study prior to receiving double-blind medication. The remaining 1012 patients were exposed to double-blind treatment. Nine-hundred ninety-five (995) of these patients had both baseline and post baseline bedtime symptom assessments; and 942 of these patients completed the study.

Summaries of patient demographics can be found in Appendix A. The treatment groups were similar with respect to baseline demographic characteristics and symptom scores.

Primary Efficacy Variable and Analysis

Means and the associated standard deviations and 95% confidence intervals of change in bedtime reflective TSS are reported in Table 8 and plotted in Figure 4. Least squares means and associated standard errors from the primary efficacy analysis model are also reported in Table 8.

Table 8. Study 10: Means and Least Squares Means of Primary Efficacy Variable

Change from Baseline Bedtime Reflective TSS				
Treatment (BID)	N	Mean ± SD	95% Confidence Intervals	Least Squares Mean ± SE
Placebo	198	-0.79 ± 2.18	(-1.09, -0.49)	-0.85 ± 0.14
20 mg	197	-1.34 ± 2.23	(-1.65, -1.03)	-1.26 ± 0.14
40 mg	201	-1.36 ± 2.55	(-1.71, -1.01)	-1.44 ± 0.14
60 mg	203	-1.61 ± 2.22	(-1.92, -1.30)	-1.58 ± 0.14
80 mg	196	-1.35 ± 2.03	(-1.63, -1.07)	-1.36 ± 0.14

Figure 4: Study 10 Means and 95% Confidence Intervals



The results of the sponsor's analyses found the overall treatment effect to be statistically significant (Table 9). The overall F test rejected the null that the means of all the doses (including placebo) were equal ($p = .0034$). The individual F-tests comparing each dose with placebo also rejected the nulls that the pairwise means were equal (20 mg, $p = .0415$; 40 mg, $p = .0030$; and 60 mg, $p = .0002$; 80 mg, $p = .0095$). Using the "Step-Down Procedure", all four comparisons could be tested. Baseline was statistically significant ($p = .0001$), indicating that patients with higher baseline TSS were likely to show a larger reduction in TSS, regardless of treatment.

The two treatment interaction effects were significant at the .10 level. The significant treatment-by-investigator interaction raises statistical concerns regarding the appropriateness of pooling the data from the different centers. Additionally, unless a baseline value is specified, the significant treatment-by-baseline interaction precludes the comparisons of the different doses with each other and with placebo. The sponsor chose the mean of baseline (TSS=5.869) at which to compare the doses. If taken literally, this means that the p-values comparing each dose to placebo are only valid for patients who have a baseline TSS value equal to 5.869 units. The mean of baseline at which to compare the doses was chosen *post-hoc*. Alternate analyses will be presented for this study in the discussion section (II-C4).

Although a linear trend in dose is significant ($p = .0022$) when the placebo group is included in the contrast vector, the significance does not remain when the placebo group is excluded. This is described in detail in the discussion section (II-B).

Table 9. Study 10: Intent-to-Treat Analysis of Change in Bedtime Reflective TSS (N= 995)

ANCOVA Model Covariates		P value *
Overall Treatment Differences		.0034
Baseline TSS		.0001
Investigator		.0628
Treatment by baseline interaction		.0369
Treatment by investigator interaction		.0884
Dose Response (Linear Trend)		.0022
Treatment Comparison	Mean±Standard Error * of difference in means (Active minus Placebo)	
20 mg fexofenadine vs Placebo	-0.40±0.20	.0415
40 mg fexofenadine vs Placebo	-0.58±0.20	.0030
60 mg fexofenadine vs Placebo	-0.73±0.20	.0002
80 mg fexofenadine vs Placebo	-0.51±0.20	.0095
* P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction.		

Secondary Efficacy Variables and Analyses

Patient Assessments

The results from the week 1 analysis of the bedtime reflective TSS were similar, however during week 2 only the 60 mg dose was statistically significantly different from placebo (Table 10).

Table 10: P-values for comparisons with Placebo

Dose	Week 1	Week 2
20 mg vs Placebo	.0512	.0851
40 mg vs Placebo	.0013	.0955
60 mg vs Placebo	.0027	.0002
80 mg vs Placebo	.0019	.1858

Subgroup analyses by weight categories, by age categories, by gender and by race show that there are no significant interactions with treatment.

Individual analyses of covariance were done for each bedtime reflective symptom. Comparisons between each dose group and placebo were made for every symptom. The 60 mg dose reached significance for every symptom except itchy, watery, red eyes and nasal congestion. The 20, 40 and 80 mg doses were not statistically significantly different from placebo for any of the symptoms. Each comparison was made at the mean of baseline TSS.

None of the dose groups were statistically significantly different from placebo in terms of the Patient's Willingness to Take Study Medication Again.

Physician Assessments

The physician's assessment of TSS and the individual symptoms was analyzed using an ANCOVA with baseline TSS, investigator, treatment and treatment by baseline interaction as predictor variables. Only the 60 mg dose group was statistically significantly superior to placebo for TSS and the following individual symptoms: sneezing, rhinorrhea, and itchy nose, palate and/or throat. None of the dose groups provided significant relief over placebo for itchy, watery, red eyes. All comparisons were made at the mean of baseline TSS.

Only the 60 mg dose group was statistically significantly superior to placebo for the Physician's Evaluation of Overall Effectiveness.

Adverse Events

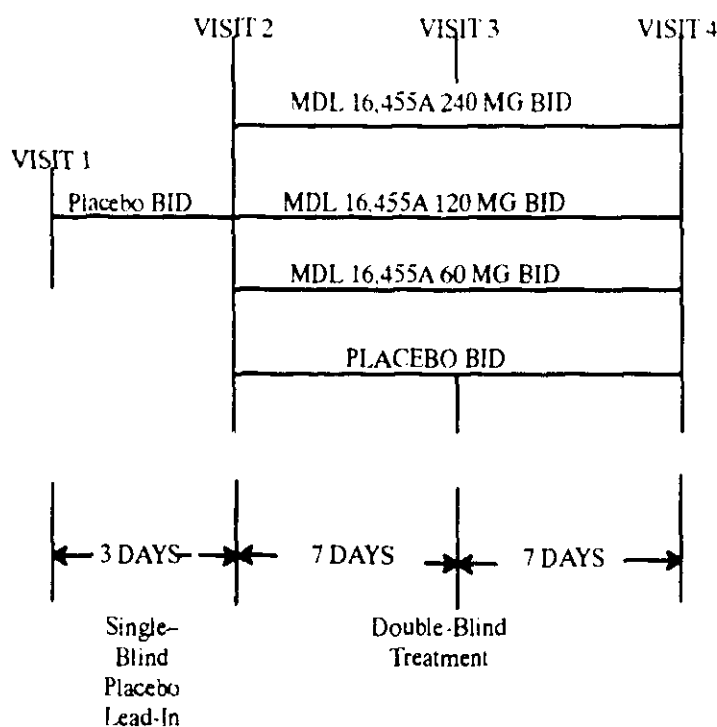
When considering all adverse events that occurred while patients were receiving double-blind study medication, 29.1% (234/804) of the patients receiving fexofenadine and 33.5% (67/200) of the patients receiving placebo experienced one or more adverse events. There was no obvious relationship between dose of fexofenadine and number of patients reporting adverse events. The System Organ Class within which most adverse events were reported in patients treated with fexofenadine was the Central and Peripheral Nervous System. The most commonly reported adverse event in patients receiving fexofenadine or placebo was headache. Headache was reported in 6.0% (48/804) of the patients receiving fexofenadine and 6.5% (13/200) of the patients receiving placebo.

3. Study PJPR0023 - Fall Study - 60 mg, 120 mg, 240 mg

a. Study Design

Figure 5 presents a schematic design of the trial. A 3-day single-blind period was followed by a 2-week double-blind period. Patients reflectively assessed and recorded individual symptoms at 7 AM and 7 PM. They instantaneously assessed and recorded individual symptoms at 7 AM, 7 PM and Bedtime (1-3 hours after the 7 PM dose). Patients that had low symptom scores during the placebo lead-in period and patients who responded to placebo were not eligible to continue. Specific qualifications for continuation are described in Dr. Michael Sevka's clinical review.

Figure 5: Study Design



*MDL 16,455A refers to Fexofenadine

Randomization occurred *after* the single-blind period. The randomization procedure is described below. The total symptom score (TSS) below refers to the sum of the second and third days of baseline TSS.

To ensure similar baseline total symptom scores (TSS) across double-blind treatment groups, a stratified randomization was used. The stratified randomization was based on the baseline 12-hour PM reflective TSS. The baseline 12-hour PM reflective TSS was defined as the sum of PM reflective TSS at days 2 and 3 during the placebo lead-in period. At visit 2, patients were placed into one of two categories depending on the baseline 12-hour PM reflective TSS:

- *LOW: BASELINE 12-HOUR PM REFLECTIVE² TSS $\geq$ 10 AND $<$ 17*
- *HIGH: BASELINE 12-HOUR PM REFLECTIVE TSS $\geq$ 17 AND $\leq$ 24*

If the patient's qualifying baseline TSS was "Low," the next available TAN was dispensed in ascending order from the lower end of the range of TANs shipped to the investigative site (e.g., began by dispensing TAN 0001, then 0002, etc). If the patient's qualifying baseline TSS was "High," the next available TAN was dispensed in descending order beginning with the highest TAN shipped to the investigative site (e.g., began dispensing TAN 0048, then 0047, etc).

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²The only reflective PM assessment in this trial is 7 PM.

b. Statistical Methods

An analysis of covariance (ANCOVA) model with baseline 7 PM reflective TSS as a covariate and investigative site and treatment as class variables was used to analyze the primary efficacy variable change in 7 PM reflective TSS.

The protocol stated that the baseline covariate in the model would be dichotomous ("LOW" or "HIGH") based on the severity of seasonal allergic symptoms during the placebo lead-in period. An amendment to the protocol dated November 15, 1994 changed the variable to be a continuous baseline symptom score. The amendment, Amendment #5, was not "approved" until 1-18-95 by investigative site #140, until 12-8-94 by investigative site #147, until 12-6-94 by all the other sites. (VOL219-P210). The last patient finished the study on November 19, 1995. This is a problem if the originally proposed analysis did not show efficacy of treatment. In addition to this change, the amendment changed the final analysis model to include adjustment for treatment-by-investigative site and treatment-by-baseline interactions if either was significant at the $\alpha = .10$ level. Neither interaction effect was significant at the more conservative level of .15. The analysis that was originally proposed was conducted by the sponsor and reviewed, although it will not be presented here. The originally proposed analysis yields results similar to those from the amended analysis.

c. Results

Patient Accounting and Demographics

A total of 1498 patients were screened for entry into the study. Of these patients, 1073 were eligible to receive single-blind placebo medication. Four hundred ninety-eight (498) patients did not qualify for double-blind treatment and were discontinued. (Most of them did not have adequate symptom scores during the placebo lead-in period.) Five hundred seventy-five (575) patients were randomized to receive treatment. Three patients discontinued the study following randomization but prior to receiving double-blind medication. The remaining 572 patients were exposed to double-blind treatment. Five hundred seventy (570) of these patients had both baseline and post baseline 7 PM reflective symptom assessments; and 544 of these patients completed the study.

Summaries of patient demographics can be found in Appendix 1. The treatment groups were similar with respect to baseline demographic characteristics and symptom scores.

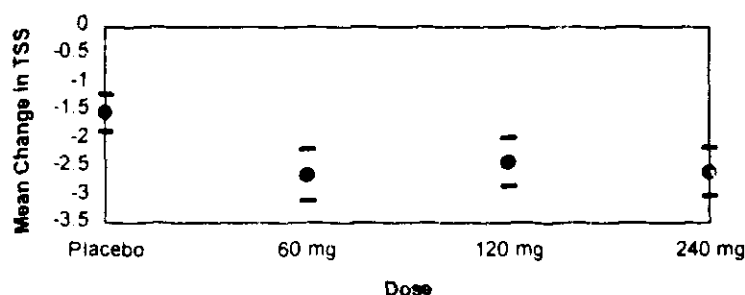
Primary Efficacy Variable and Analysis

Means and the associated standard deviations and confidence intervals of the change in 7PM reflective TSS are reported in Table 11 and plotted in Figure 6. Least squares means and associated standard errors from the primary efficacy analysis model are also reported in Table 11.

Table 11. Study 23: Means and Least Squares Means of Primary Efficacy Variable

Treatment (BID)	N	Change from Baseline 7PM Reflective TSS		
		Mean ± SD	95% Confidence Intervals	Least Squares Mean ± SE
Placebo	141	-1.53 ± 2.00	(-1.86, -1.20)	-1.56 ± 0.20
60 mg	141	-2.55 ± 2.75	(-3.09, -2.19)	-2.64 ± 0.20
120 mg	144	-2.42 ± 2.67	(-2.85, -1.97)	-2.41 ± 0.20
240 mg	144	-2.51 ± 2.61	(-3.01, -2.15)	-2.58 ± 0.20

Figure 6: Study 23 Means and 95% Confidence Intervals



In the primary analysis, an analysis of covariance, treatment was a significant factor (Table 12). The overall F test rejected the null that the means of all the doses (including placebo) were equal ($p = .0003$). The individual F-tests comparing each dose with placebo also rejected the nulls that the pairwise means were equal (60 mg, $p = .0001$; 120 mg, $p = .0026$; and 240 mg, $p = .0003$). Using the "Step-Down Procedure", all three comparisons could be tested. Baseline was also statistically significant ($p = .0001$), indicating that patients with higher baseline TSS were likely to show a larger reduction in TSS, regardless of treatment. Investigative site was not found to be statistically significant ($p = .4012$).

Table 12. Study 23: Intent-to-Treat Analysis of 7 PM Reflective TSS (N= 570)

ANCOVA Model Covariates		P value *
Overall Treatment Differences		.0003
Baseline TSS		.0001
Investigator		.4012
Dose Response (Linear Trend)		.0036
Treatment Comparison	Mean ± Standard Error * (Active-Placebo)	
60 mg MDL 16,455A vs Placebo	-0.97 ± 0.30	.0001
120 mg MDL 16,455A vs Placebo	-0.75 ± 0.29	.0026
240 mg MDL 16,455A vs Placebo	-0.96 ± 0.30	.0003
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline		

Secondary Efficacy Variables and Analyses

Patient Assessments

The results from weekly analyses of the 7PM reflective TSS were similar. All comparisons with placebo were **highly** statistically significant (Table 13).

Table 13: P-values for comparisons with Placebo

Dose	Week 1	Week 2
60 mg vs Placebo	.0003	.0066
120 mg vs Placebo	.0039	.0120
240 mg vs Placebo	.0002	.0059

Individual analyses of covariance were done for each 7 PM reflective symptom. Comparisons between each dose group and placebo were made for every symptom. Every comparison for every symptom was statistically significant (p<.02).

Subgroup analyses by weight categories, by age categories, by gender and by race show that there were no significant interactions with treatment.

The 7AM and 7PM instantaneous diary card assessments were indications of the efficacy of the drug at the end of the dosing intervals. All doses were highly statistically significantly superior to placebo for both instantaneous assessments (Table 14).

Table 14: P-values for comparisons with Placebo

Dose	7AM Instantaneous	7PM Instantaneous
60 mg vs Placebo	.0002	.0003
120 mg vs Placebo	.0107	.0044
240 mg vs Placebo	.0007	.0008

Physician Asses

The results of the Physician's Evaluation of Overall Effectiveness analysis were not favorable to fexofenadine. None of the dose comparisons with placebo were statistically significant.

Adverse Events

When considering all adverse events that occurred while patients were receiving double-blind study medication, 29.3% (126/430) of the patients receiving fexofenadine and 45.1% (64/142) of the patients receiving placebo experienced one or more adverse events. There was no obvious relationship between dose of fexofenadine and number of patients reporting adverse events. The System Organ Class within which most adverse events were reported in patients treated with fexofenadine was the Central and Peripheral Nervous System. The most commonly reported adverse event in patients receiving fexofenadine or placebo was headache. Headache was reported in 5.8% (25/430) of the patients receiving fexofenadine and 9.2% (13/142) of the patients receiving placebo.

4. Study PJPR0024 - Fall Study - 40 mg, 60 mg, 120 mg

a. Study Design (identical to Study 23)

The design, and exclusion and inclusion criteria were identical to those in Study 23 except patients were randomized either to placebo BID, 40 mg BID, 60 mg BID, or 120 mg BID.

b. Statistical Methods

The primary analysis presented in the study report is identical to that of Study 23. An analysis of covariance (ANCOVA) model with baseline 7 PM reflective TSS as a covariate and investigative site and treatment as class variables was used to analyze the primary efficacy variable change in 7 PM reflective TSS. An amendment to the protocol identical to the one in Study 23 was dated November 15, 1994, approved by 15 sites on December 6, 1994, and approved by Site #151 on December 8, 1994. The last patient finished the study on November 30, 1994. The originally proposed analysis yields results similar to those from the amended analysis (VOL243-P148).

One investigator in this study, Craig LaForce, was suspected of altering the data to allow patients to qualify for the study. The primary analysis was performed with and without his data; both will be reviewed here. The secondary analyses were only performed without his data. (V242-P146). LaForce's data is Safety Evaluable, but is not considered Intent-to-Treat or Protocol Correct.

c. Results

Patient Accounting and Demographics

A total of 1345 patients were screened for entry into the study. Of these patients, 1046 were eligible to receive single-blind placebo medication. Four hundred fifty-seven (457) patients did not qualify for double-blind treatment and were discontinued. (Most of them did not have adequate symptoms scores during the placebo lead-in period.) Five hundred eighty-nine (589) patients were randomized to receive treatment. One patient discontinued the study following randomization but prior to receiving double-blind medication. The remaining 588 patients were exposed to double-blind treatment. Five hundred eighty-four (584) of these patients had both baseline and post baseline 7 PM reflective symptom assessments; and 550 of these patients completed the study.

Summaries of patient demographics can be found in Appendix 1. The treatment groups were similar with respect to symptom scores and all baseline demographic characteristics except for height. The people receiving 60 mg were significantly shorter than the placebo and 40 mg groups.

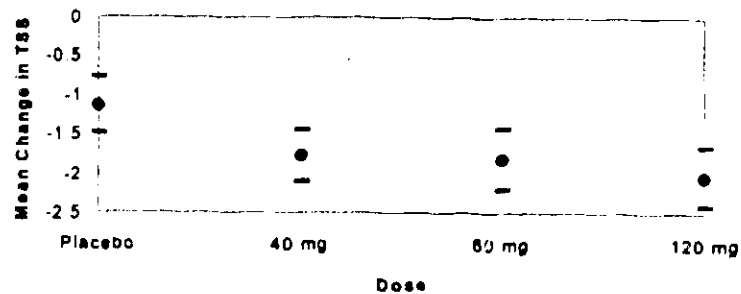
Primary Efficacy Variable and Analysis

Means (without data from Site 155) and the associated standard deviations and confidence intervals of the change in 7PM reflective TSS are reported in Table 15 and plotted in Figure 7. Least squares means and associated standard errors from the primary efficacy analysis model (without data from Site 155) are also reported in Table 14.

Table 15. Study 24 Means and Least Squares Means of Primary Efficacy Variable EXCLUDING SITE 155

Treatment (BID)	N	Change from Baseline TSS		
		Mean ± SD	95% Confidence Intervals	Least Squares Mean ± SE
Placebo	137	-1.12 ± 2.16	(-1.48, -0.76)	-1.21 ± 0.18
40 mg	135	-1.76 ± 1.97	(-2.09, -1.43)	-1.86 ± 0.18
60 mg	138	-1.80 ± 2.30	(-2.18, -1.42)	-1.86 ± 0.18
120 mg	135	-2.02 ± 2.29	(-2.41, -1.63)	-2.11 ± 0.18

Figure 7: Study 24 Means and 95% Confidence Intervals



The sponsor included both treatment by investigator interaction effect and treatment-by-baseline interaction effect in preliminary models to test for these effects. Neither interaction effect was statistically significant. However, when the treatment-by-baseline interaction effect was included in the model without the treatment-by-investigator interaction effect, the former effect was statistically significant ($p = .0916$). The sponsor reported this significance, but chose to leave the treatment-by-baseline interaction effect out of the final model because their "policy" is to test both interaction effects at the same time. This policy is not specified in the protocol. A model including the treatment by baseline interaction is presented in the discussion section (II-C-4-c) of this review. The sponsor's analyses will be reviewed here.

In the primary analysis (an analysis of covariance), **excluding Site 155**, treatment is a significant factor (Table 16).

**Table 16. Study 24: Intent-to-Treat Analysis of 7 PM Reflective TSS (N=545)
EXCLUDING SITE 155**

ANCOVA Covariates		P value *
Treatment		.0020
Baseline TSS		.0001
Investigator		.0001
Dose Response (Linear Trend)		.0005
<i>Treatment Comparison</i>	<i>Mean±Standard Error *</i> <i>(Active-Placebo)</i>	
40mg MDL 16.455A vs Placebo	-0.65±0.25	.0087
60mg MDL 16.455A vs Placebo	-0.66±0.24	.0075
120mg MDL 16.155A vs Placebo	-0.91±0.25	.0002
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.		

The overall F test rejected the null that the means of all the doses (including placebo) were equal ($p=.0020$). The individual F-tests comparing each dose with placebo also rejected the nulls that the pairwise means were equal (40 mg, $p=.0087$; 60 mg, $p=.0075$; 120 mg, $p=.0002$). Using the "Step-Down Procedure", all three comparisons could be tested. The coefficient of baseline was also statistically significant ($p=.0001$), indicating that patients with higher baseline TSS were likely to show a larger reduction in TSS, regardless of treatment. Unlike Study 23, investigative site was found to be statistically significant ($p=.0001$). Thus, a treatment-by-investigative site interaction effect was added to the model, (without the treatment-by-baseline interaction effect), and was not found to be statistically significant ($p=.6259$) V243-P135.

Although a linear trend in dose is significant ($p=.0005$) when the placebo group is included in the contrast vector, the significance does not remain when the placebo group is excluded. This is explained in detail in the discussion section.

In the primary analysis, **including Site 155**, treatment was a significant factor (Table 17). The overall F test rejected the null that the means of all the doses (including placebo) were equal ($p=.0003$). The individual F-tests comparing each dose with placebo also rejected the nulls that the pairwise means were equal (40 mg, $p=.0018$; 60 mg, $p=.0018$; 120 mg, $p=.0001$). Using the "Step-Down Procedure", all three comparisons could be tested. The coefficient of baseline was also statistically significant ($p=.0001$). Investigative site was found to be statistically significant ($p=.0002$). Again, although a linear trend in dose was significant ($p=.0001$), the sponsor inappropriately included placebo in the equation.

**Table 17. Study 24: Analysis of 7 PM Reflective TSS (N = 584)
INCLUDING SITE 155**

<i>ANCOVA Covariates</i>		<i>P value *</i>
Treatment		.0003
Baseline TSS		.0001
Investigator		.0002
Dose Response (Linear Trend)		.0001
<i>Treatment Comparison</i>	<i>Mean±Standard Error *</i> <i>(Active-Placebo)</i>	
40mg MDL 16,455A vs Placebo	-0.65±0.25	.0018
60mg MDL 16,455A vs Placebo	-0.66±0.24	.0018
120mg MDL 16,455A vs Placebo	-0.91±0.25	.0001
* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.		

Secondary Efficacy Variables and Analyses

Patient Assessments

The results from the weekly analyses of the 7PM Reflective TSS were similar (Table 18). All comparisons with placebo were statistically significant.

**Table 18: P-values for comparisons with Placebo
EXCLUDING SITE 155**

Dose	Week 1	Week 2
40 mg vs Placebo	.0054	.0143
60 mg vs Placebo	.0135	.0168
120 mg vs Placebo	.0011	.0019

Subgroup analyses by weight categories, by age categories, by gender and by race show that there were no significant interactions with treatment.

The 7AM and 7PM instantaneous diary card assessments were indications of the efficacy of the drug at the end of the dosing intervals. All doses were statistically significantly superior to placebo for the 7PM instantaneous assessment, but only the 40 mg and 120 mg doses were statistically significantly superior to placebo for the 7AM instantaneous assessment (Table 19).

**Table 19: P-values for comparisons with Placebo
EXCLUDING SITE 155**

Dose	7AM Instantaneous	7PM Instantaneous
40 mg vs Placebo	.0426	.0009
60 mg vs Placebo	.0579	.0222
120 mg vs Placebo	.0038	.0073

Physician Assessments

The results of the Physician's Evaluation of Overall Effectiveness analysis were not favorable to fexofenadine. None of the dose comparisons with placebo were statistically significant.

Adverse Events

When considering all adverse events that occurred while patients were receiving double-blind study medication, 35.9% (158/440) of the patients receiving fexofenadine and 33.8% (50/148) of the patients receiving placebo experienced one or more adverse events. There was no obvious relationship between dose of fexofenadine and number of patients reporting adverse events. The System Organ Class within which most adverse events were reported in patients treated with fexofenadine was the Respiratory System. The most commonly reported adverse event in patients receiving fexofenadine or placebo was headache. Headache was reported in 5.5% (24/440) of the patients receiving fexofenadine and 8.1% (12/148) of the patients receiving placebo.

II. Discussion

A. Introduction

Studies 9, 10, 23 and 24 were submitted by the sponsor to support the claim that fexofenadine provides relief of the symptoms of seasonal allergic rhinitis. The results from Studies 10, 23 and 24 found fexofenadine statistically significantly superior to placebo. Even though the sponsor found a statistically significant linear dose response in these studies, calculations of dose response without the placebo group reveal that symptoms do not decrease significantly with increasing dose. The results from these calculations are presented below.

Study 9 was not conclusive because the sponsor used the "Closed Procedure" for multiple comparisons and the second comparison made was not significant. Consequently, the third and fourth comparisons of the 40 mg and 20 mg doses with placebo could not be made.

Results from Studies 10, 23 and 24 indicated that 60 mg BID was the lowest effective dose. Studies 10 and 24 had a statistically significant treatment-by-baseline interaction effect. The significance of this interaction effect makes the results of the studies difficult to interpret. A possible reason for the significance of the interaction effects and an alternate interpretation of the results is presented below.

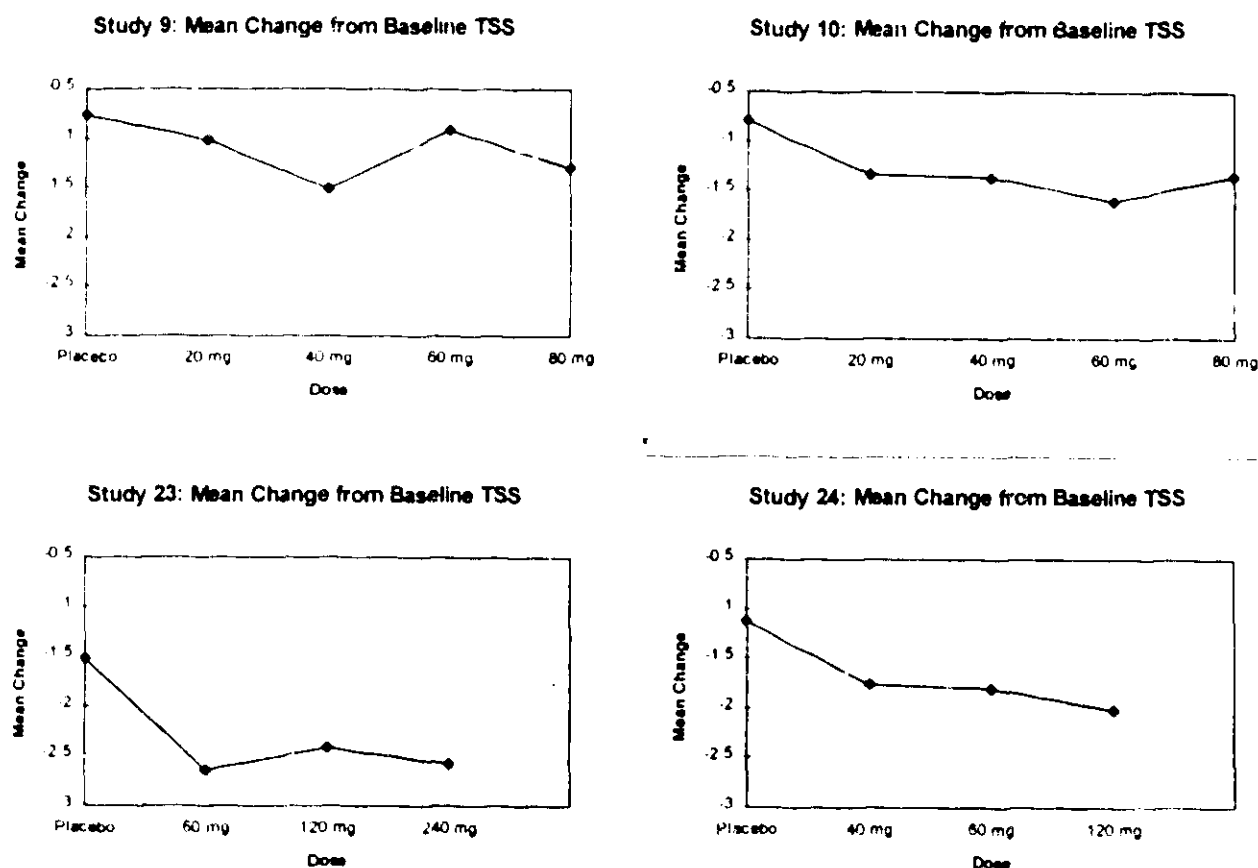
Compliance with double-blind treatment in all four studies was very high. It ranged from one patient's 50% compliance in Study 10 to two other patients' 175% compliance in Studies 9 and 24. These high compliance rates are examined below.

Additionally, the potential impact of missing data on the results in the four placebo controlled clinical trials is explored in this discussion.

B. Linear Contrasts

Though in each of the symptom score assessments, all of the fexofenadine treatment groups demonstrate a superiority in comparison to the placebo groups, it appears that there is no significant increase in relief of SAR symptoms with increasing dose. Using the intent-to-treat population, Figure 8 below displays the mean percent change in TSS from baseline for all treatment groups. When the placebo group is excluded from the contrasts for the linear trend equations, the linear trends are no longer statistically significant in any of the studies (Study 9, $p=0.4718$; Study 10, $p=0.4561$; Study 23, $p=0.3888$; Study 24 excluding Site 155, $p=0.8487$).

Figure 8: Mean Changes in Total Symptom Scores



There was no strong evidence that any dose above 40 mg was more effective than the 40 mg dose. In Study 24 however, analyses of TSS assessments within 24 hours of the first dose of double-blind medication showed that the 40 mg dose had a slower onset of action than did the 60 or 120 mg treatments. Statistically significant symptom reduction was first observed for the 40 mg dose group with the 7 AM instantaneous assessment on day 2 (12 hours following the first dose of double-blind study medication). For the 60 and 120 mg dose groups, statistically significant reduction was observed with the bedtime instantaneous assessment on day 1 (1 - 3 hours

following the first dose). Also, the only onset-of-action trial did not include any doses lower than 60 mg. For these reasons, it was determined that the 60 mg dose is the lowest, most efficacious dose found in these studies.

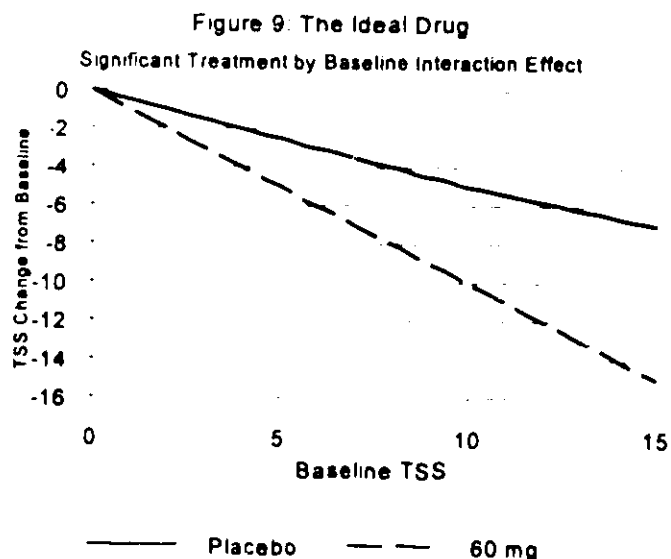
C. Treatment-by-Baseline Interaction

1. Introduction

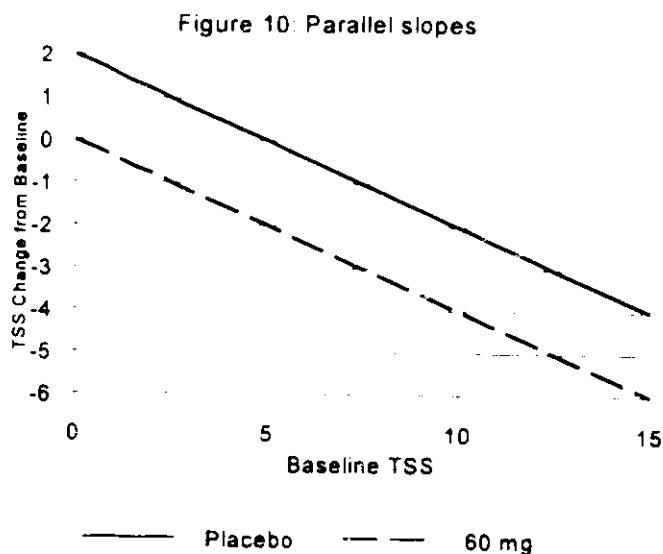
In Studies 10 and 24, a treatment-by-baseline interaction effect was statistically significant ($\alpha < .10$). When a treatment-by-baseline interaction effect is significant, the different doses cannot be compared to each other statistically without specifying a baseline at which to compare them. The sponsor recognized the significant interaction effect in Study 10 and chose the mean of baseline at which to compare the doses. The sponsor did not recognize the significant interaction effect in Study 24. However, a significant treatment interaction with baseline does not necessarily indicate a problem with the drug.

2. Example

The ideal drug would decrease Total Symptom Score by one unit for every unit of baseline (Figure 9). For example, a patient with a baseline score of 1 would have a decrease in symptoms of 1 unit while a patient with a baseline score of 5 would have a decrease in symptoms of 5 units. There is a 100% reduction of symptoms at every baseline value. The placebo response may or may not have the same slope as the drug. If it does not have the same slope as the drug, the treatment by baseline interaction effect will be significant.



Assuming placebo does not decrease symptoms quite as effectively as 100%, the slope may look like the placebo slopes look in Figures 9 and/or 10. If the slope of the drug is equal to that of placebo, as it is in Figure 10, the drug will obviously not work as effectively as it did in Figure 9.



Thus, even though a significant treatment-by-baseline interaction effect causes problems in interpretation of the results, if the slope of the drug is steeper than that of placebo, then the presence of the significant interaction effect actually signifies a *more* effective response.

When more than one dose of the drug is in the study, there is more chance that there will be a significant treatment-by-baseline interaction. In these studies, none of the doses relieved average TSS to a significantly greater degree than did the others. As seen below, all the slopes were different from one another and the values of the slopes were not in any particular order according to dose. In four studies, with four to five different doses (including placebo), it is not surprising to find two significant treatment-by-baseline interaction effects (Studies 10 and 24).

3. Ordinary Least Squares

Ordinary least squares regression equations were used to find the estimated slopes of placebo and selected doses of the drug. For each study, the slopes of placebo, 60 mg dose and the next highest dose of the study were plotted (Figure 11).³ (Note that patients in Studies 9 and 10 had a greater spread of baseline values than did patients in Studies 23 and 24. Interim analyses in 9 and 10 influenced the design of 23 and 24.)

- In four of these cases (Study 9, 60 mg; Study 23, 60 mg; Study 23, 120 mg; and Study 24, 60 mg), the slopes of fexofenadine were greater than those of the placebo group.
- In three of the remaining cases (Study 9, 80 mg; Study 10, 60 mg; and Study 24, 120 mg) the slopes were about equal to those of the placebo group.
- In only one case (Study 10, 80 mg) was the slope of the drug less than that of placebo;

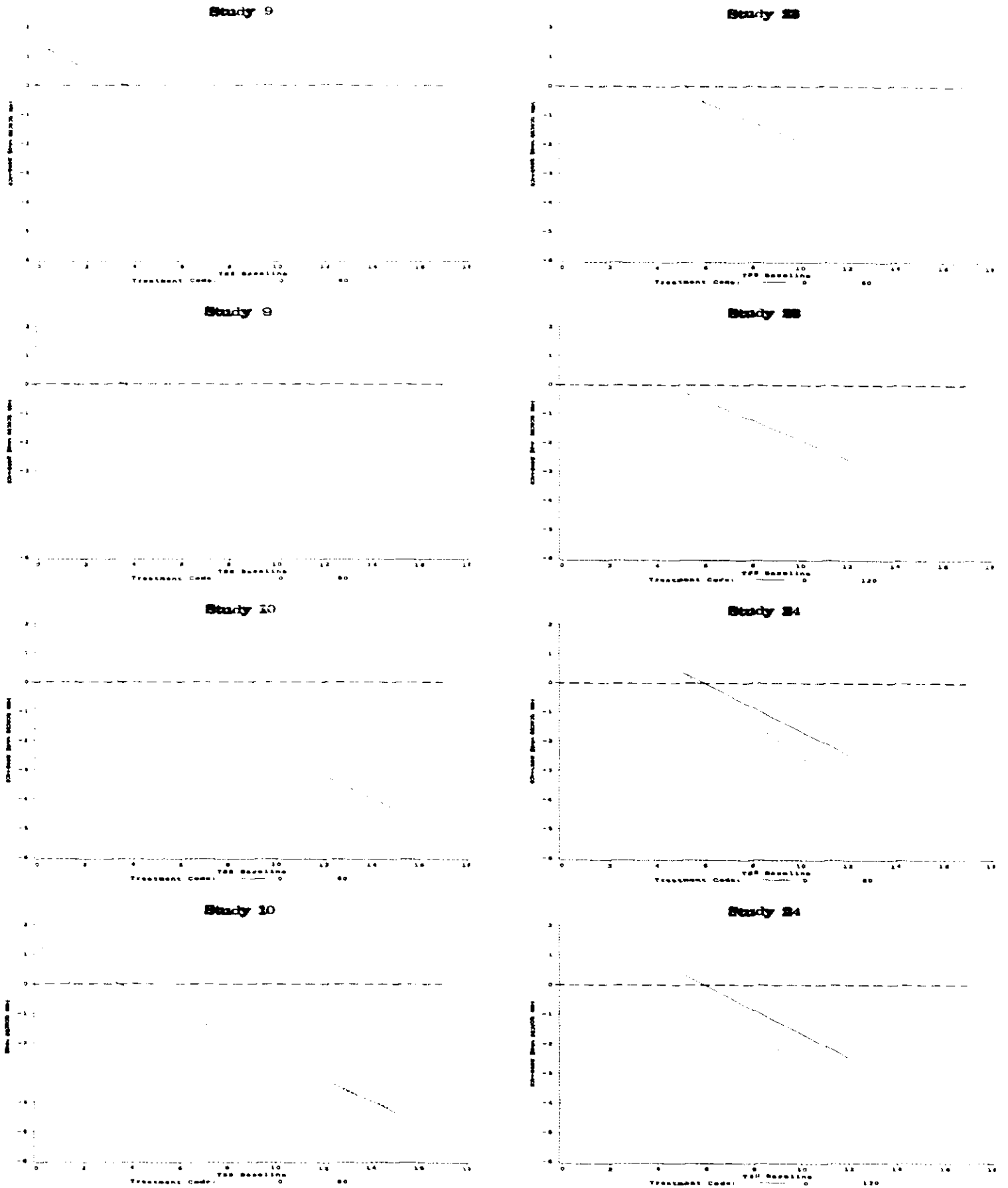
³ Since investigator was not included in the models that estimated these lines and these analyses are *post-hoc*, these plots are only descriptive.

however, the estimated line of the drug had a lower intercept than did placebo.

When the slopes between placebo and drug are parallel and the intercept of drug is lower, there is no treatment-by-baseline interaction. The parallel slopes indicate that for every unit increase of baseline TSS, the drug decreases symptoms at the same rate that placebo does. The lower intercept of the drug means that the drug gives more relief than placebo.

Even though the significant treatment by baseline interaction effects do not indicate problems with the study or with the drug, they do pose problems of interpretation of the results of the analyses of covariance. As noted above, in order to compare doses, a baseline at which to compare them must be chosen.

Figure 11: Ordinary Least Squares Regression Lines



4. Alternate Analyses

a. Introduction

One solution to the treatment-by-baseline interaction problem is to look only at the placebo group and one other dose. For each of the two studies with significant treatment-by-baseline interaction effects, the primary efficacy variable was reanalyzed using the placebo group and the 60 mg dose only. For each of the two studies, the data was divided into two separate datasets at the mean of baseline. Two analyses of variance were performed on the two doses (placebo, 60 mg). Thus, the overall treatment effect of the 60 mg dose was evaluated separately for the different baseline groups of patients.

b. Study 10

The mean and median of baseline TSS were 5.6839 and 5.5, respectively. Dividing the data in half at the mean of baseline, two analyses of variance were performed on the placebo and 60 mg patients (Table 20). Treatment was significant in the low baseline cohort, while it was not significant in the high baseline cohort. The absolute difference between mean change from baseline TSS in the placebo group and mean change from baseline TSS in the 60 mg dose group was .9533 for the low baseline cohort and .4600 for the high baseline cohort (Table 21). The variance of the change from baseline of the low baseline cohort was smaller than that of the high baseline cohort. This may have contributed to the significance of the treatment effect in the low baseline cohort and not in the high.

Table 20. Study 10: Analysis of Covariance Tables for Low and High Baseline groups

Baseline Group	n	Range of Baseline Values*	Predictor Variables	Sums of Squares	F statistic	p-value
Low	210	0-5.68	Treatment	44.36	13.58	.0003
			Investigator	40.46	.83	.6483
			Baseline	78.31	23.97	.0001
High	131	5.68-15	Treatment	11.82	2.73	.1001
			Investigator	60.63	.93	.5271
			Baseline	71.21	16.46	.0001

Table 21. Study 10: Means, Least Squares Means and Variances

Baseline group	Dose	n	Mean $\pm$ SD	Least Squares Mean $\pm$ SE	Change from Baseline TSS difference of means* (60 mg - placebo)	Variance of Change from Baseline TSS
Low	Placebo	109	.085 $\pm$ 1.9	.034 $\pm$.18	.9533	3.741
	60 mg	101	-.87 $\pm$ 1.9	-.90 $\pm$.18		
High	Placebo	89	-1.87 $\pm$ 2.03	-1.90 $\pm$.23	.4600	5.382
	60 mg	102	-2.33 $\pm$ 2.31	-2.41 $\pm$.22		

* Using the means, not the least squares means.

c. Study 24

The analyses that follow exclude data from Site 155, where the investigator, Craig LaForce was suspected of altering the data. Analyses including data from Site 155 can be found in Appendix B.

Recall the sponsor's policy was to test both treatment-by-baseline and treatment-by-investigator interactions at the same time. The treatment-by-baseline interaction effect was not significant when the treatment-by-investigator interaction effect was also in the model, however it was significant when the latter effect was left out of the model. Table 22 presents the three models the sponsor performed. The sponsor chose Model 1 to be the final model because the treatment by baseline interaction effect in Model 3 was not statistically significant, even though it was statistically significant in Model 2. The sponsor recorded the results of Model 2 in an appendix to the Clinical Study Report.

Table 22: Analysis of Covariance Tables of 3 different models sponsor performed (n=545)

Model	Predictor Variables	df	Sums of Squares	F statistic	p-value
1	Treatment	3	62.57	5.07	.0018
	Investigator	14	187.83	3.26	.0001
	Baseline	1	235.18	57.19	.0001
2	Treatment	3	28.65	2.34	.0728
	Investigator	14	189.81	3.32	.0001
	Baseline	1	254.23	62.23	.0001
	Treatment*Baseline	3	26.49	2.16	.0916
3	Treatment	3	20.52	1.66	.1753
	Investigator	14	185.68	3.22	.0001
	Baseline	1	248.35	60.20	.0001
	Treatment*Investigator	42	152.40	.088	.6875
	Treatment*Baseline	3	19.77	1.60	.1892

The mean and median of baseline TSS were 8.6703 and 8.6667, respectively. Dividing the data in half at the mean of baseline, two analyses of variance were performed on the placebo and 60 mg patients (Table 23). Treatment was not significant in the low baseline cohort, while it was significant in the high baseline cohort. The absolute difference between mean change from baseline TSS in the placebo group and mean change from baseline TSS in the 60 mg dose group was .5444 for the low baseline cohort and .5620 for the high baseline cohort (Table 24). The variance of the change from baseline in the low baseline cohort was greater than that in the high baseline cohort. This may have contributed to the significance of virtually the same difference in means in the high baseline group and not the low.

Table 23: Study 24, Analysis of Covariance Tables for Low and High Baseline groups

Baseline Group	n	Baseline Values*	Predictor Variables	Sums of Squares	F statistic	p-value
Low	144	5-8.67	Treatment	11.18	2.45	.1199
			Investigator	97.43	1.53	.1110
			Baseline	75.64	16.58	.0001
High	131	8.67-12	Treatment	20.48	5.43	.0215
			Investigator	42.18	.80	.6686
			Baseline	.55	.15	.7028

*Randomization occurred after the placebo-lead in period. No patient with a placebo lead-in average baseline TSS less than 5 or greater than 12 was allowed to continue.

Table 24: Study 24, Means, Least Squares Means and Variances

Baseline group	Dose	n	Mean ± SD	Least Squares Mean ± SE	Change from Baseline TSS difference of means* (60 mg - placebo)	Variance of Change from Baseline TSS
Low	Placebo	71	-.54 ± 2.27	-.43 ± .28	.5444	5.38
	60 mg	73	-1.081 ± 2.36	-.99 ± .28		
High	Placebo	66	-1.74 ± 1.86	-1.81 ± .26	.5620	3.82
	60 mg	65	-2.60 ± 1.97	-2.62 ± .27		

* Using the means, not the least squares means.

D. Missing Data

Missing data was studied and not found to be a problem in the four controlled clinical trials. The missing assessments were not imputed in the primary efficacy analyses. The average TSS during the treatment period for the patients with missing data were calculated using only the recorded TSS assessments. There were no differences between the different doses of fexofenadine and placebo in the number of missing entries (Table 25). Between 9% and 13% of the primary efficacy variable daily diary entries were missing over the two-week treatment period for all the

trials), however most of the missing data occurred towards the end of the studies (Table 26). Each patient made an appointment for his/her final visit on the date closest to the fourteenth day of his/her treatment period. The final visits were on the twelfth through fifteenth day of the treatment period. It is not clear if the average total symptom scores of patients with fifteen days of treatment included the entry from the fifteenth day. The number of patients with diary entries on days 11 through 14 are tabulated (Table 24) and plotted (Figure 12). There are no differences between dose groups in the number of patients with entries on these last few days of the studies.

Table 25: Number of Missing Daily Diary Entries

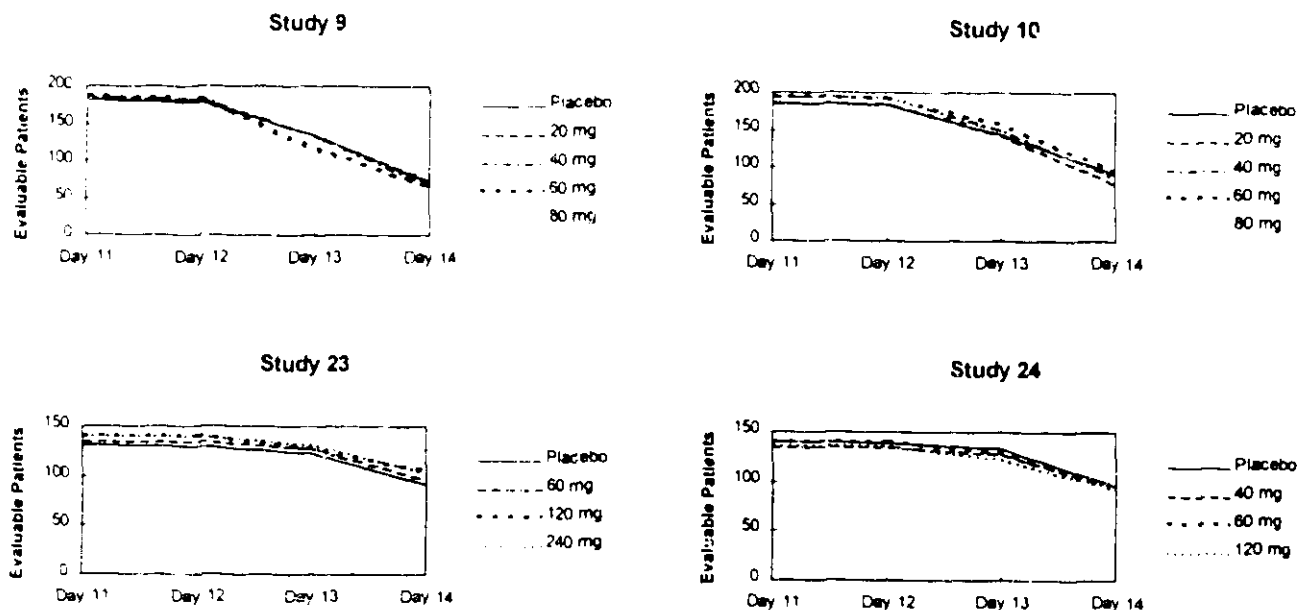
Study	Primary Efficacy Variable that was missing	Dose	n	n x 14 days = # of data points there should have been	Number of data points recorded	Number of data points missing	Percentage of data points missing
9	Bedtime Reflective	Placebo	190	2660	2409	251	9.44
		20 mg	194	2716	2449	267	9.83
		40 mg	195	2730	2474	256	9.38
		60 mg	191	2674	2423	251	9.39
		80 mg	192	2688	2417	271	10.08
		All doses	962	13468	12172	1296	9.62
10	Bedtime Reflective	Placebo	198	2772	2502	270	9.74
		20 mg	197	2758	2490	268	9.72
		40 mg	201	2814	2585	229	8.14
		60 mg	203	2842	2603	239	8.41
		80 mg	196	2744	2511	233	8.49
		All doses	995	13930	12691	1239	8.89
23	7 PM Reflective	Placebo	141	1974	1689	285	14.44
		60 mg	141	1974	1735	239	12.11
		120 mg	144	2016	1796	220	10.91
		240 mg	144	2016	1793	223	11.06
		All doses	570	7980	7013	967	12.12
24*	7 PM Reflective	Placebo	137	1918	1692	226	11.78
		40 mg	135	1890	1638	252	13.33
		60 mg	138	1932	1694	238	12.32
		120 mg	135	1890	1634	256	13.55
		All doses	545	7630	6658	972	12.74

* Site 155 was excluded from this table.

Table 26: Number of patients available for analyses on specific days during the treatment period

Study	Dose	Number of patients available for analyses at:				
		Day 1	Day 11	Day 12	Day 13	Day 14
9	Placebo	192	181	179	134	71
	20 mg	194	185	182	134	75
	40 mg	196	186	183	135	68
	60 mg	195	188	184	119	65
	80 mg	193	182	179	112	65
Totals:		970	922	907	634	344
10	Placebo	199	186	183	143	91
	20 mg	198	186	185	144	79
	40 mg	201	195	194	151	88
	60 mg	205	194	193	159	94
	80 mg	200	188	186	150	87
Totals:		1003	949	941	747	439
23	Placebo	142	131	130	123	92
	60 mg	141	135	135	128	97
	120 mg	144	141	141	128	105
	240 mg	145	141	140	132	104
Totals:		572	548	546	511	398
24	Placebo	148	140	139	133	96
	40 mg	145	135	135	128	96
	60 mg	148	141	140	130	96
	120 mg	147	136	136	123	93
Totals:		588	552	550	514	381

Figure 12: Number of Patients Available at Days 11-14



E. Compliance

Compliance was based on the actual number of capsules returned at each visit compared with the number expected to be returned. Patients were to be questioned and educated if the study drug compliance was not between 90 and 110% at any visit.

Compliance with double-blind treatment was computed by dividing the total number of doses taken during the double-blind dosing period (i.e., total number of doses dispensed minus the total number of doses returned) by the total number of doses that should have been taken based on the number of days the patient was exposed to double-blind medication. The number of days the patient was exposed to double-blind medication was estimated based on the number of days the patient recorded symptom assessments in his/her diary card.

A total of 42 patients in the four studies combined had inadequate information to compute compliance with study medication.

The average rates of compliance were 99% in Studies 9 and 10 and 100% in Studies 23 and 24 (Table 27). Average rates of compliance as high as 100% do not necessarily imply that compliance was exemplary. Further investigation reveals that a total of 41 patients had compliance below 80% or above 120% in the four studies combined (Table 28). Two patients (one in Study 9 randomized to 80 mg BID and one in Study 10 randomized to 40 mg BID) had compliance of 175%.

Table 27: Compliance Rates

Study	Treatment (BID)	N	% Compliance Mean $\pm$ SD	% Compliance Minimum	% Compliance Maximum
9	Placebo	192	99 $\pm$ 6	50	116
	20 mg	194	99 $\pm$ 4	75	108
	40 mg	196	99 $\pm$ 4	50	116
	60 mg	193	99 $\pm$ 5	50	108
	80 mg	189	100 $\pm$ 7	62	175
10	Placebo	199	99 $\pm$ 7	50	150
	20 mg	197	99 $\pm$ 4	64	108
	40 mg	201	100 $\pm$ 4	85	125
	60 mg	202	99 $\pm$ 6	50	116
	80 mg	198	99 $\pm$ 5	50	125
23	Placebo	141	100 $\pm$ 3	75	108
	60 mg	139	100 $\pm$ 3	75	109
	120 mg	144	100 $\pm$ 1	96	107
	240 mg	143	100 $\pm$ 3	92	127
24	Placebo	144	100 $\pm$ 3	75	107
	40 mg	144	100 $\pm$ 7	75	175
	60 mg	144	100 $\pm$ 2	96	108
	120 mg	145	100 $\pm$ 2	88	112

Table 28: Compliance below 80% or above 120%

Study	Number of Patients with compliance below 80% or above 120%
9	18
10	12
23	3
24	8

A possible explanation for the high compliance rates is that the number of days the patient was exposed to double-blind medication was underestimated. A patient could have remembered to take her medication, but forgot to record her symptom assessments. The denominator of the compliance rate would have been underestimated, creating a spuriously high compliance rate.

The strongest studies, Studies 23 and 24, also had the most reasonable compliance rates (except for the 175% compliant patient in Study 24). The least numbers of patients below 80% and above 120% compliant occurred in Studies 23 and 24.

III. Conclusions

Studies 9, 10, 23 and 24 were submitted by the sponsor to support the claim that fexofenadine provides relief of the symptoms of seasonal allergic rhinitis.

Study 9 was not conclusive because the sponsor used the "Closed Procedure" for multiple comparisons and the second comparison made was not significant. Consequently, the third and fourth comparisons of the 40 mg and 20 mg doses with placebo could not be made.

The results from Studies 10, 23 and 24 found fexofenadine statistically significantly superior to placebo with robust results. Even though the sponsor found a statistically significant linear dose response in these studies, calculations of dose response without the placebo group revealed that symptoms do not decrease significantly with increasing dose.

Assessments of symptoms following the first dose in Study 24 determined that 60 mg BID was the lowest dose that reached statistical significance against placebo within one to three hours of dosing.

Studies 10 and 24 had a statistically significant treatment-by-baseline interaction effect. The significance of this interaction effect makes the results of the studies difficult to interpret. Separate reanalyses of the low and high baseline groups using only the placebo and 60 mg doses found treatment to be statistically significant: 1) only in the low baseline group in Study 10; and 2) only in the high baseline group in Study 24. The large variance of the primary efficacy

variable in the high baseline group in Study 10 and in the low baseline group in Study 24 could have caused the insignificant results of these two groups. In contrast, results from these studies when the baseline by treatment interaction effect is not included are robust.

The results from Studies 10, 23 and 24 provide evidence that fexofenadine reduces symptoms of seasonal allergic rhinitis.

Appendix A

Study 9

Table A-1. Demographics: Intent-to-Treat Patients							
Baseline Characteristics	Placebo BID (n = 190)	MDL 16,455A (BID)				Total (n = 962)	P value*
		20 mg (n = 194)	40 mg (n = 195)	60 mg (n = 191)	80 mg (n = 192)		
Gender							
Male % (N)	39(74)	44(85)	36(70)	48(91)	45(86)	42(406)	0.1329
Female % (N)	61(116)	56(109)	64(125)	52(100)	55(106)	58(556)	
Age (years)							
Mean $\pm$ SD	33 $\pm$ 12	30 $\pm$ 11	32 $\pm$ 11	32 $\pm$ 12	31 $\pm$ 11	32 $\pm$ 11	0.1656
Range	11-65	12-63	12-61	12-65	12-64	11-65	
Race							
Caucasian % (N)	84(160)	87(169)	81(157)	82(157)	88(168)	84(811)	0.3582
Black % (N)	8(16)	8(16)	12(24)	7(13)	8(15)	9(84)	
Asian % (N)	2(4)	2(3)	2(3)	4(7)	1(2)	2(19)	
Other % (N)	5(10)	3(6)	6(11)	7(14)	4(7)	5(48)	
Weight (kg)							
Mean $\pm$ SD	73 $\pm$ 16	72 $\pm$ 19	73 $\pm$ 21	74 $\pm$ 20	72 $\pm$ 16	73 $\pm$ 18	0.8503
Range	33-113	32-150	30-178	38-162	31-135	30-178	
Height (cm)							
Mean $\pm$ SD	169 $\pm$ 10	169 $\pm$ 10	169 $\pm$ 10	170 $\pm$ 10	169 $\pm$ 10	169 $\pm$ 10	0.7380
Range	140-203	142-193	132-193	145-198	142-191	132-203	
Years Since First Episode Occurred							
Mean $\pm$ SD	19 $\pm$ 12	17 $\pm$ 10	18 $\pm$ 11	18 $\pm$ 10	16 $\pm$ 11	18 $\pm$ 11	0.1330
Range	2- 58	2- 58	2- 45	2- 44	2- 54	2- 58	
Successive Years of Spring Allergy							
Mean $\pm$ SD	17 $\pm$ 11	16 $\pm$ 10	17 $\pm$ 11	16 $\pm$ 10	15 $\pm$ 10	16 $\pm$ 11	0.2232
Range	2- 50	2- 58	2- 45	2- 44	2- 54	2- 58	

* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.

Study 9

Table A-2. Baseline Bedtime Symptom Assessments (Intent-to-Treat)

Baseline Symptoms	Placebo BID (n=190)	MDL 16.455A (BID)				Total (n=962)	P value*
		20 mg (n=194)	40 mg (n=195)	60 mg (n=191)	80 mg (n=192)		
Nasal Congestion							
Mean ±SD	1.6±0.9	1.6±0.8	1.7±0.9	1.6±0.8	1.8±0.9	1.7±0.8	0.4311
Range	0.0-3.0	0.0-4.0	0.0-4.0	0.0-3.0	0.0-4.0	0.0-4.0	
Sneezing							
Mean ±SD	1.2±0.8	1.1±0.8	1.1±0.8	1.2±0.8	1.1±0.8	1.1±0.8	0.5646
Range	0.0-3.5	0.0-3.0	0.0-3.0	0.0-3.0	0.0-4.0	0.0-4.0	
Rhinorrhea							
Mean ±SD	1.5±0.9	1.4±0.9	1.5±0.9	1.3±0.9	1.4±0.9	1.4±0.9	0.1359
Range	0.0-3.0	0.0-3.5	0.0-3.5	0.0-3.0	0.0-3.0	0.0-3.5	
Itchy Nose, Palate and/or Throat							
Mean ±SD	1.4±0.9	1.4±0.9	1.5±0.9	1.3±0.9	1.3±0.8	1.4±0.9	0.2828
Range	0.0-3.5	0.0-4.0	0.0-3.5	0.0-3.0	0.0-3.0	0.0-4.0	
Itchy, Watery, Red Eyes							
Mean ±SD	1.4±1.0	1.5±0.9	1.4±0.9	1.4±0.9	1.5±0.9	1.4±0.9	0.5883
Range	0.0-3.5	0.0-4.0	0.0-3.5	0.0-3.5	0.0-4.0	0.0-4.0	
TSS at Bedtime (Excluding Nasal Congestion)							
Mean ±SD	5.5±2.8	5.3±2.6	5.5±2.7	5.1±2.6	5.3±2.4	5.3±2.6	0.6102
Range	0.0-13	0.0-13	0.0-12	0.0-12	0.0-12	0.0-13	

* P value from Kruskal-Wallis test.

Study 10

Table A-3. Demographics: Intent-to-Treat Patients							
<i>Baseline Characteristics</i>	<i>Placebo BID (n=198)</i>	<i>MDL 16,455A (BID)</i>				<i>Total (n=995)</i>	<i>P value*</i>
		<i>20 mg (n=197)</i>	<i>40 mg (n=201)</i>	<i>60 mg (n=203)</i>	<i>80 mg (n=196)</i>		
Gender							
Male % (N)	45(90)	48(94)	47(94)	46(93)	41(81)	45(452)	.7536
Female % (N)	55(108)	52(103)	53(107)	54(110)	59(115)	55(543)	
Age (years)							
Mean ± SD	34 ± 12	33 ± 12	32 ± 12	33 ± 12	34 ± 12	33 ± 12	.3566
Range	12-68	12-67	12-63	12-65	12-63	12-68	
Race							
Caucasian % (N)	82(162)	77(151)	80(161)	79(160)	83(162)	80(796)	.9197
Black % (N)	6(12)	9(17)	8(17)	7(14)	7(13)	7(73)	
Asian % (N)	4(8)	6(11)	3(7)	6(13)	5(10)	5(49)	
Other % (N)	8(16)	9(18)	8(16)	8(16)	6(11)	8(77)	
Weight (kg)							
Mean ± SD	72 ± 10	73 ± 16	73 ± 16	73 ± 17	72 ± 17	73 ± 17	.9206
Range	38-130	35-151	36-114	44-133	37-144	35-151	
Height (cm)							
Mean ± SD	169 ± 10	170 ± 10	171 ± 10	170 ± 10	169 ± 10	170 ± 10	.6065
Range	127-196	150-201	145-194	146-196	145-198	127-201	
Years Since First Episode Occurred							
Mean ± SD	17 ± 12	18 ± 11	18 ± 12	18 ± 11	18 ± 11	18 ± 11	.9504
Range	3-62	2-58	2-62	2-56	2-50	2-62	
Successive Years of Spring Allergy							
Mean ± SD	17 ± 11	17 ± 11	17 ± 12	17 ± 11	17 ± 11	17 ± 11	.9575
Range	2-62	2-58	2-62	2-56	2-46	2-62	

* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.

Study 10

Table A-4. Baseline Bedtime Symptom Assessments (Intent-to-Treat)							
Baseline Symptoms	Placebo BID (n = 198)	MDL 16,455A (BID)				Total (n = 995)	P value*
		20 mg (n = 197)	40 mg (n = 201)	60 mg (n = 203)	80 mg (n = 196)		
Nasal Congestion							
Mean ±SD	1.7±0.8	1.8±0.8	1.7±0.9	1.7±0.9	1.8±0.9	1.8±0.9	.4864
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-3.5	0.0-4.0	
Sneezing							
Mean ±SD	1.2±0.9	1.3±0.8	1.2±0.9	1.3±0.9	1.2±0.9	1.3±0.9	.5966
Range	0.0-3.5	0.0-3.5	0.0-3.5	0.0-3.0	0.0-3.0	0.0-3.5	
Rhinorrhea							
Mean ±SD	1.5±0.9	1.5±0.9	1.5±0.9	1.4±0.9	1.5±1.0	1.5±0.9	.9176
Range	0.0-4.0	0.0-3.5	0.0-3.5	0.0-3.5	0.0-4.0	0.0-4.0	
Itchy Nose, Palate and/or Throat							
Mean ±SD	1.4±0.9	1.5±0.9	1.4±0.9	1.5±0.9	1.5±0.8	1.5±0.9	.5885
Range	0.0-4.0	0.0-4.0	0.0-4.0	0.0-4.0	0.0-3.5	0.0-4.0	
Itchy, Watery, Red Eyes							
Mean ±SD	1.4±0.9	1.6±0.9	1.4±1.0	1.5±1.0	1.5±1.0	1.5±1.0	.2790
Range	0.0-4.0	0.0-4.0	0.0-3.5	0.0-4.0	0.0-3.5	0.0-4.0	
TSS at Bedtime (Excluding Nasal Congestion)							
Mean ±SD	5.5±2.8	5.9±2.8	5.6±3.0	5.7±2.7	5.7±2.8	5.7±2.9	.6255
Range	0.0-15	0.0-15	0.0-15	0.5-14	0.0-14	0.0-15	

* P value from Kruskal-Wallis test.

Study 23

Table A-5. Demographics: Intent-to-Treat Patients						
Baseline Characteristics	Placebo (N=141)	MDL 16.455A (BID)			Total (N= 570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Gender						
Male % (N)	38(54)	41(58)	41(59)	45(65)	41(236)	.7050
Female % (N)	61(87)	59(83)	59(85)	55(79)	58(334)	
Age (years)						
Mean ±SD	33 ±10	33±11	32 ±10	32 ±11	33 ±11	.9165
Range	12-63	13-64	12-66	12-62	12-66	
Race						
Caucasian % (N)	88(124)	86(121)	91(131)	90(129)	88(505)	.9310
Black % (N)	6(9)	9(12)	4(6)	6(8)	6(35)	
Hispanic % (N)	5(7)	5(7)	4(6)	5(7)	5(27)	
Other % (N)	1(1)	1(1)	1(1)	0(0)	1(3)	
Weight (kg)						
Mean ±SD	74 ±17	74±18	74 ±18	73 ±18	74 ±18	.9770
Range	42-115	42-143	40-144	32-144	32-144	
Height (cm)						
Mean ±SD	169±10	170±10	170±10	171±10	170±10	.5457
Range	142-196	150-188	147-198	150-196	142-198	
Years Since First Episode Occurred						
Mean ±SD	17 ±11	17 ±11	17 ±10	17 ±12	17 ±11	.8840
Range	2- 44	2- 60	3- 52	3- 55	2- 60	
Successive Years of Fall Allergy						
Mean ±SD	17 ±11	17 ±10	17 ±10	17 ±12	17 ±11	.9480
Range	2- 44	2- 50	3- 52	3- 55	2- 55	

* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.

Study 23

Table A-6. Baseline 7 PM Reflective Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (BID) (N=141)	MDL 16,455A (BID)			Total (N=570)	P value*
		60 mg (N=141)	120 mg (N=144)	240 mg (N=144)		
Nasal Congestion						
Mean $\pm$ SD	2.3 $\pm$ 0.6	2.3 $\pm$ 0.7	2.4 $\pm$ 0.6	2.3 $\pm$ 0.6	2.3 $\pm$ 0.6	0.8459
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Sneezing						
Mean $\pm$ SD	2.0 $\pm$ 0.7	2.0 $\pm$ 0.7	2.1 $\pm$ 0.7	2.1 $\pm$ 0.7	2.0 $\pm$ 0.7	0.9077
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean $\pm$ SD	2.3 $\pm$ 0.6	2.4 $\pm$ 0.5	2.5 $\pm$ 0.5	2.3 $\pm$ 0.6	2.4 $\pm$ 0.5	0.2754
Range	0.0-3.0	0.7-3.0	0.7-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean $\pm$ SD	2.2 $\pm$ 0.7	2.3 $\pm$ 0.6	2.2 $\pm$ 0.7	2.3 $\pm$ 0.6	2.2 $\pm$ 0.6	0.6683
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery, Red Eyes						
Mean $\pm$ SD	2.3 $\pm$ 0.6	2.1 $\pm$ 0.7	2.3 $\pm$ 0.6	2.2 $\pm$ 0.7	2.2 $\pm$ 0.7	0.2371
Range	0.0-3.0	0.0-3.0	0.3-3.0	0.0-3.7	0.0-3.7	
TSS (Excluding Nasal Congestion)						
Mean $\pm$ SD	8.9 $\pm$ 1.6	8.8 $\pm$ 1.7	9.0 $\pm$ 1.9	8.8 $\pm$ 1.8	8.9 $\pm$ 1.8	0.8984
Range	5.3-12	5.0-12	5.0-12	4.3-12	4.3-12	

* P value from Kruskal-Wallis test.

Study 24

Table A-7. Demographics: Intent-to-Treat Patients						
Baseline Characteristics	Placebo (n=137)	MDL 16,455A (BID)			Total (n=545)	P value*
		40 mg (n=135)	60 mg (n=138)	120 mg (n=135)		
Gender						
Male % (N)	42(57)	46(62)	34(47)	36(49)	39(215)	.1809
Female % (N)	58(80)	54(73)	66(91)	64(86)	61(330)	
Age (years)						
Mean ± SD	33 ± 11	33 ± 11	33 ± 11	34 ± 10	33 ± 11	.8452
Range	12-60	12-63	13-62	13-59	12-63	
Race						
Caucasian % (N)	82(113)	84(114)	78(107)	75(101)	80(435)	.3536
Black % (N)	7(10)	7(9)	7(10)	7(10)	7(39)	
Hispanic % (N)	10(14)	7(9)	12(16)	15(20)	11(59)	
Other % (N)	0(0)	2(3)	4(5)	3(4)	2(12)	
Weight (kg)						
Mean ± SD	72 ± 17	75 ± 18	72 ± 19	73 ± 17	73 ± 18	.3351
Range	43-140	44-122	33-135	42-118	33-140	
Height (cm)						
Mean ± SD	170 ± 10	170 ± 9	167 ± 10	169 ± 10	169 ± 10	.0161
Range	152-193	152-189	145-203	150-193	145-203	
Years Since First Episode Occurred						
Mean ± SD	19 ± 11	17 ± 11	18 ± 11	17 ± 10	18 ± 11	.3512
Range	3- 52	2- 56	3- 50	2- 52	2- 56	
Successive Years of Fall Allergy						
Mean ± SD	18 ± 11	17 ± 11	17 ± 11	16 ± 10	17 ± 11	.5288
Range	3- 52	2- 56	2- 50	2- 52	2- 56	

* P value from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.

Study 24

Table A-8. Baseline 7 PM Reflective Symptom Assessments (Intent-to-Treat)						
Baseline Symptoms	Placebo (<i>BID</i>) (<i>n</i> = 137)	MLL 16,455A (<i>BID</i>)			Total (<i>n</i> = 545)	<i>P</i> value*
		40 mg (<i>n</i> = 135)	60 mg (<i>n</i> = 138)	120 mg (<i>n</i> = 135)		
Nasal Congestion						
Mean ± SD	2.3 ± 0.6	2.2 ± 0.7	2.3 ± 0.6	2.3 ± 0.6	2.3 ± 0.6	.5777
Range	0.7-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
Sneezing						
Mean ± SD	2.0 ± 0.6	2.1 ± 0.7	1.9 ± 0.7	2.0 ± 0.7	2.0 ± 0.7	.6191
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
Rhinorrhea						
Mean ± SD	2.3 ± 0.5	2.3 ± 0.6	2.3 ± 0.5	2.4 ± 0.5	2.3 ± 0.5	.8045
Range	0.7-3.0	0.7-3.0	0.7-3.0	0.0-3.0	0.0-3.0	
Itchy Nose, Palate and/or Throat						
Mean ± SD	2.2 ± 0.6	2.2 ± 0.6	2.2 ± 0.6	2.3 ± 0.6	2.2 ± 0.6	.8409
Range	0.7-3.0	0.0-3.0	0.3-3.0	0.0-3.0	0.0-3.0	
Itchy, Watery, Red Eyes						
Mean ± SD	2.1 ± 0.6	2.1 ± 0.7	2.2 ± 0.7	2.0 ± 0.8	2.1 ± 0.7	.2989
Range	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0	
TSS (Excluding Nasal Congestion)						
Mean ± SD	8.7 ± 1.5	8.7 ± 1.9	8.7 ± 1.6	8.6 ± 1.7	8.7 ± 1.7	.9712
Range	5.7- 12	5.0- 12	5.0- 12	5.0- 12	5.0- 12	

* *P* value from Kruskal-Wallis test.

Appendix B

The analyses that follow all include data from Site 155, where the investigator, Craig LaForce was suspected of altering the data. Analyses excluding data from Site 155 can be found in the discussion section of the body of the review.

Recall the sponsor's policy was to leave treatment by baseline interaction effects in their models only if the interaction effect was significant when the treatment by investigator interaction effect was also in the model. Table B-1 presents the three models the sponsor performed. The sponsor chose Model 1 to be the final model because the treatment by baseline interaction effect in Model 3 was not statistically significant, even though it was statistically significant in Model 2.

Table B-1: Analysis of Covariance Tables of 3 different models sponsor performed (n = 584)

Model	Predictor Variables	df	Sums of Squares	F-statistic	p-value
1	Treatment	3	83.96	6.45	.0003
	Investigator	14	190.10	2.92	.0002
	Baseline	1	278.12	64.06	.0001
2	Treatment	3	27.63	2.13	.0953
	Investigator	14	191.89	2.96	.0001
	Baseline	1	281.04	65.01	.0001
	Treatment*Baseline	3	23.54	1.82	.1433
3	Treatment	3	18.05	1.38	.2490
	Investigator	14	186.90	2.85	.0003
	Baseline	1	262.11	59.98	.0001
	Treatment*Investigator	42	170.29	0.87	.7186
	Treatment*Baseline	3	16.80	1.28	.2798

The mean and median of baseline TSS were 8.6621 and 8.6667, respectively. Dividing the data in half at the mean of baseline, two analyses of variance were performed on the placebo and 60 mg patients (Table B-2). Treatment was not significant in the low baseline cohort, while it was significant in the high baseline cohort. The absolute difference between mean change from baseline TSS in the placebo group and mean change from baseline TSS in the 60 mg dose group was .48 for the low baseline cohort and 1.02 for the high baseline cohort (Table B-3). The variance of the change from baseline in the low baseline cohort was greater than that in the high baseline cohort. This may have contributed to the significance of treatment in the high baseline

group and not the low.

Table B-2. Study 24: Analysis of Covariance Tables for Low and High Baseline groups

Baseline Group	n	Baseline Values*	Predictor Variables	Sums of Squares	F statistic	p-value
Low	140	4.7-8.66	Treatment	8.53	1.72	.1916
			Investigator	119.51	1.61	.0805
			Baseline	59.56	12.03	.0007
High	154	8.66-12	Treatment	36.44	9.38	.0026
			Investigator	41.81	0.72	.7634
			Baseline	4.96	1.28	.2603

*Randomization occurred after the placebo-lead in period. No patients with a placebo lead-in average baseline TSS less than 5 or greater than 12 was allowed to continue. The patients with average baseline TSS values less than 5 are not protocol-correct.

Table B-3. Study 24: Means, Least Squares Means and Variances of Change from Baseline

Baseline group	Dose	n	Mean ± SD	Least Squares Mean ± SE	Difference of means of Change from Baseline TSS (60 mg - placebo)	Variance of Change from Baseline TSS
Low	Placebo	73	-0.40 ± 2.44	-0.32 ± .30	.48	5.74
	60 mg	67	-0.88 ± 2.34	0.82 ± .31		
High	Placebo	74	-1.59 ± 1.85	-1.62 ± .24	1.02	3.99
	60 mg	80	-2.61 ± 2.02	-2.61 ± .24		

*Using the means, not the least squares means.

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Concur: Dr. Wilson *W* 6/12/96
Dr. Nevius *BN* 6/19/96

cc.

Orig. NDA 20-625

HFD-570 / Division File

HFD-570 / GStrange

HFD-570 / J.Jenkins, M.Himmel, M.Sevka

HFD-715 / Division File. Chron

HFD-715 / E.Nevius, S.Wilson, B.Bono

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**STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES
ADDENDUM II - STUDY 7**

<u>NDA#:</u>	20-625	Date:	JUN 3 1996
<u>Applicant:</u>	Marion Merrell Dow Inc. / Hoechst Marion Roussel, Inc		
<u>Name of Drug:</u>	Fexofenadine hydrochloride, or Fexofenadine		
<u>Indication:</u>	Treatment of patients with seasonal allergic rhinitis		
<u>Documents Reviewed:</u>	July 31, 1995	Volumes 1.1, 1.173, 1.174	
	Sept 27, 1995	Electronic Data	
<u>Statistical Reviewer:</u>	B.Bono, M.S.		
<u>Medical Input:</u>	M.Sevka, M.D.		
<u>Key words:</u>	QTc intervals, carryover effect, F-statistic, Analysis of Variance		

Summary of Review

- After reading the statistical review of Study 7 (dated June 3, 1996), the medical officer requested a more detailed examination of a possible carryover effect.
- Two signs of a possible carryover effect are described in this addendum.
 1. The dose received during one period affects the measurements of baseline days in subsequent periods.
 2. The dose received during one period affects the rate of change of measurements over time in subsequent periods.
- The sponsor conducted a repeated measures analysis of variance on QTc interval measurements days 1, 2 and 8 (see Study 7, Addendum, dated June 3, 1996). For each measurement in the data set, a variable called "carryover" was created that indicated the dose the subject took during the period prior to the period that measurement was recorded. No significant carryover effect was detected in the sponsor's model. This analysis provides an evaluation of both types of carryover effect.
- Plots of QTc measurements did not demonstrate differences between subjects who received placebo in the first period compared to subjects who received placebo in the last period (see Study 7, Addendum, dated June 3, 1996).
- In this addendum, the differences in average values of baseline days for each pair of periods (periods 1 and 2, periods 2 and 3, and periods 3 and 4) are compared among the different doses of the first of the two periods. There were no statistically significant differences found.
- Using descriptive statistics, plots (Addendum, dated June 3, 1996), the sponsor's analysis (Addendum, dated June 3, 1996) and a simple, straightforward analysis in this addendum, there does not appear to be a carryover effect in Study 7.

I. Background

Study 7 was a four period crossover study with eight days of treatment per period (Placebo, 40 mg, 200 mg, 400 mg) and two weeks of washout between periods. Measurements of QTc intervals were taken on the first day of every period, before treatment was administered. Thus, there were four baseline measurements for each subject. The electrocardiograms were read by a machine and by a doctor, Dr. Morganroth. The different types of measurements were analyzed separately in the sponsor's application and in this review. This review focuses on whether or not there is a statistically significant carryover effect even after the 14- to 28-day washout period.

Two ways a drug can cause a carryover effect are:

- The drug may cause the subsequent baseline day QTc intervals to lengthen, (i.e., Baseline Day of Period 2 is higher than Baseline Day of Period 1).
- The drug may cause the dose in the subsequent period to increase the QTc intervals at a higher rate, (i.e., the slope of the QTc intervals over time in Period 2 is greater than the slope of the QTc intervals over time in Period 1).

The reviewer's graphs and means reported in the review of Study 7 (Addendum, dated June 3, 1996), examined both of these types of carryover effect. The QTc interval measurements on days 1, 2 and 8 for subjects who received placebo in the first period were compared to those of subjects who received placebo in the last period (See Study 7, Addendum, dated June 3, 1996). The graphs and means demonstrated that there were only small, inconsistent differences between the QTc intervals of these different groups of subjects. Neither the baseline days, nor the change from baseline day to days 2 and 8 appeared to differ between the two groups. Thus, neither type of carryover effect was evident from these descriptive statistics.

The sponsor's analyses, reported in the review of Study 7 (Addendum, dated June 3, 1996), appeared to examine both types of carryover effect. The sponsor conducted a repeated measures analysis of variance on QTc interval measurements days 1, 2 and 8. For each measurement in the data set, a variable called "carryover" was created that indicated the dose the subject took during the period prior to the period that measurement was recorded. No statistically significant carryover effect was detected (Morganroth, $p=0.1014$; Machine, $p=0.2940$). Thus the QTc interval measurements of a given subject during a given period were not influenced by the dose the subject received in the previous period. This analysis appeared to demonstrate that the measurements on days 1, 2 and 8 were not statistically significantly different among the four periods and that the change from baseline day to days 2 and 8 of QTc intervals was not statistically significantly different among the four periods.

To further investigate a possible carryover effect, a more straightforward approach is used in this review to examine the differences among the baseline days of the four periods. If fexofenadine did produce a carryover effect, the baseline day of Period 2 compared to the baseline day of Period 1 would be a measure of the effect the drug has in raising the subject's baseline level before Period 2 begins. The means between the differences in baseline QTc measurements of the two periods of subjects assigned to drug during Period 1 can be compared to those of the subjects

assigned to placebo during Period 1. Similarly, the baseline day of Period 3 compared to that of Period 2 and the baseline day of Period 4 compared to that of Period 3 would also be measures of the possible carryover effect. Analyses of variance were performed on the differences in the means of measurements between the first day of Periods 1 and 2, between the first day of Periods 2 and 3, and between the first day of Periods 3 and 4. The treatment to which the subject was assigned on the first of the two periods was a factor in the ANOVA model.

II. Results of Analysis of Variance

The average differences between Day 1 of Period 1 and Day 1 of Period 2 for each of the Period 1 treatment groups are presented in Table 1. Similarly, Tables 2 and 3 report the average differences comparing Period 2 to Period 3 for the Period 2 treatment groups and Period 3 to Period 4 for the Period 3 treatment groups, respectively. The small differences and large standard deviations yield wide, overlapping confidence intervals. These confidence intervals depict no differences among the different doses the subjects received during the prior period.

**Table 1: Day 1 Period 1 compared to Day 1 Period 2
(n = 10 for each treatment group)**

Machine data				Morganroth data			
Dose in Period 1	Mean of difference between Day 1 Period 1 QTc and Day 1 Period 2 QTc (msec)	Std dev	95% Confidence Interval	Dose in Period 1	Mean of difference between Day 1 Period 1 QTc and Day 1 Period 2 QTc (msec)	Std dev	95% Confidence Interval
Placebo	0.88	13.10	(-8.4, 10.1)	Placebo	-6.30	7.39	(-11.5, -1.1)
40 mg	3.08	6.98	(-1.8, 8.0)	40 mg	-3.75	8.75	(-9.9, 2.4)
200 mg	1.31	8.02	(-4.3, 7.0)	200 mg	-0.34	8.31	(-6.2, 5.5)
400 mg	-2.94	5.12	(-6.5, 0.7)	400 mg	-2.26	5.13	(-5.9, 1.4)

**Table 2: Day 1 Period 2 compared to Day 1 Period 3
(n = 10 for each treatment group)**

Machine data				Morganroth data			
Dose in Period 2	Mean of difference between Day 1 Period 2 QTc and Day 1 Period 3 QTc (msec)	Std dev	95% Confidence Interval	Dose in Period 2	Mean of difference between Day 1 Period 2 QTc and Day 1 Period 3 QTc (msec)	Std dev	95% Confidence Interval
Placebo	2.04	8.27	(-3.5, 7.9)	Placebo	1.77	5.72	(-2.3, 5.8)
40 mg	1.21	4.35	(-1.9, 4.3)	40 mg	5.79	7.72	(0.4, 11.2)
200 mg	2.39	8.12	(-3.3, 8.1)	200 mg	1.52	7.04	(-3.4, 6.5)
400 mg	3.21	10.98	(-4.5, 10.9)	400 mg	2.42	15.19	(-8.3, 13.1)

**Table 3: Day 1 Period 3 compared to Day 1 Period 4
(n = 10 for each treatment group)**

Machine data				Morganroth data			
Dose in Period 3	Mean of difference between Day 1 Period 2 QTc and Day 1 Period 3 QTc (msec)	Std dev	95% Confidence Interval	Dose in Period 3	Mean of difference between Day 1 Period 2 QTc and Day 1 Period 3 QTc (msec)	Std dev	95% Confidence Interval
Placebo	-2.55	6.08	(-6.8, 1.7)	Placebo	-1.04	10.73	(-8.6, 6.5)
40 mg	-0.69	5.13	(-4.3, 2.9)	40 mg	-5.64	9.82	(-12.6, 1.3)
200 mg	-4.93	8.14	(-10.7, 0.8)	200 mg	3.12	7.92	(-8.7, 2.5)
400 mg	-4.76	15.70	(-15.8, 6.3)	400 mg	-9.73	19.82	(-23.7, 4.2)

These average differences in QTc measurements between the first days of the different pairs of periods (1 and 2, 2 and 3, and 3 and 4) were modeled using an analysis of variance (ANOVA). The treatment the subject was assigned in the first of the two periods was used as a factor in the ANOVA. The F-statistic tests whether any of the means are different from each other. The means of the differences were not found to be statistically significantly different among the different treatment groups for any of the different pairs of period comparisons (Table 4). This means that no carryover effect of drug on the QTc intervals was found after the washout period was over.

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Table 4: Results of Analyses of Variance

	Periods compared	F-statistic for treatment: tests for any difference between means of the different treatments	p-value for F-statistic
Machine	1 and 2	0.82	0.4891
	2 and 3	0.10	0.9593
	3 and 4	0.43	0.7321
Morganroth	1 and 2	1.12	0.3548
	2 and 3	0.42	0.7385
	3 and 4	0.84	0.4820

III. Conclusions

The medical officer requested a more detailed review than was presented in the Study 7 Addendum to check for a possible carryover effect. An examination of means of the differences between three pairs of four QTc baseline measurements and their confidence intervals indicate no carryover effect. The statistical tests (F-statistics from analyses of variance models) appear to confirm this observation.

These results, together with plots of the QTc measurements (Addendum, dated June 3, 1996), and the results the sponsor provided from their repeated measures ANOVA (Addendum, dated June 3, 1996), demonstrate no significant carryover effect.

Thus, the results of Study 7 do not provide evidence of a carryover effect of fexofenadine after 14 to 28 days of washout period.

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Concur: Dr. Wilson *EW* 6/15/96

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Orig. NDA 20-625

HFD-570 / Division File

HFD-570 / J.Jenkins, M.Himmel, M.Sevka

HFD-715 / Division File, Chron

HFD-715 / E.Nevius, S.Wilson, B.Bono

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**STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES
ADDENDUM - STUDY 7**

Date: JUN 3 1996

NDA#: 20-625
Applicant: Marion Merrell Dow Increase. / Hoechst Marion Roussel, Increase.
Name of Drug: Fexofenadine hydrochloride, or Fexofenadine
Indication: Treatment of patients with seasonal allergic rhinitis
Documents Reviewed: July 31, 1995 Volumes 1.1, 1.173, 1.174
Sept 27, 1995 Electronic Data
Statistical Reviewer: B.Bono, M.S.
Medical Input: M.Sevka, M.D.
Key words: Random effects, mixed model, repeated measures, QTc intervals, equivalence, gender, covariance structure

Summary of Review

- A review of descriptive statistics indicates that, in general, there was very little increase (less than four milliseconds) in QTc intervals with increasing dose and length of use.
- Measurements from the machine match closely with measurements from Dr. Morganroth.
- It is inappropriate to statistically conclude that there is no relationship between fexofenadine and QTc intervals based on the sponsor's analysis.

I. Background Information

A. Introduction

Two of the currently approved non-sedating anti-histamines cause Q-T interval prolongation, an adverse pharmacologic effect on cardiac repolarization. Fexofenadine is the acid metabolite of terfenadine, one of the approved anti-histamines that causes this adverse event. Q-T interval prolongation has been associated with torsades de pointes. Corrected Q-T (QTc) intervals were measured in Study 7 independently by both a machine and a physician, Dr. Morganroth. Study 7 was a crossover trial with four periods. Each period consisted of one day of baseline followed by eight days of double-blind treatment and fourteen days of washout. The null hypothesis was that there were no differences in mean QTc intervals among the treatment groups over the course of three days (1, 2 and 8). The sponsor performed a statistical analysis on the data and found no statistically significant increase in QTc intervals with increasing length of use of drug or with increasing dose of drug. The medical officer was primarily interested in the differences in QTc intervals between the first and eighth days. This review addressed the question of whether use of

fexofenadine is related to an increase in QTc intervals based on the data from Study 7.¹

B. Clinically Relevant Increase from Baseline

From a clinical point of view, increases in QTc intervals from baseline of 20 or 30 milliseconds (msec) would be alarming, however, there is no lower limit that would be considered safe. Since a clinically meaningful difference cannot be determined, this report will attempt to identify any difference between dose groups in QTc interval changes, regardless of magnitude.

C. Summary of Study Design

Study 7 was a crossover trial with four periods and 40 healthy subjects (20 males, 20 females). Figure 1 represents the design of the study. Subjects entered the clinic the evening prior to the first dose of each period. Placebo was administered at 8 a.m. and 8 p.m. on the first day to establish baseline QTc intervals. On day two of each period, the subject started the double-blind treatment to which he was randomized for that period. The study included four doses: placebo, 40 mg, 200 mg and 400 mg, administered BID at 8 a.m. and 8 p.m., beginning on day two and continuing through day 7 of each period. On day eight at 8 a.m., the last dose was administered. Serial measurements were performed at 1, 2, 3, 4, 6, 8 and 12 hours after the 8 a.m. dose on days 1, 2 and 8 of each period. On days three through seven, measurements were taken at 0, 4 and 8 hours after the 8 a.m. dose. Only two measurements were taken on day nine, at 0 and 12 hours after the 8 a.m. dose. On days ten and eleven, measurements were taken at 8 a.m. Following day eleven, subjects were discharged from the clinic and asked to return to the clinic in ten days (13 days from the final dose on day eight) to be checked-in for the beginning of the next treatment period. At least a 14-day (and not more than a 28-day) washout period was included between the last dose of one period and the first dose of the following period.

D. Machine vs. Morganroth Data

The measurements obtained from the machine were similar to those obtained from Dr. Morganroth, except the Morganroth data were consistently slightly greater and more variable than the machine data (see Figures 2 through 5 and Table 1).²

¹ Dr. Morganroth measured the QTc intervals twice. The QTc interval measurements from the first time increased with increasing period, regardless of treatment group. This phenomenon was not seen in the machine data. The sponsor hypothesized that the reason for this increase was that the ECG's were not completely blinded and thus sent the same ECG's to Dr. Morganroth, (this time completely blinded), to be re-analyzed. The second time Dr. Morganroth measured the intervals, the results were more consistent with the results from the machine. (See the medical officer's review for further discussion.) The sponsor did not submit the first Morganroth data in electronic form. Therefore, this review focuses on the results of the machine reading and the second Morganroth reading.

² As can be seen from the graphs in Figures 2 through 5, the QTc intervals of females are generally longer than those of males.

Table 1: Mean of QTc intervals (using all measurements)

Dose	MORGANROTH DATA				MACHINE DATA			
	Mean	Std Dev	Min	Max	Mean	Std Dev	Min	Max
Placebo	398.0	23.8	326	556	390.9	22.2	330	530
40 mg	397.7	21.2	330	464	392.0	20.4	328	517
200 mg	398.8	22.0	333	474	390.6	20.0	331	502
400 mg	401.2	21.2	334	474	392.2	19.6	321	444
all doses	398.9	22.1	326	556	391.4	20.6	321	530

Neither the machine data nor the Morganroth data appeared to increase in mean QTc intervals between the baseline day (day 1) to the end of treatment (day 8) consistently across treatment groups when studying males and females together (Figures 2 through 5, Table 2).

Table 2: Changes in QTc Intervals

Treatment group	Mean Change in QTc intervals (Day 8 - Day 1)			
	MORGANROTH		MACHINE	
	Females	Males	Females	Males
Placebo	7.99	-3.69	6.11	-4.67
40 mg	3.61	0.60	3.98	1.56
200 mg	8.02	-.39	5.73	0.47
400 mg	10.34	0.37	9.46	-1.98

There was a slight increase in mean QTc intervals among females. Since this increase was present in both the placebo groups and the drug groups, it does not appear to be drug related. However, the average of QTc intervals among placebo subjects was calculated using the placebo groups from all the periods. An increase in QTc intervals among placebo subjects in the fourth period could be related to fexofenadine because these subjects were on fexofenadine for the first three periods. Therefore, QTc interval means of subjects who received placebo in the first period were compared to those of subjects who received placebo in the last period (Figures 6 through 9, Table 3).

Table 3: Changes in QTc Intervals of Subjects during their Placebo period

Mean changes in QTc intervals (Day 8 - Day 1)						
Period that subjects were on Placebo	n		MORGANROTH		MACHINE	
	F	M	Females	Males	Females	Males
	1	4	6	7.56	-0.076	3.53
2	5	5	7.45	5.35	5.35	3.65
3	5	5	7.97	-4.63	9.18	-3.50
4	6	4	8.74	-17.97	5.90	-15.52

The graphs indicate that there were only small, inconsistent differences between the QTc intervals of these different groups of subjects. Table 3 shows that, according to Dr. Morganroth's measurements, the increases among females were less than one second with increasing period, demonstrating that there was no carryover effect. According to the machine's measurements, there was no consistent increase in change from baseline with increasing period among females.

Based on the raw means of the data, both the Morganroth data and the machine data support the claim that fexofenadine *does not* affect QTc intervals.

E. Summary of Sponsor's Analysis

The sponsor performed a random effects repeated measures analysis on the means of the hourly measurements on days 1, 2 and 8. Machine and Morganroth data were analyzed separately. Thirty-nine out of the forty randomized subjects completed all four periods. One subject was discontinued on day two of the fourth period (his placebo period) and thus did not have a control period. The sponsor used his data from the other periods in the analyses.³

³ This is a conservative approach. The procedure in SAS®, "PROC MIXED", assumes that missing data is missing-at-random. The subject whose data is missing for day eight of the last period had very high QTc intervals the first two days of the last period due in part to an electrolyte imbalance related to gastroparesis. The patient was hospitalized for the gastroparesis and could not complete the study. Since the QTc intervals were high (451-508 msec) data for day eight of the last period could be classified as informative missing data. The two options the sponsor had for analyzing the data from this subject were to impute the data point for day eight of the last period or to leave it missing and let the computer procedure assume it was missing-at-random or non-informative missing data. If the sponsor had imputed the data, the imputed QTc interval would follow the trend seen in the first two days, thus the placebo period for this subject would have a high QTc interval. If fexofenadine does cause the QTc interval to increase, imputing the data would make placebo appear closer to drug. If fexofenadine causes the QTc interval to decrease, imputing the data would make placebo appear farther from drug. Since the primary question of interest here is whether fexofenadine causes *prolongation* of QTc intervals, the approach the sponsor used is considered conservative.

As in any statistical modeling problem, we look at data as having two components, model and error. In the longitudinal data setting it becomes particularly difficult to separate out these two components of variation due to the correlation induced by having repeated measurements. This difficulty arises not just from the application of particular methods but from the *a priori* choice of models. Choosing a longitudinal model includes choosing a covariance structure to impose on the error term. The longitudinal nature of these data should be exploited in order to utilize the added information available from measuring outcomes repeatedly on each individual.

The sponsor originally chose $\sigma^2 I$ to be the covariance structure of the error term of each subject (where σ^2 is the variance of the measurement error for each of the three time points and I is the identity matrix). This structure assumes that there is no correlation between time points ($\rho = 0$) and that the measurement error for every person during every period is the same (σ^2) at every time point.⁴ The results reported in Table 4 are from a model which assumes this structure. After a telephone conversation with the sponsor's statisticians, Robert Ahlbrandt and Michael Mosier, the sponsor re-analyzed the data using different covariance structures such as compound symmetry, exchangeable correlation and an unrestricted structure. All the usual criteria employed to assess a repeated measures model (ie., Akaike's Information, Shwartz's Bayesian, and the statistic derived from restricted maximum likelihood) concluded that the models with different covariance structures fit equally well. Additionally, the sponsor found that the conclusions of the models were robust to the choice of covariance structure.⁵

⁴ The two assumptions are not unrealistic. We know from a clinical perspective that QTc intervals of a given subject vary greatly from hour to hour and day to day. In other words, a person's average measurements on one particular day provide little information about the person's measurements on another day. Therefore, the correlation between time points within a subject is probably close to zero. Additionally, the second assumption is reasonable. From a clinical point of view, we do not know if the variance of QTc intervals over the course of a given day is the same across people. It may very well be. After modeling the data from Study 7, the sponsor found that, from a statistical point of view, the variance of QTc intervals was similar across subjects.

⁵ The sponsor reported the results of the new analyses to the statistical reviewer in a telecon on May 10, 1996.

Table 4: Sponsor's Analyses

Model Factor	p-value*	
	MORGANROTH	MACHINE
Period	.0035	.0025
Day	<.0001	<.0001
Treatment	.4260	.8384
Day by Treatment interaction	.4125	.9607
Carryover	.1014	.2940
Linear Trend Across Doses, at Day 8	.3547	.5456

Least-Squares Mean Change QTc ± SE (Day 8 - Day 1)			
Treatment (BID)	n	MORGANROTH	MACHINE
Placebo	39	4.6 ± 1.5	2.6 ± 1.5
40 mg	40	2.1 ± 1.5	2.8 ± 1.5
200 mg	40	3.8 ± 1.5	3.1 ± 1.5
400 mg	40	5.4 ± 1.5	3.7 ± 1.5

*Adjusted treatment means and p-values are from an analysis of variance model which adjusted for period, day, treatment, day by treatment interaction, and carryover.

†Subject 009-37 was dropped from the study on Day 2 of Treatment Period 4 (placebo). Thus, n=39 for the placebo treatment group.

Treatment was not found to be a statistically significant factor using either set of data (Morganroth, p=0.4260; machine, p=0.8130). This could be due to the low power of the test.

II. Review discussion and comments

In any statistical analysis, accepting the null hypothesis does not yield the conclusion that it is true. Several factors of the data or the method of analysis influence how much we believe that not rejecting the null hypothesis was the correct decision.

Power represents the ability of the decision rule to correctly recognize that the null hypothesis is false. (The null hypothesis is that the means of the QTc changes from baseline among all dose groups are equal.) In this example, one would generally want the power of the test to correctly recognize a QTc interval difference 80% of the time, and overlook a QTc interval difference only 20% of the time.

It was uncertain how to calculate the power for this Study because it was a random effects, repeated measures 5-way analysis of variance of a crossover trial with unbalanced design

(because one subject dropped out). It is probable though, that one would need very high power in order to detect the observed differences, because the common standard deviation of QTc intervals on all three days was almost five times as large as the average difference in QTc intervals between baseline and day eight using the Morganroth data and almost six times as large using the Machine data (Table 5). A simple two-way analysis of variance on the difference in QTc interval measurements from the first day to the eighth day was performed in order to get an approximate estimate of the power of the sponsor's analysis.

Table 5 presents the mean changes in QTc intervals for both males and females together. The maximum difference in mean change from baseline QTc intervals occurred between the 400 mg and 40 mg groups using the Morganroth data (3.24 msec) and between the 400 mg and placebo groups using the machine data (1.44 msec). Ignoring the period effect and the fact that the subjects' assessments across periods were correlated, a two-way analysis of variance with treatment, a categorical baseline and treatment by baseline interaction effect did not find a statistically significant difference in change from baseline QTc intervals among any two of the dose groups (Morganroth $p=0.5388$, machine $p=.9780$). This analysis, in effect, assumes that there are 39 different subjects per treatment, or 156 subjects total. (None of the data from the subject without a control period was used.) The power calculated from these analyses is 71% using Morganroth data and 62% using machine data.⁶

Table 5: Mean Changes in QTc Intervals

Dose	MORGANROTH DATA Day 8 - Day 1				MACHINE DATA Day 8 - Day 1			
	Mean	S.d. Dev	Min	Max	Mean	S.d. Dev	Min	Max
Placebo	4.60	8.68	-18	27	2.56	9.63	-28	30
40 mg	2.11	9.40	-19	21	2.84	9.90	-18	33
200 mg	3.82	9.07	-21	21	3.25	8.68	-14	23
400 mg	5.35	10.67	23	24	4.00	9.64	-18	25
all groups	3.97	9.48	-23	27	3.16	9.40	-28	33

The power calculation of this analysis assumed there were 156 subjects, and did not include all of the factors that were in the sponsor's analysis (such as the day, period and carryover effects). The sponsor's analysis probably had less power to detect the observed difference because the Study actually only had 39 or 40 subjects, (not 156 subjects) and because the extra factors used

⁶Using Dr. Morganroth's measurements, the maximum observed differences in change from baseline QTc intervals among the doses was 3.24 msec. With about 71% power, the analysis of variance did not detect this difference. This means that there was about a 71% chance that the true difference was less than this difference and about a 29% chance that the true difference was greater than or equal to this difference. Using the machine's measurements, the maximum observed differences in change from baseline QTc intervals among the doses was 1.44 msec. With power of 62%, there was about a 62% chance that the true difference was less than this difference and about a 38% chance that the true difference was greater than or equal to this difference.

degrees of freedom:

Based on both the reviewer's and the sponsor's statistical analysis of the data, neither the Morganroth data nor the machine data support the fact that fexofenadine *affects* QTc intervals. While achieving moderately substantial power, these analyses did not find differences as small as 3.24 and 1.44 msec to be statistically significant. Thus, the review of this study finds no statistical evidence that fexofenadine increases QTc intervals.

III. Conclusions

In Study 7, the Morganroth data agree with the machine data. The greatest observed difference occurred between the 40 mg and the 400 mg dose groups (3.24 msec). The greatest observed difference between the placebo groups and a dose group was 1.44 msec. These differences were not statistically significant using either the sponsor's or the reviewer's analyses. The results from Study 7 can be used to describe QTc intervals following treatment with fexofenadine. However, they cannot be used to prove that there is no relationship between fexofenadine and QTc intervals. Graphs and descriptive statistics show that there does not appear to be a difference greater than about three milliseconds among any of the treatment arms in increases in QTc intervals.

Figure 1: Design of Study 7

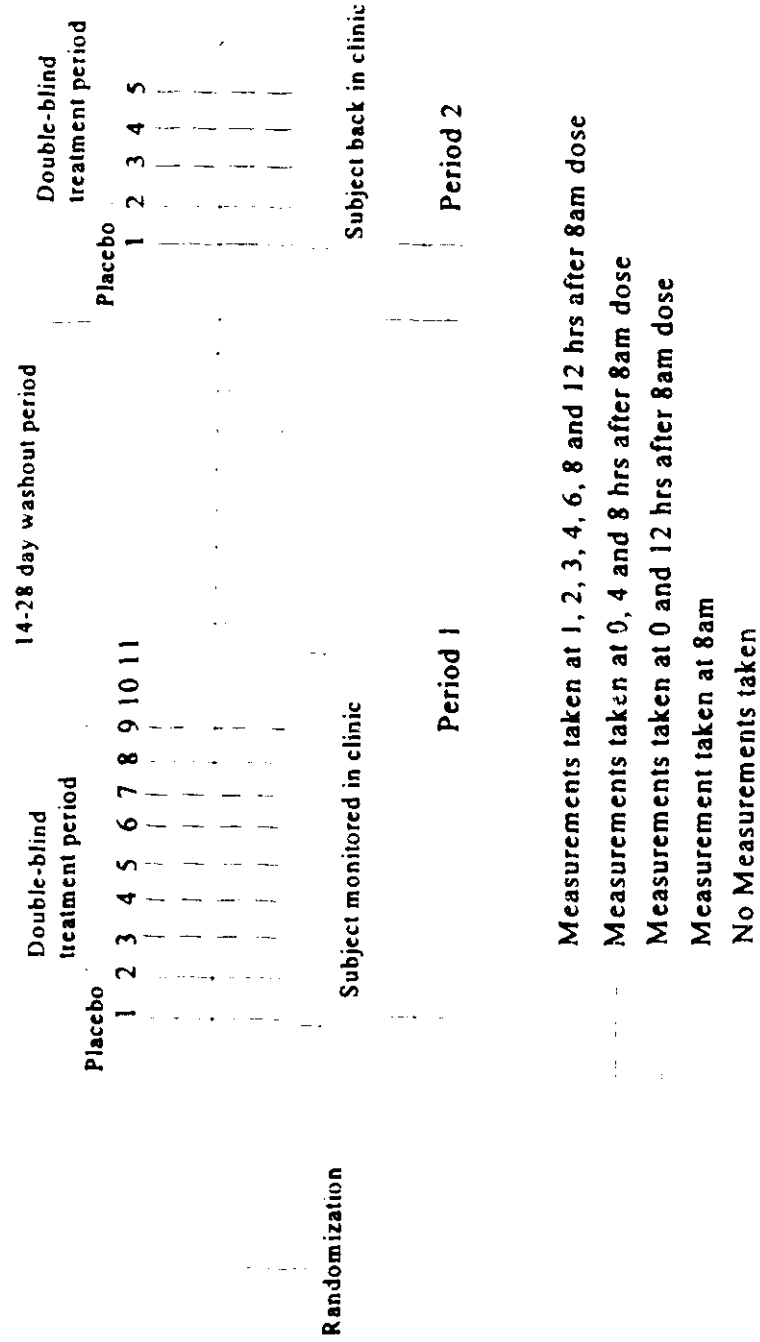
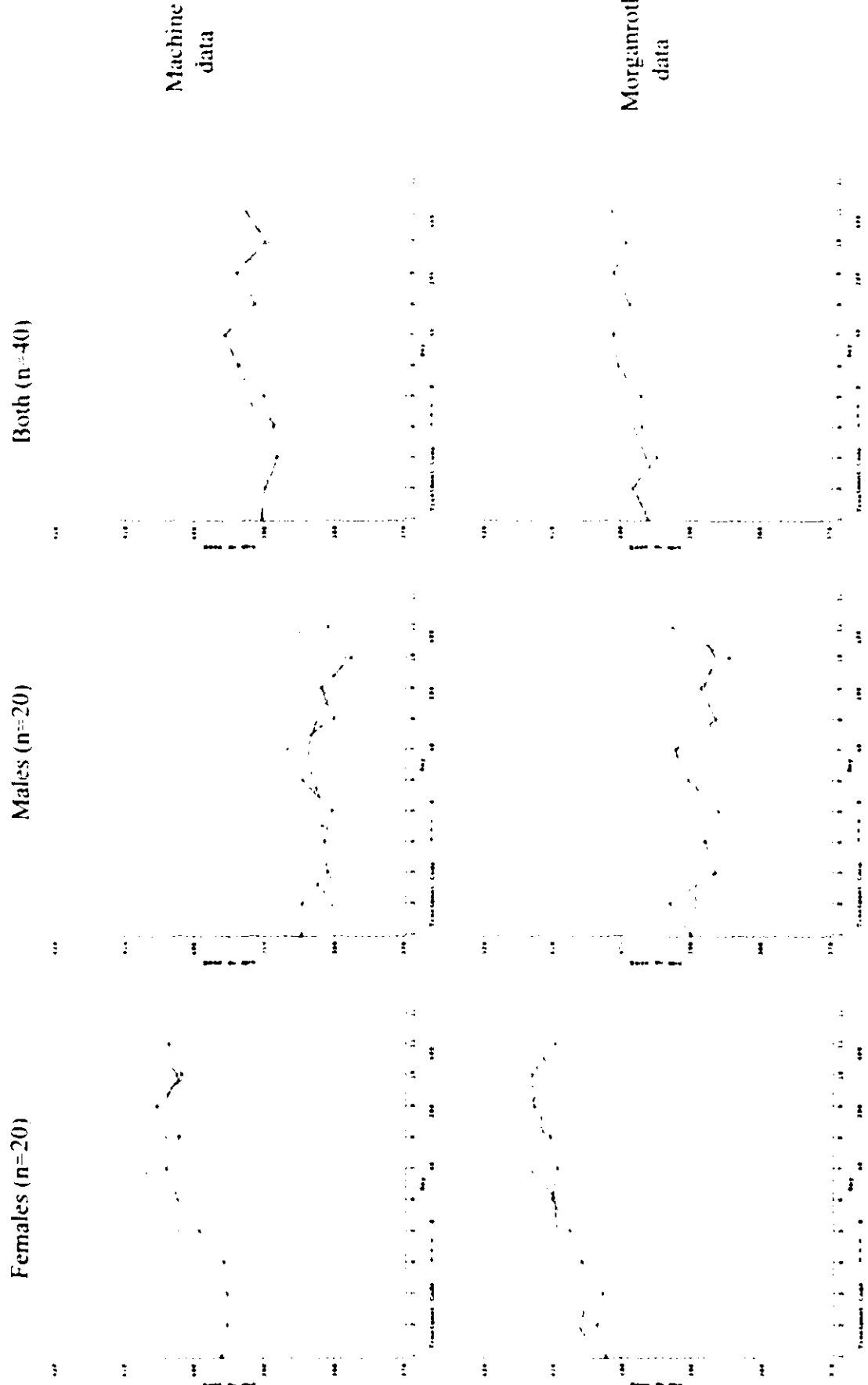


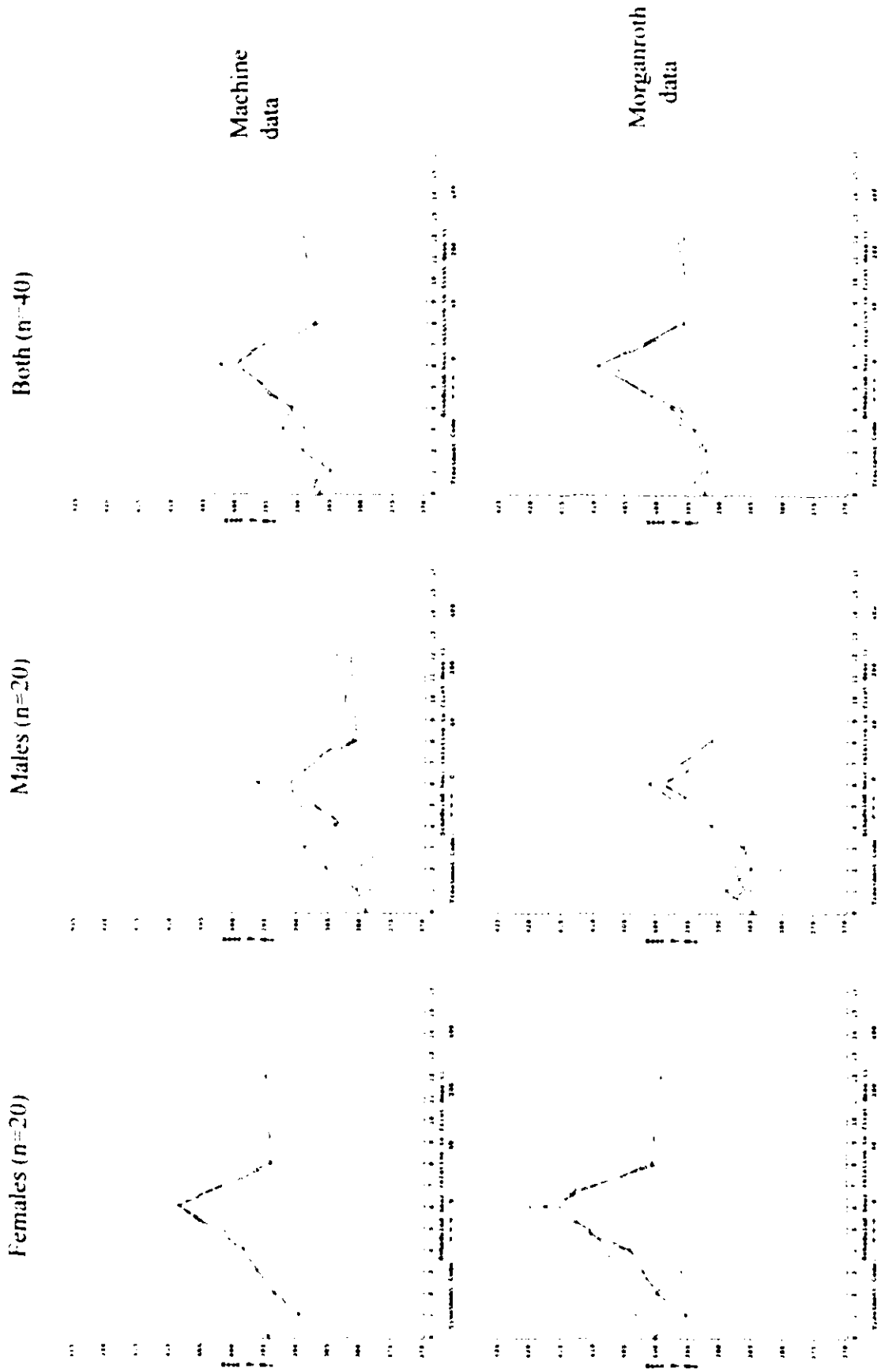
Figure 2: I s 1 - 11



X axis: Days 1-11 of all periods
 Y axis: Mean of QTc intervals

Note: Since there were four periods, each subject is represented four times in each graph. Also, the means on days 1, 2 and 8 were calculated from 7 measurements, while the means on days 3-7, day 9 and days 10-11 were calculated from 3, 2 and 1 measurement(s) respectively.

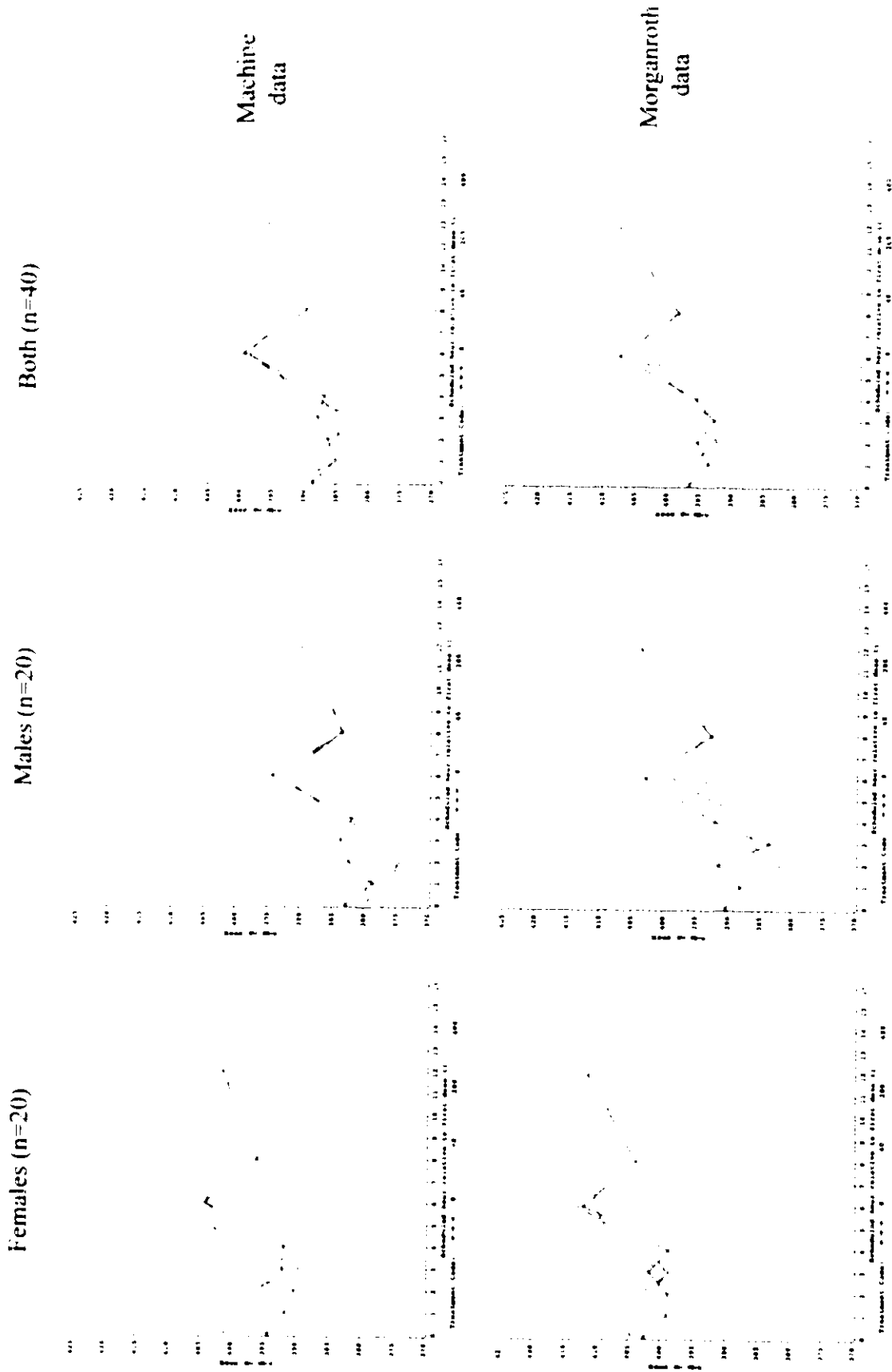
Figure 3: DAY 1



X axis: Scheduled hour relative to first dose
 Y axis: Mean of QTc intervals

Note: Since there were four periods, each subject is represented four times in each graph.

Figure 3: DAY 2



X axis: Scheduled hour relative to first dose
 Y axis: Mean of QTc intervals

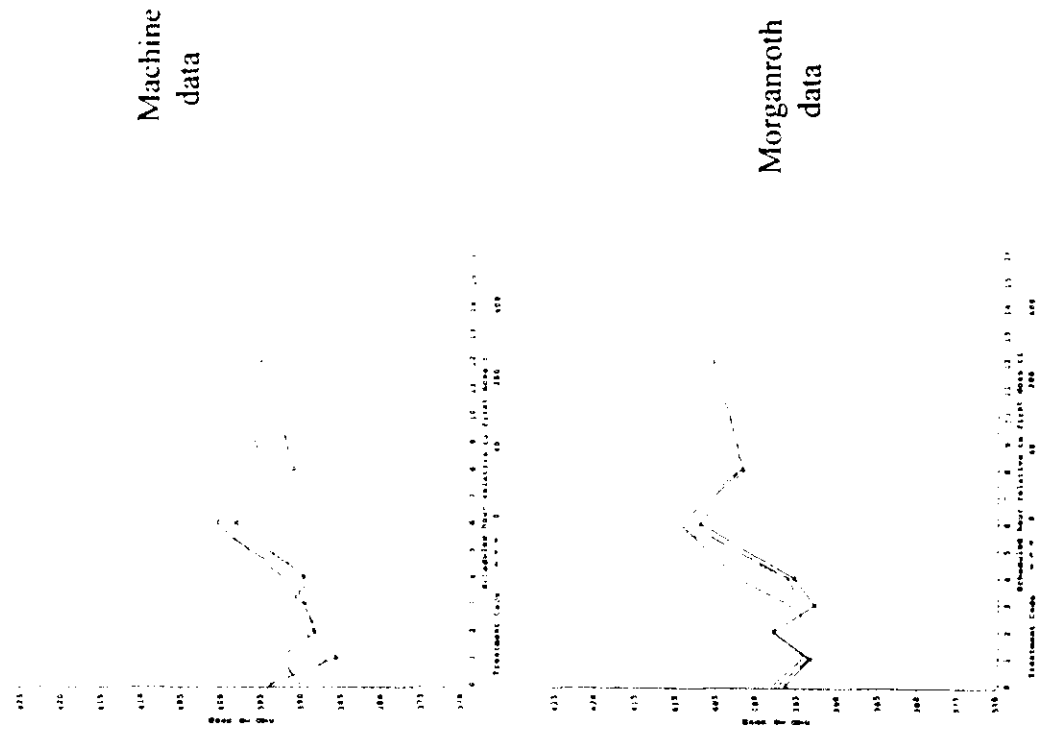
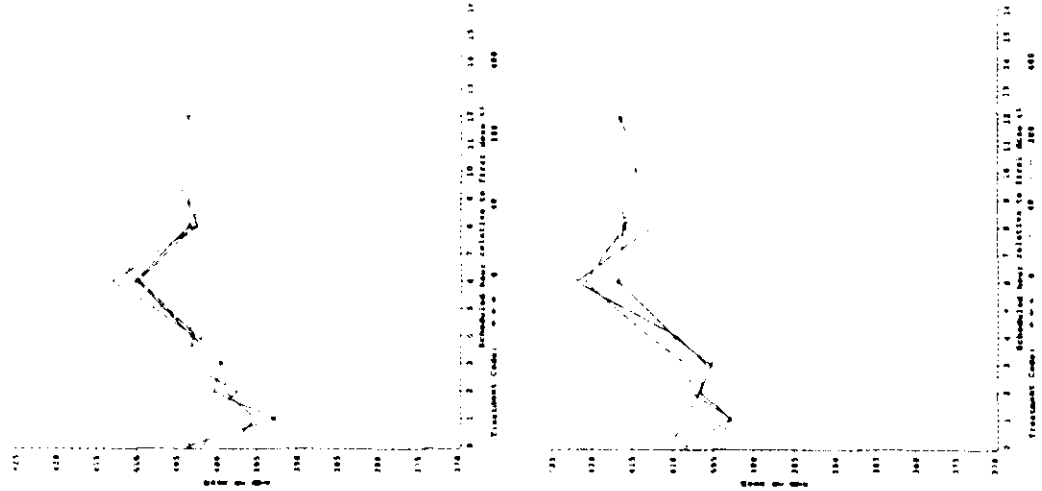
Note: Since there were four periods, each subject is represented four times in each graph.

Figure 3: DAY 8

Females (n=20)

Males (n=20)

Both (n=40)



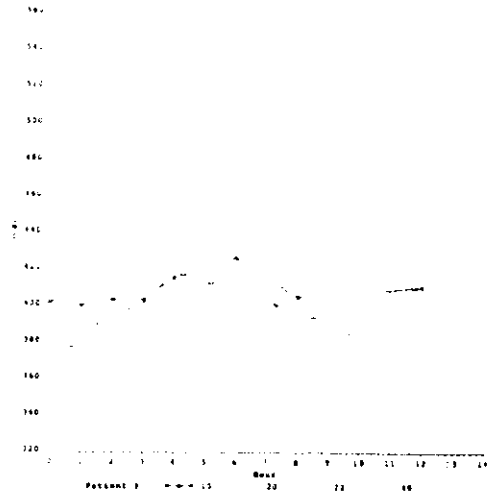
X axis: Scheduled hour relative to first dose

Y axis: Mean of QTc intervals

Note: Since there were four periods, each subject is represented four times in each graph.

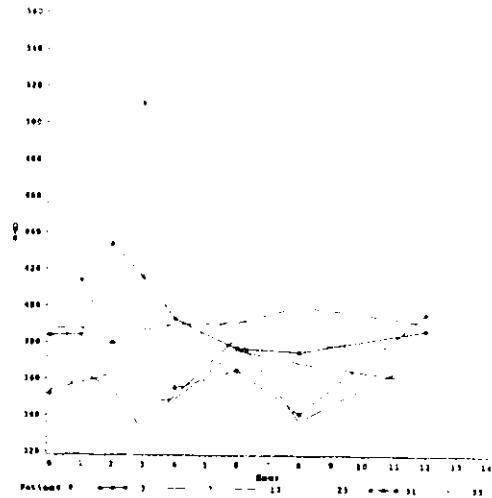
**Figure 6: Placebo in First Period
MACHINE**

FEMALES (n=4)



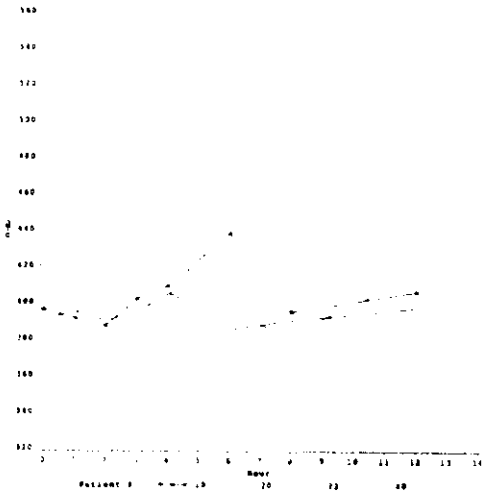
(n=4)

MALES (n=6)

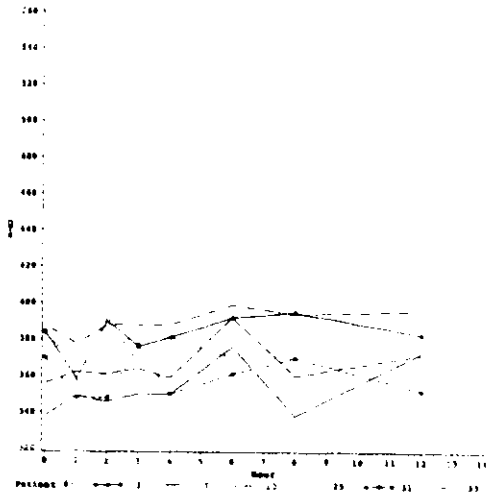


(n=6)

Day 1

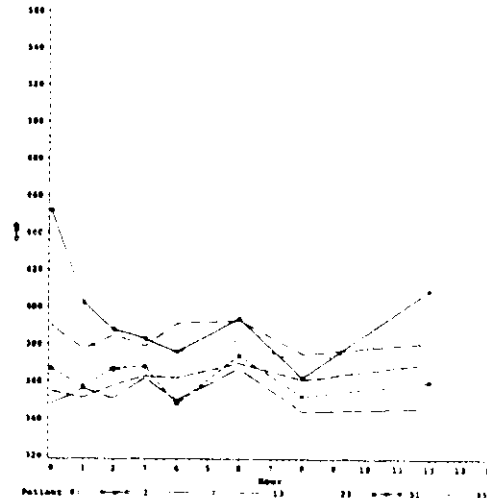
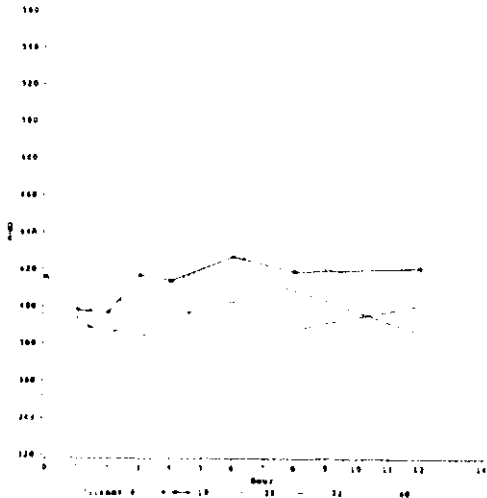


(n=4)



(n=6)

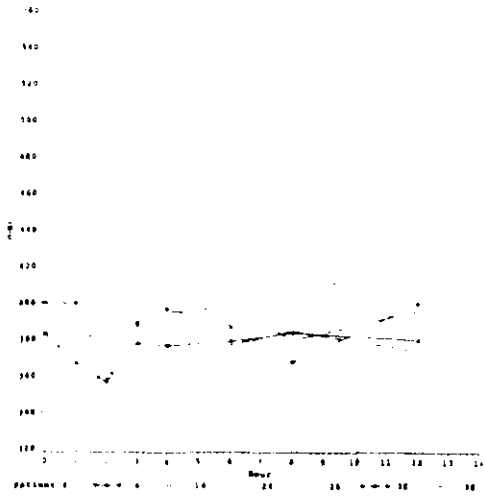
Day 2



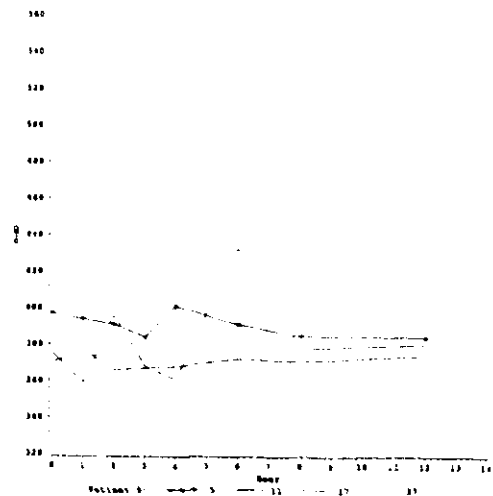
Day 8

**Figure 7: Placebo in Last Period
MACHINE**

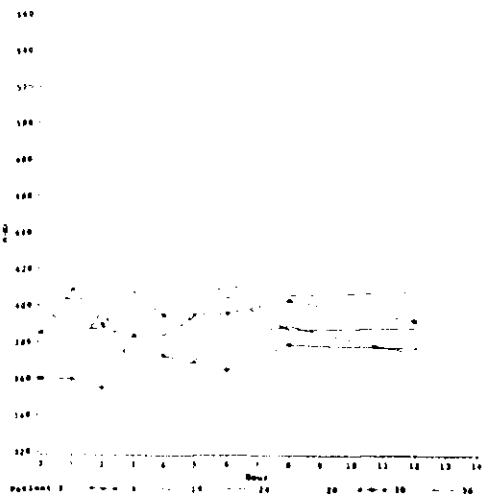
FEMALES (n=6)



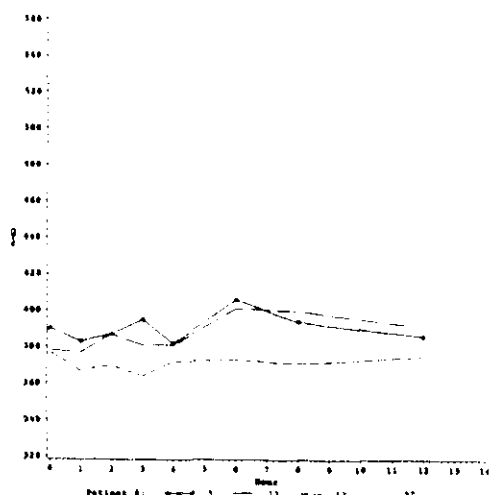
MALES (n=4)



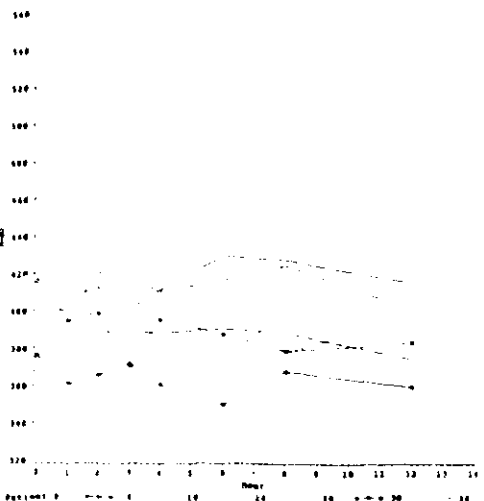
(n=6)



(n=4)



(n=6)



(n=3)

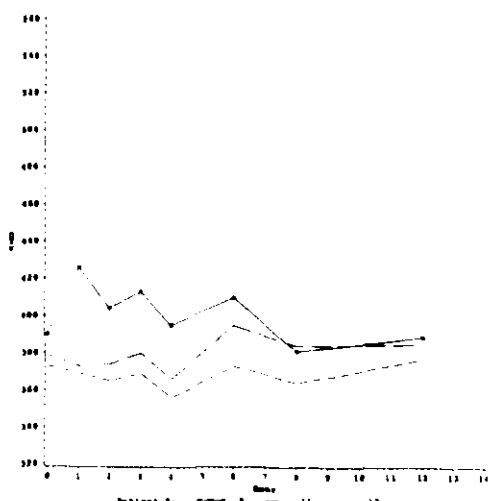
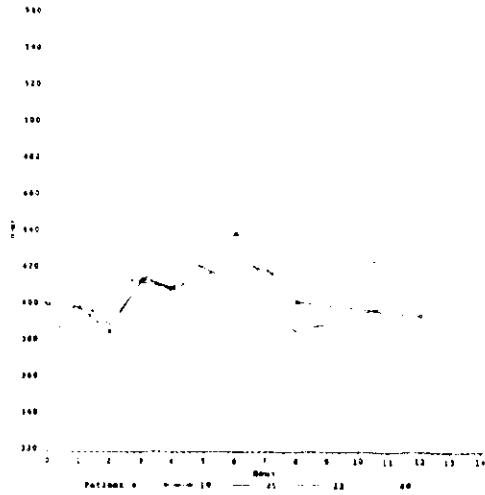


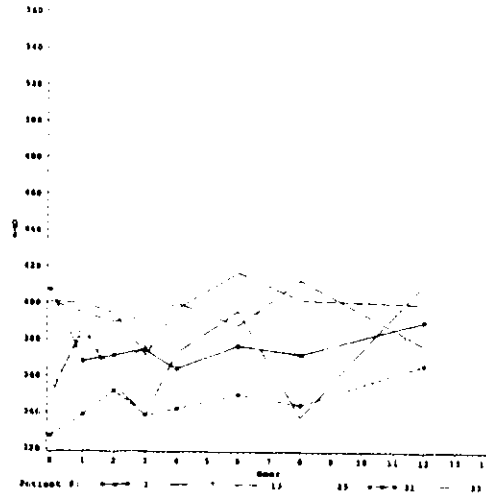
**Figure 8: Placebo in First Period
MORGANROTH**

FEMALES (n=4)



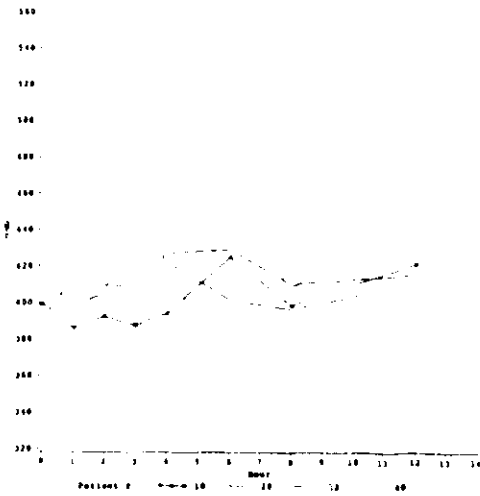
(n=4)

MALES (n=6)

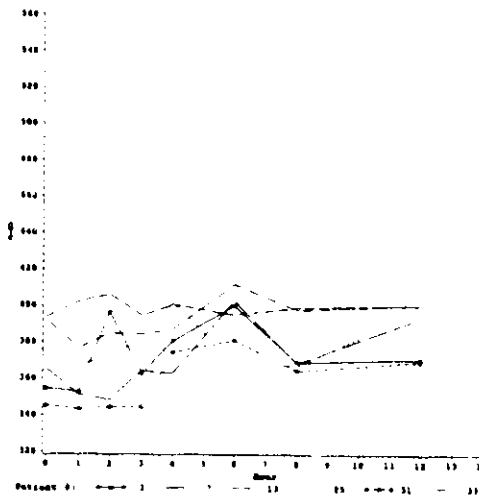


(n=6)

Day 1

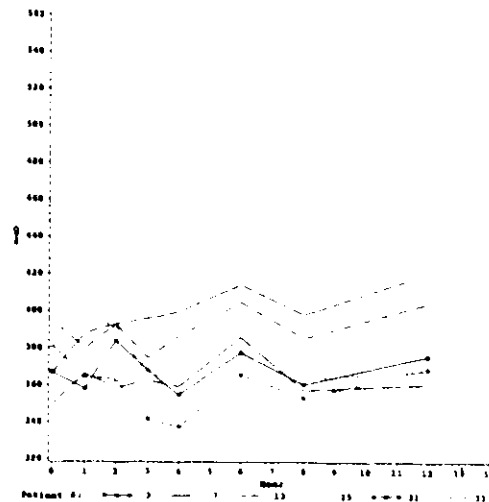
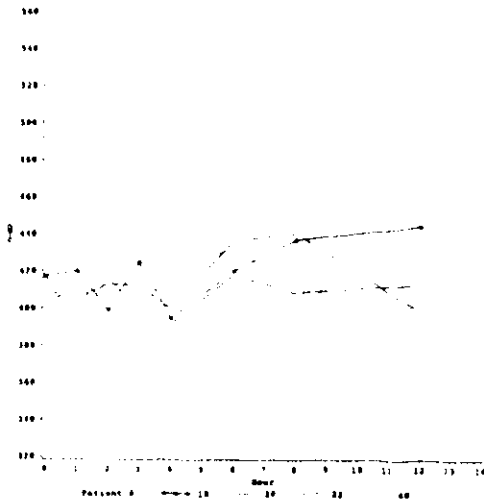


(n=4)



(n=6)

Day 2



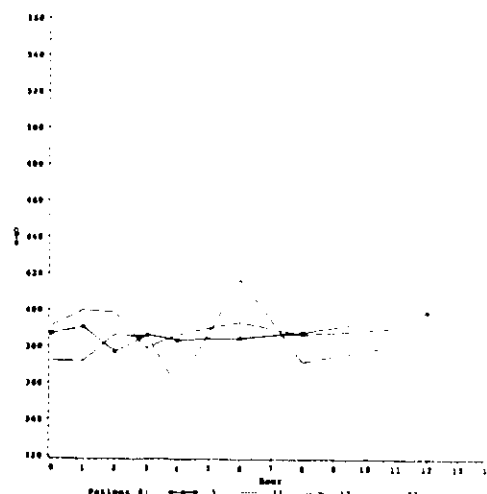
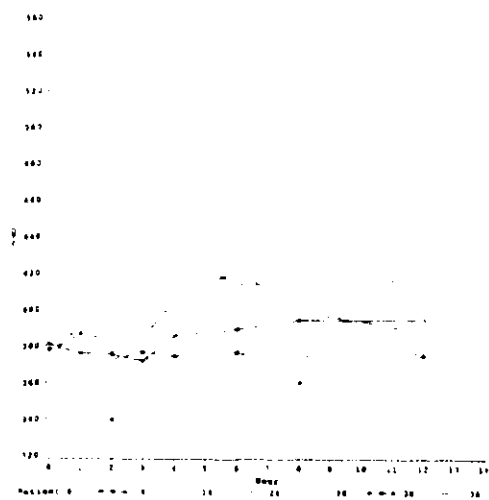
Day 8

Figure 9: Placebo in Last Period MORGANROTH

FEMALES (n=6)

MALES (n=4)

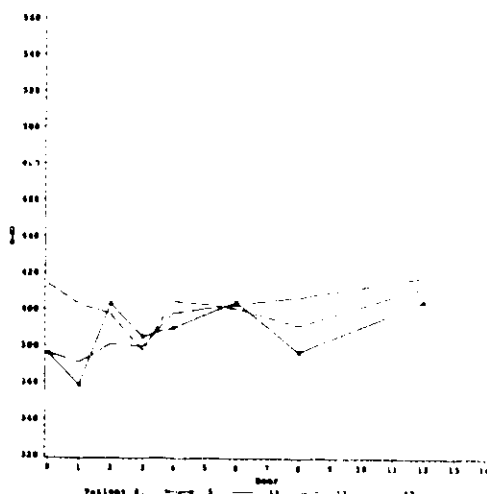
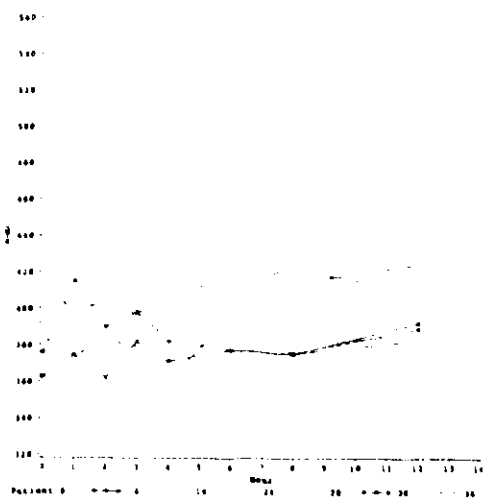
Day 1



(n=6)

(n=4)

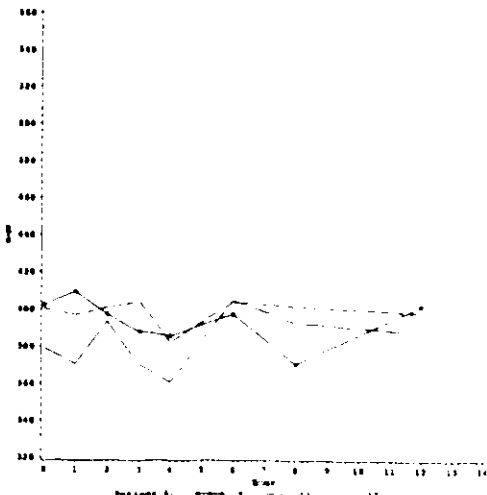
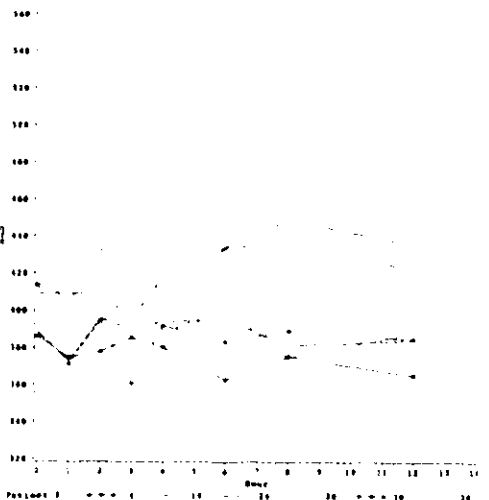
Day 2



(n=6)

(n=3)

Day 8



Barbara Bono

Barbara Bono, M.S.
Statistician

Concur: Dr. Wilson *SEN 6/3/96*
Dr. Nevius *EN 6/3/96*

cc:
Orig. NDA 20-625
HFD-570 / Division File
HFD-570 / Jjenkins, MHimmel, MSevka
HFD-715 / Division File, Chron
HFD-715 / BBono
HFD-715 / ENevius, SWilson

bb/May 16, 1996/NDA/20625/STAT/95-07-31.RE2

Clinical Pharmacology & Biopharmaceutics Review

Allegra[®] Capsules (Fexofenadine HCl) NDA 20-625 Hoechst Marion Roussel, Inc Kansas City, MO 64134-0627	Type of Submission: New NDA, NME Submission Dates: 7/31/95 10/16/95 11/20/95 Reviewer: Brad Gillespie, PharmD

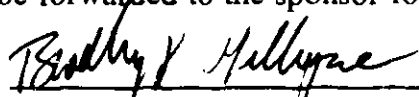
Synopsis Intended for twice daily administration, each Allegra[®] capsule contains 60 mg of fexofenadine hydrochloride (MDL 16,455A), the carboxylic acid metabolite of terfenadine. This new molecular entity maintains the anti-histaminic activity of the parent compound, without its danger of potential cardiac consequences (*Torsades de Pointes*).

In support of this application, the sponsor has submitted the results of clinical studies as well as pharmacokinetic trials.

In this review, a total of 14 human pharmacokinetic trials were evaluated. The pivotal bioequivalence study demonstrated that the full-scale, pilot-scale and oral solution formulations used in the clinical program were all bioequivalent to one another. A slight food effect was reported (fed versus fasted $AUC_{0-\infty}$: -21%; $p=0.007$, C_{max} : -14%; $p=0.098$). Mean single-dose pharmacokinetic parameters after a 60 mg oral dose were: C_{max} : 209 ng/mL (CV 45%), $AUC_{0-\infty}$: 1348 ng·hr/mL (CV 41%), T_{max} : 1.42 hours (CV 50%) elimination half-life: 13.05 hours (CV 30%) and oral clearance: 51 L/hr (CV 53%). Similar mean multiple-dose parameters included: $C_{max,ss}$: 286 ng/mL (CV 50%), $C_{min,ss}$: 32 ng/mL (CV 32%), $AUC_{0-12,ss}$: 1521 ng·hr/mL (CV 41%), $T_{max,ss}$: 1.31 hours (CV 45%) plasma elimination half-life: 14.40 hours (CV 39%) and oral clearance: 44 L/hr (CV 45%). Population estimates suggest that MDL 16,455 disposition is similar between healthy volunteers and seasonal allergic rhinitis patients and that non-weight normalized oral clearance is about 18% faster in male than female patients. Fexofenadine, with one enantiomeric center is given as a racemate. While urinary excretion rates suggest that the enantiomers are excreted at equal rates, the plasma R(+) form dominates S(+) by a ratio of approximately 1.7:1 throughout the entire time-course following a dose. Competitive binding data predicts that the enantiomers are equipotent. Mass balance data show that feces and urine are the major routes of elimination (approximately 80 and 11%, respectively) with only minor metabolism. Additionally, *in vitro* metabolism studies also show only minor metabolism. Dose proportionality was demonstrated over the range of 20 to 120 mg twice daily. While females consistently experienced relatively higher plasma concentrations than males, weight-normalized oral clearance rates were similar across studies. Higher mean plasma concentrations were also observed in the elderly (80 mg

single-dose approximate C_{max} : 422 ng/mL, AUC_{0-24} : 2915 ng-hr/mL compared to 210 ng/mL and 1584 ng-hr/mL in young, healthy subjects). Substantial differences were not observed in hepatically impaired patients, while the renally impaired showed substantially higher plasma levels (C_{max} and AUC approximately +93% and +133%, respectively, compared to normals). Pharmacokinetically significant drug interactions were reported when MDL 16,455A was given concomitantly with erythromycin (C_{max} +82% and AUC +109%) and ketoconazole (C_{max} +135% and AUC +164%). However, these pharmacokinetic interactions were not accompanied by the ECG changes (QTc interval prolongation) seen in the classic terfenadine-erythromycin/ketoconazole interactions. The sponsor has proposed a satisfactory dissolution method and FDA has set an appropriate dissolution specification. The sponsor attempted to establish a pharmacokinetic/pharmacodynamic relationship. However, no correlation was evident between the pharmacodynamic endpoint Total Symptom Score (a composite clinical endpoint comprised of itchy nose, itchy eyes, rhinorrhea and sneezing), and MDL 16,455 plasma concentrations. Achiral protein binding was reported to be constant over the range of 50 to 5000 ng/mL ($76.6 \pm 2.3\%$). Overall, the assay methodology used by the sponsor across studies was satisfactorily validated. However, an appropriate cross-method validation was not submitted.

Recommendation The Human Pharmacokinetics portion of NDA 20-625 has been reviewed by the Office of Clinical Pharmacology & Biopharmaceutics and has been found to be acceptable provided that the sponsor satisfactorily addresses Labeling Comments 1 - 4. General comments 1 - 12 should also be forwarded to the sponsor for future reference.

 3/15/96
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

RD  3/11/96
FT  3/15/96
Dale P. Conner, PharmD, Team Leader

Biopharm Day: 3/14/96: Drs Collins, Fleischer, Mehta, Conner, Chen, Gillespie (Bill), Zhu, Machado, Bono, Honig and Sevka

cc:
HFD-570 (NDA 20-625, Divisional File, Strange, Sevka)
HFD-870 (Conner, ChenM, Hunt, Gillespie)
HFD-880 (Fleischer)
HFD-860 (Malinowski)
HFD-850 (Lesko, Chron, Drug [Clarence Bott: Rm 13B311, Reviewer])
HFD-340 (Viswanthan)
HFD-205 (FOI)

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Background The free-base of fexofenadine HCl (MDL 16,455A), MDL 16,455 has been previously identified as the active carboxylic acid metabolite of terfenadine. Terfenadine has been approved for US marketing for over ten years. Elevated terfenadine levels, whether a result of hepatic dysfunction, concomitant medications or overdose have been associated with *Torsades de Pointes*. MDL 16,455 was found in animal models to demonstrate the same anti-histaminic properties as the parent compound without the cardiac consequences. Therefore, the sponsor has initiated clinical studies to determine if this drug product is safe and effective in humans for the treatment of allergic rhinitis.

In support of this clinical program, the sponsor has submitted the results of four adequate and well controlled clinical studies. A total of 21 pharmacokinetic studies were performed to characterize drug disposition in humans.

Fexofenadine's proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis. The proposed recommended dose for adults and pediatric patients 12 years of age, or older is 60 mg, twice daily.

¹To be retained in OCPB Drug Files

Summary of Clinical Pharmacology & Biopharmaceutics

I. BIOAVAILABILITY/BIOEQUIVALENCE

A. Bioavailability: Absolute bioavailability was not determined for this product. Its bioavailability relative to a solution is evaluated below, in the Bioequivalence section.

B. Bioequivalence: The bioavailability of a MDL 16,455A oral solution and pilot-scaled capsule batch were compared to each other and to that of a full-scale batch in Study PJPR0025. All formulations were bioequivalent to each other (i.e., pilot vs. full, pilot vs. solution and full vs. solution). A replicate design (only capsule treatment arms replicated) allowed the estimation of intra- as well as inter-subject variability. Within-subject variability appears to be higher when subjects were administered capsules from the full-scale batch than when given pilot-scaled capsules (AUC: CV-25% versus 18%; C_{max} : CV-37% versus 25%).

C. Food Effect: The effect of food on the absorption of MDL 16,455A administered as a single 80 mg (2 x 40 mg to-be-marketed capsules) dose was evaluated in Study PJPR0026. Relative bioavailability was less in the fed (drug administration following a standardized high fat breakfast) versus the fasted group (AUC_{0-∞}: -21%; $p=0.007$; C_{max} : -14%; $p=0.098$). Time to maximal concentrations (T_{max}) was delayed only slightly (+7%).

II. PHARMACOKINETICS

A. Single-Dose: After a single 60 mg (oral solution) dose, the mean C_{max} was 209 ng/mL (CV 45%), the mean AUC_{0-∞}: 1348 ng·hr/mL (CV 41%), the mean T_{max} : 1.42 hours (CV 50%) and the mean plasma elimination half-life: 13.05 hours (CV 30%). Oral clearance was 51 L/hr (CV 53%) (Study PJPR 0011).

B. Multiple-Dose: After multiple-dose administration (60 mg oral solution every 12 hours for ten doses) the mean $C_{max,ss}$ was 286 ng/mL (CV 50%), the mean $C_{min,ss}$ (pre-dose): 32 ng/mL (CV 32%), AUC_{0-12hr,ss}: 1521 ng·hr/mL (CV 41%), $T_{max,ss}$: 1.31 hours (CV 45%), and the mean plasma elimination half-life: 14.40 hours (CV 39%). Oral clearance was 44 L/hr (CV 45%) (Study PJPR0011).

C. Population: Population analysis suggests that non-weight normalized MDL 16,455 oral clearance is approximately 18% faster in male compared to female patients, MDL 16,455A is dose proportional within the dosage range of 40 to 240 mg and MDL 16,455 oral clearance is similar between healthy volunteers and SAR patients (Studies PJPR0023/0024: Report K-95-0154-DS).

D. Stereochemistry: While this drug is given as a racemate, enantiomeric data indicates that the plasma R(+) species dominates the S(-) form by a ratio of about 1.7:1 across the

entire dosing range of study PJPR0011. However, the urinary excretion data intimates that the enantiomers are renally eliminated at similar rates. Pre-clinical data (Study No. C-93-0247-R: Competitive receptor binding studies with MDL 16,455 and its enantiomers to rat brain histamine H₁-receptors) show that both enantiomers displace mepyramine from its H₁ binding site to a similar degree, suggesting that the isomers are equipotent. Therefore, while the results of an enantiomer interconversion study might be useful, they are probably not crucial.

III. METABOLISM/MASS BALANCE

Subjects received 60 mg MDL 16,455A, orally, every 12 hours for 4 days. The ninth dose was radiolabeled ([¹⁴C]MDL 16,455A). Significant radioactivity was subsequently detected in the blood and saliva, with feces and urine being the major routes of elimination (approximately 80 and 11%, respectively). Analysis of urine and fecal samples showed about 73% of the dose administered recovered as unchanged drug, 4.3% as a radioactive impurity, 3.6% as the methyl ester of MDL 16,455 (hypothesized to have been transformed by colonic micro flora) and 1.5% as the de-alkylated metabolite (MDL 4,829). Other minor components comprised about 3% of the administered dose. Approximately 6% of the radioactivity detected in the urine and feces was not identified. These data suggest that when MDL 16,455A is given as an oral solution, it undergoes only minor metabolism (Study PJPR 0008). This hypothesis is supported by *in vitro* drug metabolism experiments which incubated [¹⁴C]MDL 16,455A in human liver microsomes, S9 liver fractions and human liver slices. In these *in vitro* models, only negligible metabolism was detected (Project Report No. K-95-0137-D).

IV. DOSE PROPORTIONALITY

In Study PJPR0011, volunteers received single- and multiple-dose regimens of 20, 60, 120 and 240 mg oral MDL 16,455A solution. The C_{max} and AUC of MDL 16,455 were proportional (confidence interval analysis of normalized parameters) between 20 and 120 mg (single- and multiple-dose). The urinary recoveries were relatively consistent (mean cumulative percent of dose excreted in urine: 7.64 - 11.76%). Study PJPR0007, a cardiac safety study, examined the dose proportionality of MDL 16,455A when dosed as 40, 200 and 400 mg oral solution. No linearity was demonstrable over these dosing intervals.

V. SPECIAL POPULATIONS

Gender Effect: The sponsor compared drug disposition between genders in a dose proportionality study (PJPR0007). In healthy volunteers, bioavailability was higher in females relative to males (AUC: +33%, C_{max}: +46%). While renal clearance is approximately the same in both genders, non-weight adjusted oral clearance was substantially higher in males than females (+44%). However, this difference is blunted somewhat by the average weight difference observed of +16% (males versus females). The gender effect reported in the elderly population study was less pronounced (AUC:

+5%, C_{max} : +18%, elimination half-life: +32%). Weight-adjusted oral clearance rates were nearly identical between genders. Estimated MDL 16,455 oral clearance (non-weight normalized) (Report K-95-0154-DS: Population data from protocols PJPR0023/0024) in seasonal allergic rhinitis patients was approximately 18% faster in male versus female patients. As in the normal subjects, a nearly proportional weight difference of +21% (males versus females) was observed.

B. Elderly: After an overnight fast, geriatric (≥ 65 years of age) subjects (11 male, 9 female) received a single 80 mg dose of MDL 16,455A. The mean C_{max} observed was 387 ng/mL (CV 65%) and 456 ng/mL (CV 41%) for males and females, respectively. $AUC_{0-\infty}$ was 2847 ng·hr/mL (CV 57%) and 2983 ng·hr/mL (CV 29%) while $t_{1/2}$ was 13.3 hours (CV 25%) and 17.5 hours. Weight normalized oral clearance was similar between genders (males: 0.46 L/hr/kg, CV 64%; females: 0.49 L/hr/kg, CV 76%). The portion of dose excreted in the urine was 9.7% (CV 87%) for males and 8.7% (CV 66%) for females (Study PJPR0020).

C. Hepatic Impairment: Seventeen subjects stratified by degree of hepatic impairment (Mild-to-Moderate: n=10, Moderate-to-Severe: n=7) received a single 80 mg dose of oral MDL 16,455A. The mean C_{max} observed was 266 ng/mL (CV 55%) and 281 ng/mL (CV 68%) for the Mild-to-Moderate and Moderate-to-Severe groups, respectively. Mean $AUC_{0-\infty}$ was 1700 ng·hr/mL (CV 40%) and 2176 ng·hr/mL (CV 78%), $t_{1/2}$: 11.29 hours (CV 35%) and 16.01 hours (CV 35%). Mean oral clearance was similar in both groups (Mild-to-Moderate: 50 L/hr, CV 38%; Moderate-to-Severe: 56 L/hr, CV 72%). The portion of dose excreted in the urine was 9.64% (CV 59%) and 8.40% (CV 50%) for the Mild-to-Moderate and Moderate-to-Severe groups, respectively (Study PJPR0021). Plasma protein binding experiments, utilizing serum obtained from hepatically impaired patients in this study, demonstrated that plasma protein binding profiles (range: 50 - 5000 ng/mL) were similar to those obtained from normal subjects (Report No. K-95-0208-D).

D. Renal Impairment: Twenty-nine subjects stratified by degree of renal impairment (Mild-to-Moderate [CrCl 41-80 mL/min]: n=9, Moderate-to-Severe [CrCl 11-40 mL/min]: n=10, Dialysis [CrCl ≤ 10 mL/min]: n=10) received a single 80 mg dose of oral MDL 16,455A. The mean C_{max} observed was 392 ng/mL (CV 60%), 443 ng/mL (CV 73%) and 382 ng/mL (CV 36%) for the Mild-to-Moderate, Moderate-to-Severe and Dialysis groups, respectively. $AUC_{0-\infty}$ was 3197 ng·hr/mL (CV 70%), 4534 ng·hr/mL (CV 64%) and 3371 (CV 31%), $t_{1/2}$: 22.85 hours (CV 40%), 24.78 hours (CV 36%) and 18.05 hours (CV 57%). Oral clearance was similarly lower in the Moderate-to-Severe (24 L/hr, CV 59%) and dialysis (25 L/hr, CV 37%) groups compared to the Mild-to-Moderate group (35 mL/hr, CV 66%). The portion of dose excreted in the urine was 6.55% (CV 78%), 2.44% (CV 119%) and 0.34% (CV 202%) for the Mild-to-Moderate, Moderate-to-Severe and dialysis groups, respectively (Study PJPR0013). Plasma protein binding

experiments, utilizing serum obtained from renally impaired patients in this study, demonstrated that plasma protein binding profiles (range: 50 - 5000 ng/mL) were similar to that obtained from normal subjects (Report No. K-95-0208-D).

In an ideal situation, special population subjects are selected and appropriately age/weight matched to normal volunteers, to reduce inter-subject variability. Thus, these study designs were sub-optimal in that control arms were not included. Nevertheless, special population pharmacokinetics are compared to those of normal subjects (from Study PJPR0026) in Table A. While subject weights are relatively uniform between studies, special population patients were substantially older than the healthy, young volunteers. Thus the demonstrated age effect may be contributing to the increased bioavailability in special populations.

This cross-study comparison shows a substantial increase in MDL 16,455A bioavailability in geriatric and renally impaired patients. However, the relatively benign safety profile of this drug probably makes these increases not clinically relevant. The changes in bioavailability in renally impaired subjects suggests that urinary excretion may play a greater role in drug elimination than is indicated by the mass balance (only ~ 10% of administered dose recovered unchanged in the urine). Thus, a substantial portion of drug identified in the feces could be present because of non-absorption (versus biliary excretion)

Table A. Comparison of Special Population Pharmacokinetics to Normal Subjects (80 mg Single-Dose MDL 16,455A)

	Age (yrs)	Weight (kg)	Gender	C _{max} (ng/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hours)	CL _{CR} (L/hr)	% Excreted in Urine unchanged
Geriatric ♂	71.5 (6)	80.1 (11)	11 ♂	387 (65)	2847 (57)	13.3 (25)	37.3 (68)	9.65 (86)
Geriatric ♀	72.8 (6)	64.9 (17)	9 ♀	456 (41)	2983 (29)	17.5 (72)	28.4 (49)	8.68 (66)
Mild-to-Moderate Hepatic Impairment	50.6 (19)	81.7 (17)	9 1 ♀	269 (55)	1700 (40)	11.29 (35)	50.0 (38)	9.64 (59)
Moderate-to-Severe Hepatic Impairment	48.4 (15)	79.8 (19)	4 ♀ 3 ♂	281 (68)	2176 (78)	16.01 (35)	56.1 (72)	8.40 (50)
Mild-to-Moderate Renal Impairment	47.8 (29)	70.8 (24)	4 ♀ 5 ♂	392 (60)	3197 (70)	22.85 (40)	34.8 (66)	6.55 (78)
Moderate-to-Severe Renal Impairment	44.2 (30)	79.6 (34)	3 ♀ 7 ♂	443 (73)	4534 (64)	24.78 (37)	23.5 (59)	2.44 (119)
Dialysis Patients	48.6 (25)	81.5 (18)	3 ♀ 7 ♂	382 (36)	3371 (31)	18.85 (57)	24.6 (37)	0.34 (201)
Healthy Males	24.9 (25)	79.3 (16)	25 ♂	210 (38)	1584 (40)	14.4 (39)	53.8 (35)	-----

DRUG INTERACTIONS

Erythromycin: Concomitant multiple-dose administration of MDL 16,455A (120 mg every 12 hours for 6.5 days) and erythromycin (500 mg every 8 hours for 6.33 days) resulted in significant increases in the bioavailability of MDL 16,455A (C_{max} +82%, AUC +109%). The renal clearance rate of MDL 16,455 increased significantly (4.09 vs 3.66 L/hr, $p < 0.001$) when co-administered with erythromycin and the total amount of MDL 16,455 excreted increased by 128%. No significant ECG changes (QTc interval prolongation) were observed. MDL 16,455A had no demonstrable effect on the pharmacokinetics of erythromycin.

B. Ketoconazole: Concomitant multiple administration of MDL 16,455A (120 mg every 12 hours for 6.5 days) and ketoconazole (400 mg once-daily for 7 days) resulted in significant increases in the bioavailability of MDL 16,455A (C_{max} +135%, AUC +164%). The renal clearance rate of MDL 16,455 was not affected by ketoconazole co-administration but the total amount excreted increased by 130%. No significant ECG changes (QTc interval prolongation) were observed. MDL 16,455A had no demonstrable effect on the pharmacokinetics of ketoconazole.

These drug interactions are interesting in light of MDL 16,455's negligible metabolism. The sponsor has suggested that the mechanism of these interactions is not Cytochrome P450 inhibition, but an enhanced absorption phenomena. This hypothesis is supported by the mass balance (Study PJPR0008) which identified only minimal metabolism, and the renal impairment protocol (Study PJPR0013) which showed greater increases in bioavailability than expected (urine hypothesized to be a minor route of elimination: ~10%). Thus, a substantial amount of unchanged drug identified in the feces is probably unabsorbed (versus biliary excretion).

The relatively benign safety profile of MDL 16,455A probably makes these pharmacokinetic interactions not clinically relevant. However, definitive mechanism identification may prove useful to the sponsor. Important information may be obtained from a cimetidine interaction and/or an absolute bioavailability (to document the extent of non-absorption) study.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

The sponsor attempted to link MDL 16,455 concentrations to the pharmacodynamic endpoint Total Symptom Score (TSS: a composite clinical endpoint comprised of itchy nose, itchy eyes, rhinorrhea and sneezing). However, no clear correlation could be obtained with this endpoint (Studies PJPR0023/0024: Report K-95-0154-DS).

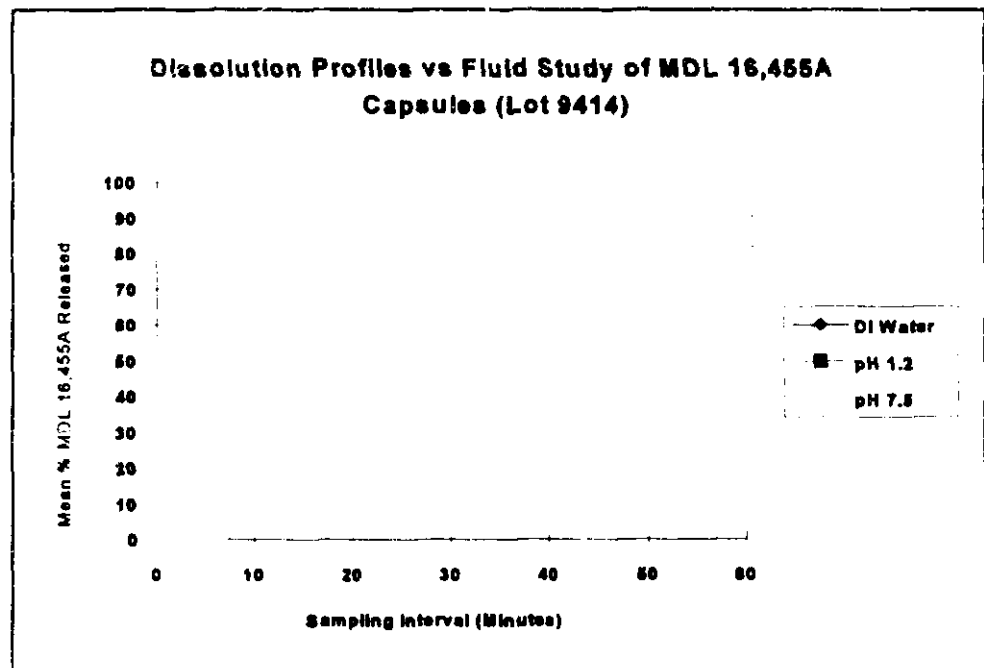
VII. FORMULATIONS

Six pivotal efficacy and safety studies utilized a combination of 20, 40 and 60 mg capsules. The composition of the granulation formulation was identical in all six studies, only the size of the capsule and the amount of fill differed. Four of the studies used pilot-sized batches (PJPR0009: lots RN9323 & RA9404, PJPR0010: lots RN9323 & RA9404, PJPR0014: RA9404 & RB9434 and PJPR0024: lots RB9434 & RF9422), while a fifth and sixth (PJPR0023: RF9414; PJPR0017: RH9411) utilized production-sized batches. Two key drug interaction studies (PJPR0018: erythromycin and PJPR0028: ketoconazole) used lot RH9411, a production-scaled batch. The majority of the remaining clinical studies (including the critical studies PJPR0003, PJPR0004 and PJPR0007) utilized an oral solution of fexofenadine in 1.5% glacial acetic acid and 98.5% propylene glycol. The pivotal bioequivalence study (PJPR0025) compared this solution (lot 73048) to pilot- (lot RN9323) and full production-scaled (lot RF 9414) batches. As in the clinical studies, the bio-studies mainly utilized a combination of oral solutions, pilot-sized capsule batches and 60 mg production-scaled capsule batches.

IX. DISSOLUTION

In establishing dissolution conditions, the sponsor performed dissolution testing in selected media to include deionized water, pH 1.2 and pH 7.5 buffer. Mean results are presented below, in Figure A.

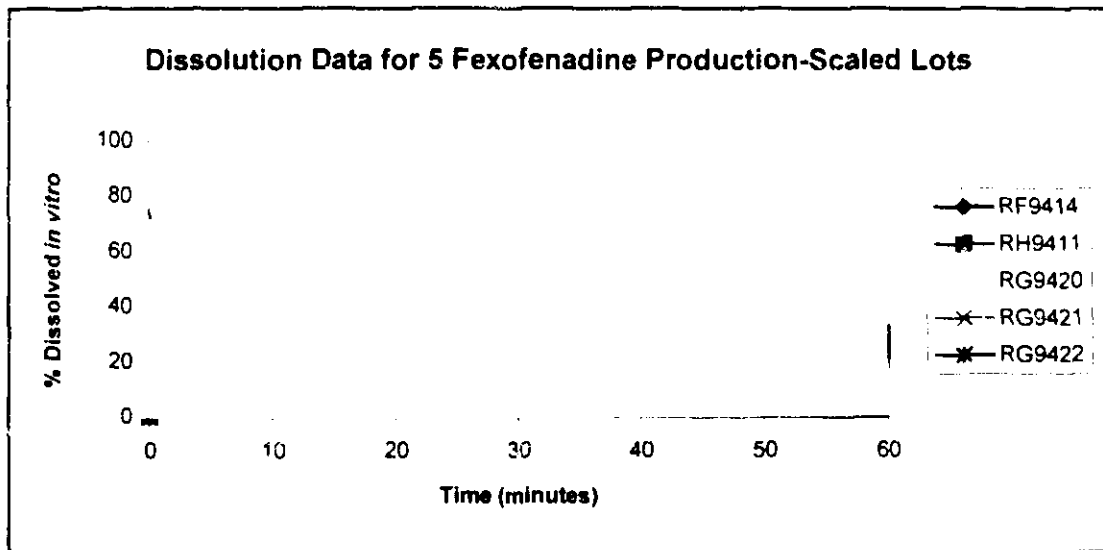
Figure A.



Dissolution behavior was comparable in water and pH 7.5 buffer and considerably slower in the acidic medium. These data support the sponsor's proposal to utilize water as the dissolution testing medium for MDL 16,455A.

Time (min)	Mean	CV	Range
5			
15			
30			
45			
60			

Figure B.



While the sponsor has proposed a dissolution specification of $Q =$ in 45 minutes, these data support a release specification of $Q =$ in 45 minutes. At this level, 75 of 78 capsules tested would meet the specification.

Assay performance across studies was satisfactory, with the exception of the analysis of MDL 16.455 (urine) in Study PJPR0018, where the measures of accuracy and precision at the lower limits of quantitation (percent of nominal and CV, respectively, of QC samples) were unsatisfactory.

The sponsor has attempted to link the different analytical methods across studies by performing a cross-laboratory validation study. However, the study is incomplete, in that while all of the major analytical sites are examined, a common method was utilized. Thus, the sponsor has compared the analytical facilities but not the actual methods.

COMMENTS

1. Study protocol PJPR0025 (pivotal Bioequivalence Study) states that nutritious, caffeine-free meals will be served to volunteers. Meal standardization between volunteers is also required for bioequivalence testing. The sponsor is requested to clarify if meals were, indeed, standardized.
2. Also in study PJPR0025, the sponsor utilized the standard bioequivalence criteria (1992 FDA Guidance on Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design) to analyze the bioequivalence data. It should be noted that this method is not suitable for analyzing replicate design bioequivalence data. Data were re-analyzed by FDA utilizing a modified model. Data using this method supported bioequivalence between the pilot-scale, full-scale capsule and oral solution formulations.
3. The pharmacodynamic endpoint Total Symptom Score (TSS), which was attempted to be linked to drug concentrations obtained in Studies PJPR0023/0024, was comprised of four symptoms: itchy eyes, itchy nose, rhinorrhea and sneezing. Weaker responses to the symptoms of itchy eyes and nose compared to those obtained for rhinorrhea and sneezing may have diluted the TSS. If either of the two relatively stronger symptoms had been selected as the pharmacodynamic endpoint, a better pharmacokinetic/pharmacodynamic relationship may have been observed.
4. Dissolution data submitted for 5 production-scaled capsule lots support a single dissolution specification of $Q =$ in 45 minutes (compared to $Q =$ in 45 minutes, as proposed by the sponsor).
5. The sponsor's attempt to link the analytical methods across studies is incomplete in that while all of the major analytical sites are examined, a common method was utilized. Thus, the sponsor has compared the analytical facilities but not the different assay methods.

6. The sponsor's enantiomer discussion does not fully explain the different enantiomer concentrations observed in the multiple-dose pharmacokinetic study (PJPR0011). While not required, the sponsor may wish to perform an enantiomer interconversion study to help explain these differences in enantiomer disposition. Additionally, a stereospecific protein binding study may help explain these differences.
7. In the hepatic and renal impairment studies (PJPR0021 and PJPR0013, respectively) the protocol did not include gender-, age- and weight-matched control arms. In future special population studies, the sponsor is encouraged to add such an arm to reduce inter-subject variability.
8. Assay validation data were acceptable from all studies with the exception of the urine MDL 16,455 data from the erythromycin drug interaction study (PJPR0018). In this case, precision reported at the claimed limit of quantitation (LOQ) was unsatisfactory. Thus, the LOQ should be revised upward from 0.1 to 0.2 µg/mL.
9. The original protocol called for the enrollment of 20 subjects to appropriately power the hepatic impairment study. However, in the study report, the sponsor states that the 17 subjects enrolled should provide sufficient power. The sponsor is requested to explain these power calculations.
10. In the ketoconazole and erythromycin drug interaction studies (PJPR0028 and PJPR0018, respectively), the sponsor does not describe the content or standardization of the meals provided to study participants. The sponsor is requested to submit these details.
11. Since there are no significant ECG changes associated with the pharmacokinetic interaction observed with ketoconazole and erythromycin (PJPR0028 and PJPR0018, respectively), as in the terfenadine-ketoconazole interaction, MDL 16,455A can probably be safely co-administered with these drugs. However, this type of interaction (with a known cytochrome P450 3A inhibitor) is not expected with a drug which is excreted mainly unchanged. Therefore, the sponsor is encouraged to further investigate the mechanism of this interaction.
12. Subject confinement during the course of the ketoconazole and erythromycin studies (PJPR0028 and PJPR0018, respectively) is not addressed in the study protocol or final report. The sponsor is requested to clarify this issue.

LABELING COMMENTS (Clinical Pharmacology Section)

1. In the discussion of MDL 16,455 elimination, the labeling states that the principal routes of elimination are renal and biliary. While many studies identified

9

unchanged drug in the urine, no human studies have been submitted identifying biliary excretion (versus non-absorption) as the source of drug in the feces. Thus, this claim should be omitted from the label.

2. The paragraph on pharmacokinetics in special populations should be modified to the following:

Consistent with its negligible metabolism, the pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects. In a comparison across studies, renal disease was associated with an increase in peak plasma levels (Mild-to Moderate renal impairment: +86%, Moderate-to-Severe renal impairment: +110%, dialysis patients: +81%) and elimination half-life (Mild-to-Moderate renal impairment: +59%, Moderate-to-Severe renal impairment: +72%, dialysis patients: +31%). In the elderly (> 65 years old), peak plasma levels increased by 84% and 117% in male and female subjects, respectively.

des
for
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effect
of
renal
impairment
on
the
pharmacokinetics
of
fexofenadine

3. In reference to the first sentence of the Drug Interactions section:
Since fexofenadine does not undergo hepatic biotransformation, it is unlikely to interact with drugs which rely upon hepatic metabolism.

This is an inference unsupported by the data submitted. In light of the unexplained drug interactions with erythromycin and ketoconazole, this statement should be omitted from the label.

4. Also in the Drug Interactions section, the fourth sentence in the second paragraph should be modified as follows:

Fexofenadine peak plasma levels following erythromycin or ketoconazole administration increased 82% and 135%, respectively.

Pivotal Bioavailability and Bioequivalence Study of the MDL 16,455A Final Formulation

Study PJPR0025 **Volumes** 1.32-1.34

OBJECTIVES (a) determine the relative bioavailability of the 60 mg full-scale MDL 16,455A capsule formulation relative to MDL 16,455A solution and 20 mg pilot-scale capsule formulations following a single 120 mg dose (b) determine the relative bioavailability of the 20 mg pilot-scale MDL 16,455A capsule formulation relative to MDL 16,455A solution following a single 120 mg dose and assess the intra subject variability (bioavailability) of the full and pilot-scaled capsule formulations

FORMULATIONS

Treatment A: 20 mg capsules, Formula Number PJCX2-001, Lot RN9323 (pilot-scale)

Treatment B: 60 mg capsules, Formula Number PJCX5-001, Lot RF9414 (full-scale)

Treatment C: Bulk drug (given as a 1.5% acetic acid/98.5% propylene glycol solution), Lot 73038

STUDY DESIGN A total of 24 healthy, non-smoking adult males were included in this open-label, randomized, 3-treatment, 5-period crossover (replicate design: subjects received Treatments A and B twice) study. After an overnight fast, subjects received a single, 120 mg dose of study medication. Volunteers continued fasting for five hours after study drug administration. At this time, regular meals were served. A washout interval of 7 days separated the dosing periods. Subjects were confined throughout each study phase. Blood samples were obtained for plasma MDL 16,455 determinations just prior to (zero hour), 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 30 and 36 hours after study drug administration.

DATA ANALYSIS

Pharmacokinetic: MDL 16,455- C_{max} , T_{max} , $AUC_{0-\infty}$, $t_{1/2}$

Statistical: Using a mixed effects model, 90% confidence intervals were calculated for the ratios of the log-transformed pharmacokinetic parameters $\Delta AUC_{0-\infty}$ and C_{max} . The lower

and upper bounds of these intervals were compared with the regulatory bioequivalence limits of 80 and 125%, respectively. For technical statistical details such as model derivation, see Dr. Ray Zhu's Statistical Review of this study (Appendix II, Attachment A).

RESULTS Twenty-one subjects completed all phases of the study. The mean plasma concentration versus time profiles for the first 12 hours after dosing are presented in Figure 1. Pharmacokinetic parameters are presented and compared in Table 1.

COMMENTS

1. The study protocol states that nutritious, caffeine-free meals will be served to volunteers. Meal standardization between volunteers, which was not mentioned in the protocol or study report, is required for bioequivalence testing. Thus, the sponsor is requested to clarify their method of meal standardization.
2. In analyzing the data, the sponsor utilized the standard bioequivalence analysis method (1992 FDA Guidance on Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design). It should be noted that this method is not suitable for analyzing replicate design bioequivalence data. Data were re-analyzed by FDA with two analysis methods

intervals. PROC MIXED and PROC GLM in SAS 6.10 were used calculate the confidence intervals corresponding to these two methods, respectively (see page 70 for more specific method details).

CONCLUSION Both pilot- and full-scaled capsule lots are bioequivalent to the oral solution, and to each other. Within-subject variability appears to be higher when subjects were administered capsules from the full-scale batch than when given pilot-scaled capsules.

Figure 1.

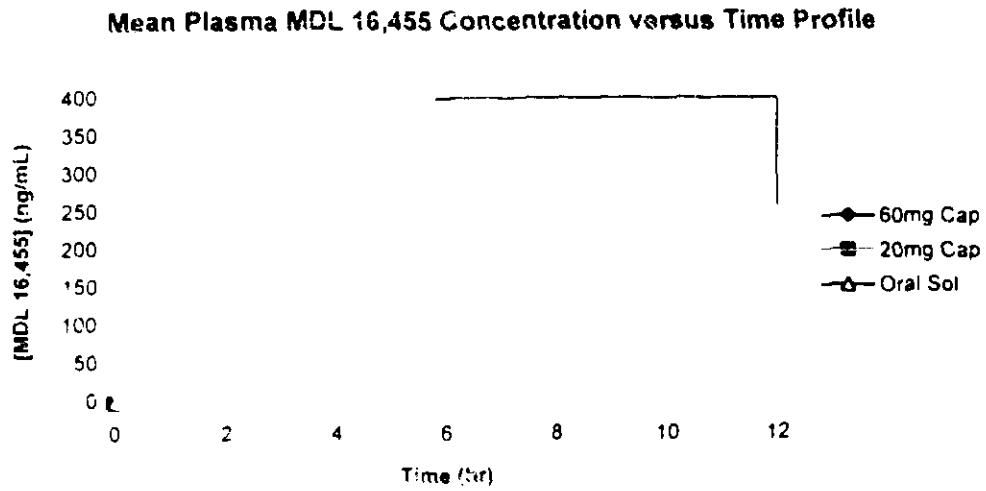


Table 1. MDL 16.455 Pharmacokinetic Parameters

Parameter	Treatment	Geom. Mean	Pair	Point Estimate	Confidence Interval	Inter-Subject Variability	Intra-Subject Variability
AUC _{0-∞} (ng·hr/mL)	A ^o	2898.65	A/B	1.053	0.969-1.145	27.1%	24.7%
	B ⁷	2751.77	A/C	1.088	0.969-1.221	29.0%	18.2%
	C ⁸	2643.87	B/C	1.033	0.920-1.159	28.7%	n/a
C _{max} (ng/mL)	A	391.11	A/B	1.042	0.938-1.157	26.5%	36.9%
	B	375.40	A/C	1.025	0.902-1.164	32.8%	25.4%
	C	381.84	B/C	0.983	0.867-1.117	30.6%	n/a
T _{max} (hour)	A	2.61	A/B	1.070			
	B	2.44	A/C	1.684			
	C	1.55	B/C	1.574			
CL _{cr} (L/hr)	A	40.80	A/B	0.958			
	B	42.57	A/C	0.931			
	C	43.84	B/C	0.971			
T _{1/2} (hour)	A	13.00	A/B	0.975			
	B	13.33	A/C	0.946			
	C	13.74	B/C	0.970			

^oProduction-Scaled Lot

⁷Pilot-Scaled Lot

⁸Solution

The Effect of Food on the Production Scale Capsule Formulation of MDL 16,455A

Study PJPR0026 Volumes 1.35-1.36

INVESTIGATOR AND LOCATION

OBJECTIVES Primarily, to characterize the effect of food on the pharmacokinetics of oral MDL 16,455A, administered as a single dose. Secondly, to characterize the relative bioavailability of 3 different formulations (not evaluated in this review).

FORMULATIONS

TRT A & B: 40 mg capsules, Formula Number PJCX4-001, Lot RF9422
TRT C: 40 mg capsules, Formula Number PJCX4-001, Lot RJ9415
TRT D: 40 mg capsules, Formula Number PJCX4-001, Lot RJ9413
TRT E: 40 mg capsules, Formula Number PJCX4-001, Lot RJ9409

STUDY DESIGN This study was conducted utilizing a randomized 5 period crossover design. Treatments A and B utilized a single 80 mg dose of a production scale capsule formulation, while Treatments C, D and E utilized different pilot-scaled formulations. All subjects maintained an overnight fast prior to dosing. Treatments A, C, D and E were administered under fasting conditions, while Treatment B was given after a standardized, high fat breakfast. After dosing, all subjects fasted for 5 hours, after which, standardized meals were served. Since only Treatment Groups A and B received drug product from a production-scaled batch, only data from these groups are relevant to the assessment of a food effect. A six day washout period separated the treatment periods. Blood samples were obtained for MDL 16,455 determinations prior to (zero hour), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after study drug administration.

Data Analysis

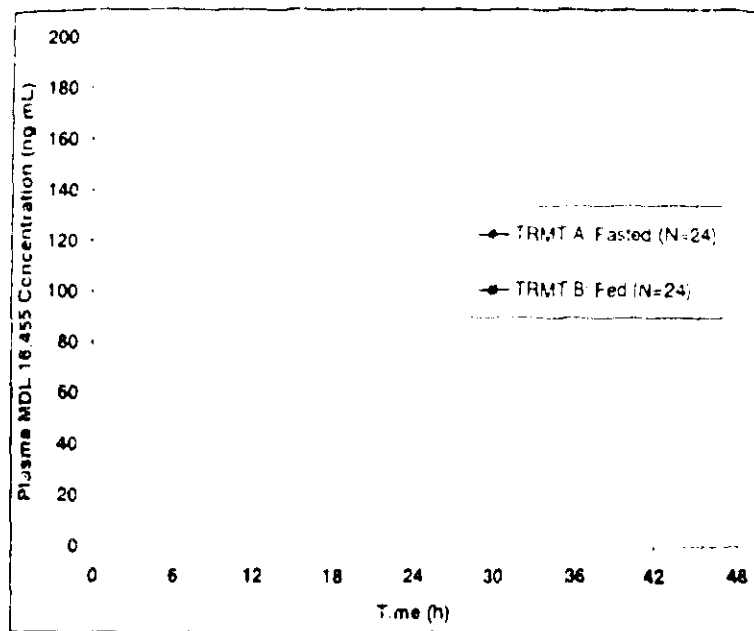
Pharmacokinetic: C_{max} , T_{max} , AUC_{0-24} , $AUC_{0-\infty}$, $t_{1/2}$, CL_{cr} , CL_{TB}

Statistical: An ANOVA model was applied to C_{max} , T_{max} , AUC_{0-24} , $AUC_{0-\infty}$, and $t_{1/2}$, then 90% confidence intervals for treatment differences were calculated.

Results Of the original 25 subjects, 24 completed all five phases of the study. Mean plasma concentration-time data are presented in Figure 2. Mean pharmacokinetic parameters are presented and compared in Table 2.

Conclusion The small decreases in AUC and C_{max} and minor increase in T_{max} , coupled to a wide therapeutic index for this product suggest that MDL 16,455A can be safely administered without regard to food.

Figure 2.



Mean Plasma MDL 16,455 Concentrations Following Administration of 80 mg MDL 16,455A Under Fed Versus Fasted Conditions

Table 2. Treatment Comparisons for Plasma MDL 16,455 Fed vs. Fasted Pharmacokinetic Parameters

Parameter	Units	Fasted Mean (%CV)	Fed Mean (%CV)	Change	Fasted Geometric Mean	Fed Geometric Mean	p-value	90% CI
AUC_{0-∞}	ng·hr/mL	1584 (40)	1254 (26)	-21%	1472	1222	0.007	75-92
C_{max}	ug/mL	209.8 (38)	180.0 (31)	-14%	195.0	173.7	0.098	79-100
T_{max}	hours	2.88 (38)	3.08 (22)	+7%	2.69	3.00		
CL_{po}	L/hour	53.8 (35)	63.1 (24)	+17%	50.7	61.0	0.007	108-134
t_{1/2}	hours	14.4 (39)	14.0 (26)	-3%	13.7	13.5		

Single and Multiple Dose Pharmacokinetics of Oral MDL 16,455A in Healthy, Male Volunteers

Study PJPR0011 Volumes 1.55-1.60

INVESTIGATOR AND LOCATION

BACKGROUND It is hypothesized that terfenadine is oxidized to both an inactive metabolite (MDL 4,829) and an alcohol (MDL 17,523). MDL 17,523 is then rapidly metabolized to the active carboxylic acid metabolite: MDL 16,455.

OBJECTIVES (1) To characterize the single and multiple dose pharmacokinetics and dose proportionality of MDL 16,455A at oral doses over the anticipated therapeutic dose range (2) To characterize the single and multiple dose pharmacokinetics and dose proportionalities of the MDL 16,455A enantiomers

FORMULATIONS MDL 16,455A was supplied as the bulk drug substance (Lot 73038).

<u>Treatment Group A:</u>	20 mg MDL 16,455A
<u>Treatment Group B:</u>	60 mg MDL 16,455A
<u>Treatment Group C:</u>	120 mg MDL 16,455A
<u>Treatment Group D:</u>	240 mg MDL 16,455A

STUDY DESIGN This open-label, single- and multiple-dose, randomized four-way crossover study enrolled 24 normal, healthy male volunteers. In each period, volunteers received a single dose of one of the above treatments on Day 1, followed by seven doses (one dose every 12 hours) of the same treatment on Days 3 through 7. A 14 day washout period separated the treatment periods. Serial blood samples (1 hour before, 0.5, 1, 1.5, 3, 6, 9, 12, 18, 24, 30, 36 and 48 hours after dosing) were collected following the first dose of MDL 16,455A. Additionally, trough samples were collected prior to the morning dose on Days 5 and 6. These samples were assayed for achiral MDL 16,455. Serial blood samples were also collected after the last (tenth) dose for both achiral and chiral (R(+) and S(-) enantiomers) analysis. Urine samples were collected after the first and last dose and analyzed for achiral MDL 16,455, terfenadine, MDL 4,829, MDL 17,523 as well as for R(+) and S(-) MDL 16,455 enantiomers.

DATA ANALYSIS

Single-Dose Pharmacokinetics: C_{max} , t_{max} , $AUC_{(0-7)}$, $AUC_{(0-\infty)}$, $t_{1/2}$, CL_{po} , $A_{e(0-48)}$, CL_R ,
Urinary Excretion half-life

Steady-State Pharmacokinetics: $C_{max,ss}$, $C_{min,ss}$, $C_{max,ss}/C_{min,ss}$ Ratio, $t_{max,ss}$, $AUC_{(0-12),ss}$,
 $t_{1/2,ss}$, $CL_{po,ss}$, $A_{e(0-12),ss}$, $CL_{R,ss}$

Enantiomers: Both blood and urine ratios were calculated at each time point.

Statistics: Between treatment comparisons for the single- and multiple-dose groups were made utilizing natural log-transformed data. Before log-transformation, values of the AUC, C_{max} and C_{min} parameters were normalized to the lowest (20 mg) dose. An appropriate ANOVA model was used to produce least squares (LS) means for each treatment and 90% confidence intervals for their ratios.

RESULTS Twenty-three of the original 24 subjects completed all four periods of the study. Single- and multiple-dose mean plasma MDL 16,455 concentration versus time profiles are presented in Figures 3 and 4, respectively. Mean single-dose pharmacokinetic parameters are presented, and normalized parameters are compared in Table 4. Similar multiple-dose data are presented in Table 5. Mean steady-state MDL 16,455 R(+) and S(-) concentration versus time profiles appear in Figure 5. Mean percent plasma enantiomer abundance versus time estimates are presented in Figure and Table 6. Urinary excretion data are presented in Table 7. Urinary enantiomer data suggests that the stereoisomers are eliminated in the urine at a similar rate (see Figure 7).

DISCUSSION Data presented suggest that fexofenadine plasma pharmacokinetics are proportional within the dosage range of 20 to 120 mg. Enantiomeric data indicates that the plasma R(+) species dominates the S(-) form by a ratio of about 1.7:1 across the entire dosing range of this study. However, the urinary excretion data intimates that both enantiomers are renally eliminated at similar rates. Fortunately, pre-clinical data (Study No. C-93-0247-R: Competitive receptor binding studies with MDL 16,455A and its enantiomers to rat brain histamine H_1 -receptors) show that both enantiomers displace mepyramine from its H_1 binding site to a similar degree.

COMMENT

1. Since renal elimination does not appear to favor one enantiomer over another, increases in the R(+) form relative to S(-) could be a result of: preferential

absorption (with similar renal elimination of either enantiomer), preferential non-renal elimination or enantiomer interconversion. While not required, the sponsor may find it useful to perform an enantiomer interconversion study.

CONCLUSION The sponsor has adequately demonstrated the dose proportionality of MDL 16,455 between the dosage range of 20 to 120 mg. While the sponsor's inquiry to MDL 16,455 enantiomer pharmacokinetics should be considered incomplete, no further studies are needed since both enantiomers are approximately equipotent.

6 Pages

Purged

A Double-Blind, Randomized, Placebo-Controlled, Four-Period Crossover Pharmacodynamic and Safety Study of MDL 16,455A in Normal Subjects

Study PJPR0007 Volumes 1.61-1.72

INVESTIGATOR AND LOCATION

Miami, FL

OBJECTIVES (1) To characterize the effect on QT interval for normal subjects administered the following multiple dose regimen of MDL 16,455A (40 mg BID, 200 mg BID and 400 mg BID). (2) to characterize the multiple dose plasma and urine pharmacokinetics of MDL 16,455A (3) to assess any gender differences in bioavailability of MDL 16,455A

Only gender-related differences in bioavailability will be addressed in this review.

FORMULATIONS MDL 16,455A was supplied as the bulk drug substance (Lot

<u>Treatment Group A:</u>	40 mg MDL 16,455A
<u>Treatment Group B:</u>	200 mg MDL 16,455A
<u>Treatment Group C:</u>	400 mg MDL 16,455A
<u>Treatment Group D:</u>	Placebo

STUDY DESIGN This multiple-dose, double-blind, randomized four-way crossover study enrolled 40 normal, healthy, adult volunteers (20 females and 20 males). In each period, volunteers fasted from 12 hours prior to study drug administration until after the four hour blood sample was collected. After this time, subjects will resume standardized, low fat, high fiber, caffeine-free meals. All volunteers received placebo, BID on Day 1, followed by twelve doses (one dose every 12 hours) of study medication on Days 2 through 7. A final single dose was given on the morning of Day 8. A 10 day washout period separated the treatment periods. Serial blood samples were collected (just prior to and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 and 72 hours after dosing) after the last dose of MDL 16,455A. Additionally, trough samples were collected prior to the morning dose on Days 2, 6 and 7. Urine samples were collected before and after the last dose. Blood and urine samples were analyzed for achiral MDL 16,455. Subjects will remain confined until the last blood sample is collected (Day 11).

DATA ANALYSIS

Pharmacokinetic: Plasma- $AUC_{(0-12,ss)}$, $C_{max,ss}$, $CL_{po,ss}$. Urine- CL_R , A_e

RESULTS Of the original 40 volunteers, 39 subjects completed all phases of the study. Mean plasma concentration versus time profiles are presented in Figure 8. Mean and dose-normalized plasma and urine pharmacokinetic parameters are presented and compared in Tables 8 and 9, respectively. Pharmacokinetic parameters grouped by gender are in Table 10.

CONCLUSIONS Linearity was not demonstrated over the dosage ranges administered in this study. Bioavailability was higher in females relative to males (AUC: +33%, C_{max} : 46%). While renal clearance is approximately the same in both genders, non-weight adjusted oral clearance was substantially higher in males than females (+44%). However, this difference is blunted somewhat by the average weight difference observed of +16% (males versus females).

2 Pages

Purged

Report K-95-0154-DS: Population Pharmacokinetic/Pharmacodynamic
Analysis of Data from Protocols PJPR0023 and PJPR0024

Studies PJPR0023/24 **Volumes** 1.89-1.92

INTRODUCTION Clinical Studies PJPR0023 and PJPR0024 were conducted primarily to assess the safety and efficacy of MDL 16,455A for relief of the signs and symptoms of seasonal allergic rhinitis (SAR) and secondarily to investigate the population pharmacokinetics and pharmacodynamics of MDL 16,455A in patients.

OBJECTIVES (1) assess dose proportionality and determine the impact, if any, of population demographic variables on MDL 16,455 disposition. (2) compare pharmacokinetic parameters obtained from patients to parameters obtained from normal volunteers. (3) determine if there is a relationship between MDL 16,455 plasma concentrations and pharmacodynamic endpoints.

FORMULATIONS

20 mg capsules, Formula Number PJCX2-001, Lot Number RB9434
40 mg capsules, Formula Number PJCX4-001, Lot Number RF9422
60 mg capsules, Formula Number PJCX5-001, Lot Number RF9414

STUDY DESIGN A total of 1,160 patients were enrolled in two double-blind, randomized, placebo-controlled, parallel group clinical studies. Patients were randomized to receive either placebo, 40 mg, 60 mg, 120 mg or 240mg BID for 17 days during the fall allergy season. On the 17th day of the study, two blood samples were collected for MDL 16,455 plasma determinations (between 1 to 3 and 9 to 11 hours after MDL 16,455A administration). The change from baseline to the double-blind treatment period for the PM Reflective Total Symptom Score (TSS) was utilized as the primary efficacy parameter for the pharmacokinetic/pharmacodynamic analysis.

ASSAY

Assay Performance

	PJPR0023	PJPR0024
Linearity		
Accuracy		
Precision		
Sensitivity		
Specificity		

DATA ANALYSIS

Pharmacokinetic: Population pharmacokinetic parameters for MDL 16,455 were estimated using nonlinear mixed effects modeling (NONMEM). Four basic pharmacokinetic models were evaluated: one-compartment iv (1CIV), two-compartment iv (2CIV), one-compartment oral (1CPO) and two-compartment oral (2CPO). The oral models also included absorption rate constant (k_a). The selection of an appropriate model was based on 3 evaluation criteria: a significant reduction (log-likelihood ratio test; critical value=3.84 for χ^2 , 1 df, $P=0.005$) in the objective function value (OFV), the goodness-of-fit parameters and a random distribution of observed and predicted values along the line of unity. After a base model was selected, Bayesian estimates (NONMEM POSTHOC option) of oral clearance (CL_{po}) were calculated for each patient and then a stepwise multi variate linear regression was performed with CL_{po} as the dependent variable and with covariates age, weight, gender, race, concomitant medications, dose and protocol as independent variables. Covariates showing significant influence ($p < 0.10$) were then evaluated using NONMEM by comparing the full model (covariate included) with the reduced model.

Pharmacodynamic: Changes in PM Reflective Total Symptom Score (TSS) from baseline was scatter plotted versus MDL 16,455 plasma concentrations 1 to 3 hours post dose.

RESULTS Useful plasma samples were obtained from 836 patients and 758 pharmacodynamic endpoint measurements from 759 patients were obtained and included in the pharmacokinetic and pharmacodynamic analyses, respectively. A summary of mean plasma MDL 16,455 concentrations are presented in Table 11. It was impossible to

establish a relationship between changes in PM Reflective TSS from baseline versus Plasma MDL 16,455 concentration (See Figures 9 and 10). A one-compartment oral fixed K_a , weight adjusted volume model was selected as the base model (see Table 12 for a summary of results using various base models). Linear regression of the estimates for CL_{po} versus potential patient demographic variables indicated that patient age and gender were potential covariates for further NONMEM analysis. A summary of the NONMEM results using various expanded models are presented in Table 13. Only gender was found to significantly lower the OFV. Population parameter estimates for the final model are presented in Table 14. Predicted versus actual plasma concentrations appear in Figure 11. Weighted residual plots were randomly scattered and did not suggest any trends. Summary statistics on POSTHOC individual parameter estimates are presented in Table 15 and Figure 12. Dose normalized plasma concentrations appear similar (Table 16). Mean oral clearance of patients and healthy subjects are compared in Table 17. No relationship between changes in PM reflective TSS and MDL 16,455 concentrations 1 to 3 hours post-dose was observed.

COMMENT

Total Symptom Score (TSS) was comprised of four symptoms: itchy eyes, itchy nose, rhinorrhea and sneezing. Weaker responses to the symptoms of itchy eyes and nose compared to those obtained for rhinorrhea and sneezing may have diluted the TSS. If either of the two relatively stronger symptoms had been selected as the pharmacodynamic endpoint, a better pharmacokinetic/pharmacodynamic relationship may have been observed.

CONCLUSIONS Population analysis suggests:

- Non-weight adjusted MDL 16,455 oral clearance is approximately 18% faster in male versus female patients
- MDL 16,455 is dose proportional within the dosage range of 40 to 240mg
- MDL 16,455 oral clearance is similar between healthy volunteers and SAR patients
- A relationship between MDL 16,455 plasma concentrations and pharmacodynamic effect could not be established. This suggests that either an imperfect pharmacodynamic endpoint was selected or that doses administered are beyond the peak of the dose response curve.

5 Pages

Purged

Pharmacokinetics and Metabolism of
[¹⁴C]MDL 16,455A in Healthy, Male Volunteers

Study PJPR0008 Volumes 1.41-1.48

INVESTIGATOR AND LOCATION

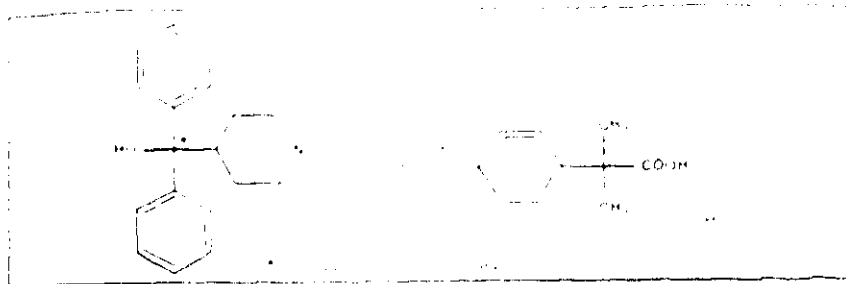
BACKGROUND It is hypothesized that terfenadine is oxidized to an alcohol (MDL 17,523). MDL 17,523 is primarily metabolized to the active carboxylic acid metabolite: MDL 16,455. Terfenadine and the alcohol metabolite can also be oxidized to an inactive metabolite (MDL 4,829).

OBJECTIVES (1) To characterize the mass balance of [¹⁴C]-labeled MDL 16,1455. (2) To characterize the metabolism of MDL 16,455A after steady-state administration and isolate and identify any metabolites formed.

FORMULATIONS

MDL 16,455A 15 mg/mL solution, Lot Number:
3038(MMD)MM931008

[¹⁴C]MDL 16,455A 15 mg/mL solution, Lot Number:
73136(MMD)ID-884-92A



Chemical Structure of MDL 16,455A

STUDY DESIGN This open-label, multiple-dose study enrolled six healthy male volunteers. Subjects received 60 mg MDL 16,455A every 12 hours for four days. On Day 5, the volunteers received a single 60 mg oral dose of [¹⁴C]MDL 16,455A (approximately 100 μCi radioactivity). Serial blood, urine, fecal and saliva samples were then collected (see Table 18 for sample collection schedule).

d

Results Of the six subjects who began this study, 4 left the clinic before reaching the release criteria (two consecutive samples should measure less than two times the radioactivity background for plasma, urine and feces). However, with the exception of one subject, this did not appear to significantly affect the total recovery of radioactivity. A mean fecal/urinary recovery of 91.52% was observed in the remaining five subjects (see Figure 13 and Table 20 for chemical structures and incidence, respectively, for the compounds identified in the urine and fecal samples). None of the alcohol metabolite (MDL 17,523) was detected in any of the plasma samples. However, one plasma sample contained terfenadine (Day 3 trough: 93.9 pg/mL; LOQ was 50 pg/mL for this assay). Insufficient sample remained for mass spectroscopy confirmation. The sponsor suggests that this is an aberrant finding, and not actually terfenadine, since it was obtained 72 hours after dosing, no MDL 17,523 was detected, and no terfenadine was detected in the previous sample or in any of the patient's urine samples. Trough MDL 16,455 levels for Days 3, 4 and 5 establishing steady-state, are presented in Table 21. Mean plasma time-concentration (ng/mL and radioactivity ng-eq/mL) data are presented in Table 22. Mean plasma and urine pharmacokinetic parameters are in Tables 23a and 23b.

Discussion Point-to-point comparisons of MDL 16,455 to [¹⁴C]-radioactivity (mean ratios approximately 1.00) suggest that MDL 16,455 undergoes minimal metabolism. The concentration of terfenadine in the trough sample of one subject was minor and probably

aberrant. No MDL 17,523 was detected in any of the plasma or urine samples and MDL 4,829 was detected in only very small quantities in the urine (1.47% of dose) and feces (trace). The other compounds identified in the urine and fecal samples (see Figure 13) are probably the result of dosage impurities, or in the case of MDL 16,455's methyl ester, via transformation by intestinal flora.

Conclusion Significant radioactivity was detected in the blood and saliva, with feces and urine being the major routes of elimination (approximately 80 and 11%, respectively). When given as an oral solution, MDL 16,455A undergoes only minor metabolism. The sponsor may need to further explore the possible metabolism of MDL 16,455. This should be considered in light of the pharmacokinetic interaction with ketoconazole and erythromycin (see Studies PJPR 0028 and PJPR 0018, respectively).

Table 18. Sample Collection Schedule

Matrix	Analyte	Time (hours post-dose, Day 5)

Table 19a. Assay Validation Summary (Plasma)

	Linearity	Accuracy	Precision	Sensitivity	Specificity

Table 19b. Assay Validation Summary (Urine)

	Linearity	Accuracy	Precision	Sensitivity	Specificity

3 Pages

Purged

In Vitro Metabolism of MDL 16,455 in Human Liver Fractions

Project Report No. K-95-0137-D Volume 1.1

OBJECTIVES to determine whether MDL 16,455 will undergo metabolism in an *in vitro* model using human liver microsomes, S9 fractions or slices.

MATERIALS

- References MDL 16,455A, MDL 4,829, MDL 102,038 (keto acid of MDL 16,455), MDL 9,918 (terfenadine), MDL 17,523 (terfenadine alcohol metabolite), MDL 46,016 (isopropyl terfenadine), MDL 15,177 (keto-analog of isopropyl terfenadine), MDL 47,397 (isopropyl acid of terfenadine)
- [¹⁴C]MDL 9,918 (lot 99): 24.3 μCi/mg; purity ≥ 99.7%. [¹⁴C]MDL 16,455A (lot 56A): 16.7 μCi/mg; purity ≥ 96.4%
- Proadifen HCl (SKF525A: MMD), Troleandomycin (Sigma)
- Pooled human liver microsomes (), Human liver S9 fraction and Human liver slices ()

METHODS & RESULTS To characterize the possible metabolism of MDL 16,455A, the sponsor performed four *in vitro* experiments.

- 1) Radiolabelled MDL 16,455 was incubated with human liver microsomes and human S9 liver fractions for 2 and 24 hours.

Chromatograms of the 2 and 24 hour incubation samples show no metabolism of [¹⁴C] MDL 16,455A under these experimental conditions. Positive controls demonstrated a metabolically active system.

- 2) MDL 16,455A was incubated with human liver microsomes and human S9 liver fractions at MDL 16,455A concentrations of 5, 10 and 30 μM for 0, 10, 20, 30, 60, 120, 180 and 240 minutes. Positive (terfenadine) and negative (buffer and tissue blank) controls were also included. All reactions were quenched with 1.6 mL of acetonitrile.

Results from this experiment demonstrated a 5 - 10% decrease in MDL 16,455 after 4 hours of incubation. However, the buffer vials increased by 5 - 10%, suggesting an approximate 10% method variability. Further, any compounds structurally related to MDL 16,455 were below the assay limit of quantitation.

- 3) MDL 16,455A was incubated at 30 μM for the same time intervals as above, in experiment 2, however, the microsomal protein concentration was increased four-fold (2 mg/mL). A known CYP 450 metabolic poison, SKF-525A: 500 μM, was added to a duplicate set of incubation vials and incubated under identical conditions.

An inhibitor of CYP3A4, troleandomycin, 100 μ M was added to a third set of vials and incubated at 0, 10, 60 and 240 minutes, also using 2 mg/mL of microsomal protein.

The results from this experiment with increased microsomal protein content exhibited a peak with a retention time similar to that of MDL 4,829 (see Figure 14). When MDL 16,455A was incubated in the presence of SKF-525A or troleandomycin, both peaks are absent.

Figure 14.



- 4) [^{14} C]MDL 16,455A was also incubated with human liver slices. Additionally, [^{14} C]MDL 9,918 (terfenadine, as a positive control), substrate blanks, tissue blanks and medium blanks were incubated. After 1, 4.5, 20 and 44 hours of incubation slices were counted on a liquid scintillation counter and vials containing medium were analyzed by

Incubation of [¹⁴C]MDL 16,455A in liver slices did not yield any detectable metabolism. The only moiety other than MDL 16,455 detected was MDL 102,038 a known radiolabeled impurity of [¹⁴C]MDL 16,455A. Figures 15 and 16 illustrate chromatograms of a 20 hour incubation of [¹⁴C]MDL 9,918 and [¹⁴C]MDL 16,455A, respectively.

Figure 15.

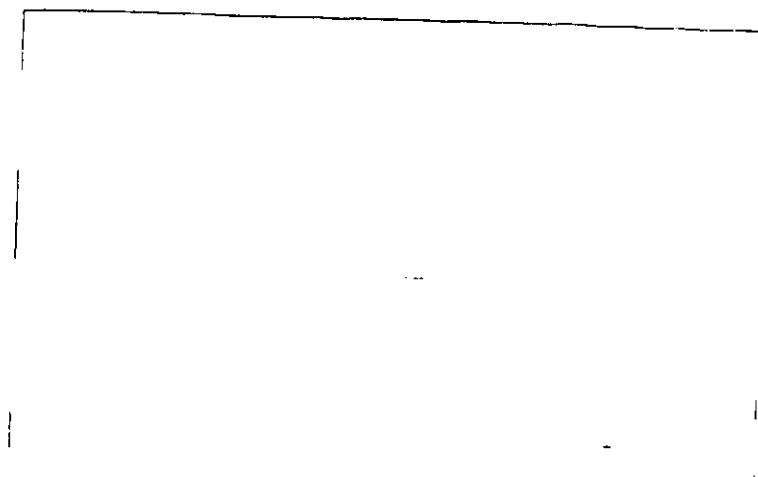
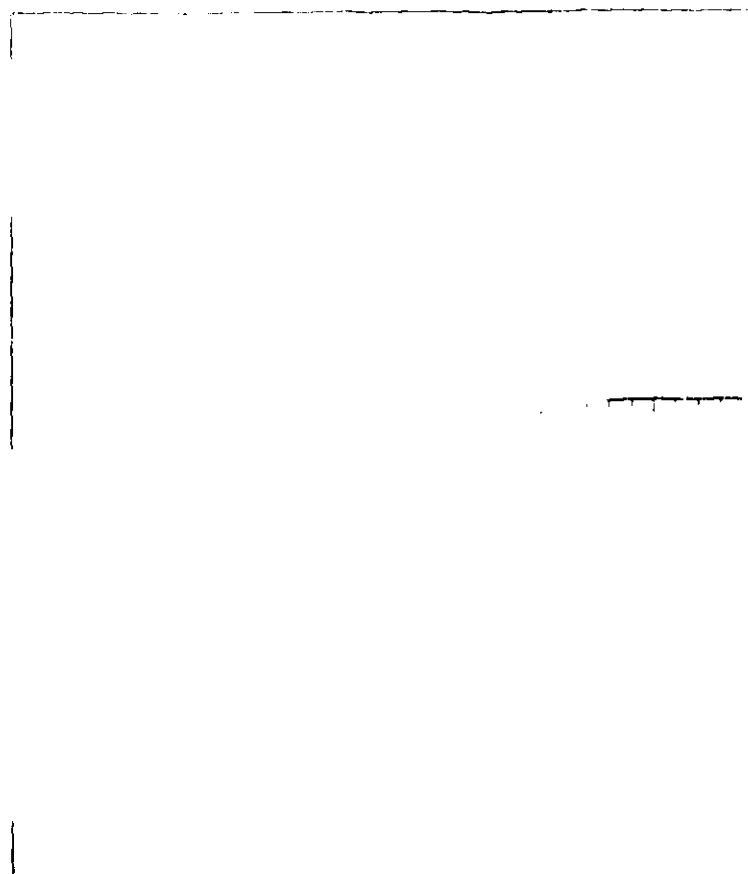


Figure 16.



CONCLUSIONS Overall, [^{14}C]MDL 16,455A shows negligible metabolism using *in vitro* models.

Pharmacokinetics of a Single Oral Dose of MDL 16,455A in Healthy Elderly Volunteers

Study PJPR0020 Volumes 1.78-1.79

INVESTIGATOR AND LOCATION

OBJECTIVES To characterize the pharmacokinetics of MDL 16,455A in healthy elderly volunteers after a single oral dose.

FORMULATION

20 mg capsules, Formula Number PJCX2-001, Lot Number RB9434 (Pilot-Scaled lot)

STUDY DESIGN This open-label, single-dose trial enrolled 20 subjects (11 male and 9 female) aged 65 years, or older (mean: 72; range: 65-80). Subjects were confined starting at 2100 the evening before the study began. Subjects were served a snack, after which they fasted until 80 mg of the study drug was administered at 0800. Food was withheld until after the 4 hour blood sample was obtained, after which standardized meals were provided. Blood samples for plasma MDL 16,455 determinations were obtained before (zero hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after study drug administration. A urine sample was collected immediately prior to and during the intervals: 0-12, 12-24 and 24-48 after dosing.

Assay Performance

Data Analysis

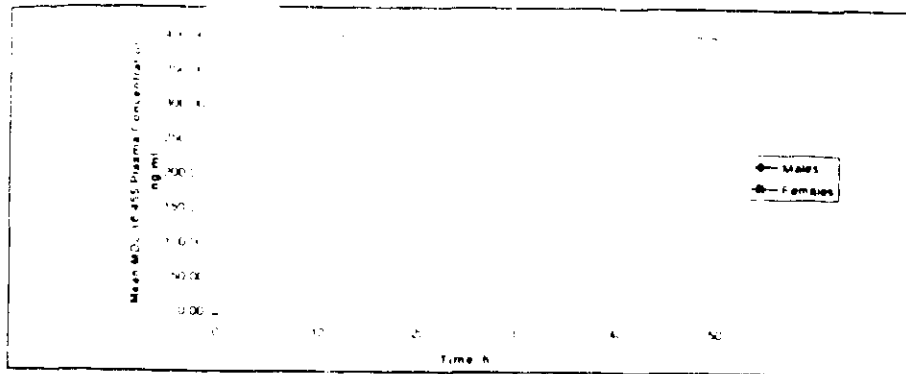
Pharmacokinetic: C_{max} , T_{max} , AUC_{0-∞}, AUC_{0-6h}, $t_{1/2}$, CL_{cr} , CL_{R} , Ae, % of MDL 16,455A oral dose excreted in urine

Statistical: Descriptive, only.

Results All 20 enrollees completed the study with no dropouts. The mean MDL 16,455 plasma concentration versus time profile for all subjects is shown in Figure 17. Pharmacokinetic parameters, stratified by gender, are presented in Table 24.

Discussion Gender differences observed appear to be weight-related. Weight adjusted oral clearance rates are comparable. Descriptive statistics of pharmacokinetic parameters are compared to normal volunteers in the Special Populations subsection of the Clinical Pharmacology & Biopharmaceutics summary. Any conclusions reached from this comparison will be reported in that section.

Figure 17.



Plot of Mean MDL 16,455 Concentrations vs Time Profile in Male and Female Elderly Subjects Following Oral Administration of 80 mg Single Dose MDL 16,455A. (N=11 for males and 9 for females)

Table 24.

Pharmacokinetic Parameters of MDT 15,155 in Male and Female Geriatric Subjects. Data is Expressed as Mean (%CV)		
Parameter	Males	Females
C_{max} , ng/ml	387.33 (64.65)	455.95 (40.69)
t_{max} , h	2.0 (42.81)	2.1 (33.18)
AUC(0- ∞), ng·h/mL	2846.53 (57.04)	2982.60 (29.45)
$t_{1/2}$, h	13.34 (24.92)	17.52 (71.62)
CL_{po} , L/h	37.32 (68.24)	28.39 (48.85)
CL_{po} , L/h/kg	0.46 (64.02)	0.49 (76.15)
A_e , mg	7.19 (86.39)	6.47 (66.31)
% of Dose	9.65 (86.39)	8.68 (66.31)
CL_R , L/h	3.10 (64.13)	2.37 (54.06)
N = 9 for $t_{1/2}$, AUC(0- ∞) and CL_{po} and N=11 for rest of parameters for males		
N = 7 for $t_{1/2}$, AUC(0- ∞) and CL_{po} and N=9 for rest of parameters for females		

Pharmacokinetics of a Single Oral Dose of MDL 16,455A in Subjects With Various Degrees of Liver Failure

Study PJPR0021 Volumes 7.1 - 7.2

INVESTIGATOR AND LOCATION

OBJECTIVES To characterize the pharmacokinetics of MDL 16,455A in subjects with various degrees of liver failure after a single 80 mg oral dose.

FORMULATION 20 mg capsules, Formula Number PJCX2-001, Lot: Number RB9432 (Pilot-Scaled lot)

STUDY DESIGN This open-label, single-dose stratified study originally planned to enroll 20 subjects: ten subjects assigned to each of two hepatic function groups (mild to moderate or moderate to severe hepatic impairment as graded by the Child-Pugh classification system, see Table 25.). Subjects fasted a minimum of 11 hours before dosing, maintaining their fast until after the 4 hour blood sample was obtained. After this, standardized meals were served for the duration of the study. Serial blood samples were collected before (zero hour), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, 60 and 72 hours after dosing. Urine samples were collected prior to dosing and during the intervals: 0-12, 12-24, 24-48 and 48-72 hours. The serial plasma samples were assayed for MDL 16,455, while the 1.5, 6 and 12 hour samples were assayed for terfenadine and MDL 17,523. Urine was assayed for MDL 16,455, only.

Data Analysis

Pharmacokinetic: C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$, CL_{po} , CL_R and A_e

Statistical: Only descriptive statistics are reported for this study.

Results Seventeen subjects (see Subject Demographics, Table 27) were enrolled and completed this study. Plasma concentration-time plots for the mild-to-moderate and moderate-to-severely hepatically impaired groups are presented in Figure 18. Plasma and urine pharmacokinetic parameters are presented in Tables 28 and 29, respectively.

Discussion Oral clearance was similar between the mild-to-moderate and moderate-to-severely impaired subjects. Thus, elimination half-life discrepancies may be related to volume differences. Descriptive statistics of pharmacokinetic parameters are compared to normal volunteers in the Special Populations subsection of the Pharmacokinetics summary. Any conclusions reached from this comparison will be reported in that section.

Table 25.

Child-Pugh Classification

**CLINICAL AND BIOLOGICAL CLASSIFICATION
OF CHRONIC LIVER DISEASE BY CHILD-PUGH**

Risk Factors and Scores

Score	1	2	3
Ascites	Absent	Minimal	Abundant**
Neurological symptoms	Absent	Transient or mild	Hepatic coma*
PT (sec) prolonged from control	1-4	4-6	> 6
Serum bilirubin ($\mu\text{mol/L}$)	< 34	34-51	> 51
Serum Albumin (g/L)	> 35	28-35	< 28
Serum bilirubin ($\mu\text{mol/L}$) for primary biliary cirrhosis	< 68	68-170	> 170

Classification of Chronic Liver Disease

Group A:	Total score $\leq$ 7
Group B:	Total score 8-9
Group C1:	Total score 10-12
(Group C2:	Total score $\geq$ 13)*

Table 26a. Plasma Assay Performance

⁹Samples assayed in first batch

¹⁰Samples assayed in second batch

¹¹Based on n=2 QC samples at each level

Table 27. Subject Demographics

Baseline Characteristics	Mild-to-Moderate % (N)	Moderate-to-Severe % (N)	Total % (N)
Gender			
Male % (N)	90% (9)	43% (3)	71% (12)
Female % (N)	10% (1)	57% (4)	29% (5)
Age (years)			
Mean ± SD	51 ± 10	48 ± 7	50 ± 8
Range	32-62	38-61	32-62
Race			
Caucasian % (N)	90% (9)	66% (5)	88% (15)
Black % (N)	10% (1)	14% (1)	12% (2)
Weight (kg)			
Mean ± SD	82 ± 14	80 ± 15	81 ± 14
Range	56.2-103.9	60.4-106.1	56.2-106.1
Height (cm)			
Mean ± SD	172 ± 6	167 ± 8	170 ± 7
Range	163-183	158-183	158-183
Diagnosis			
Alcoholic Cirrhosis % (N)	70% (7)	43% (3)	59% (10)
Viral Hepatitis C (only) % (N)	10% (1)	43% (3)	23% (4)
Idiopathic Cirrhosis % (N)	10% (1)	-	6% (1)
Viral Hepatitis B, C, D % (N)	10% (1)	-	6% (1)
Uncertain Etiology % (N)	-	14% (1)	6% (1)
Child-Pugh Classification			
Mild-to-Moderate			
A % (N)	-	-	59% (10)
Moderate-to-Severe			
B % (N)	-	-	35% (6)
C1 % (N)	-	-	6% (1)

Figure 18. Mean Plasma MDL 16,455 Concentrations in Hepatically Impaired Subjects

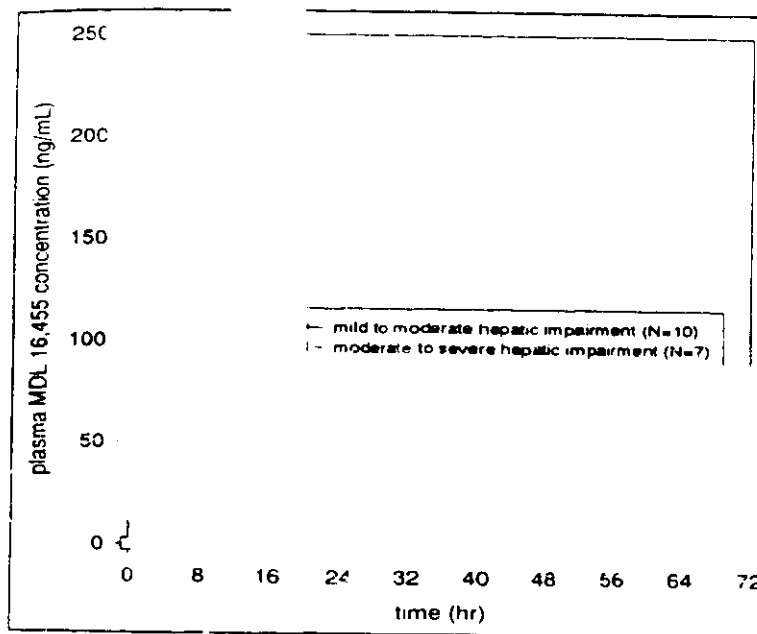


Table 28. Mean Pharmacokinetic Parameters (% CV) for Plasma MDL 16,455 in the Hepatically Impaired

Parameter	Mild-to-Moderate	Moderate-to-Severe
AUC _{0-∞} (ng·hr/mL)	1699.91 (40)	2176.02 (78)
C _{max} (ng/mL)	268.48 (55)	281.28 (68)
t _{max} (hr)	1.55 (47)	2.29 (42)
CL _{po} (L/hr)	50.01 (38)	56.06 (72)
t _{1/2} (hr)	11.29 (35)	16.01 (35)

Table 29.

Mean Single Dose Urine MDL 16,455 Pharmacokinetic Parameters			
		Mild-to-Moderate (N=10)	Moderate-to-Severe (N=7)
Cumulative Amount Excreted (mcg)	Mean	7186.22	6266.37
	SD	4208.83	3148.42
	%CV	58.57	50.24
Cumulative Percent of Dose Excreted (%)	Mean	9.64	8.40
	SD	5.64	4.22
	%CV	58.57	50.24
Renal Clearance (L/h)	Mean	4.09	3.63
	SD	1.67	1.29
	%CV	40.78	35.54

Comments

1. It would have been preferable to include a control (non-hepatically impaired) study arm. Since no "normal" subjects for comparison were included in this study, a comparison across studies will be required to assess the effect of hepatic impairment on drug disposition.
2. The original protocol called for the enrollment of 20 subjects to appropriately power this study. However, in this study report, the sponsor states that the 17 subjects enrolled should provide sufficient power. The sponsor is requested to explain these power calculations.

Pharmacokinetics of MDL 16,455A in Subjects With Renal Impairment

Study PJPR0013 Volumes 1.73-1.77

INVESTIGATOR AND LOCATION

OBJECTIVES To characterize the pharmacokinetics of MDL 16,455A in subjects with various degrees of renal impairment after a single 80 mg oral dose.

FORMULATION 20 mg capsules, Formula Number PJCX2-001, Lot Number RN9323 (Pilot-Scaled lot)

STUDY DESIGN A total of thirty male and female subjects with varying renal function were enrolled in this open-label, single-dose study. Subjects were stratified to one of three renal function groups based on creatinine clearance (CrCl). The groups were stratified as follows:

Group I	mild-to-moderate renal impairment:	CrCl 41-80 ml/min
Group II	moderate-to-severe renal impairment:	CrCl 11-40 ml/min
Group III	end-stage renal disease (dialysis patients):	CrCl $\leq$ 10 ml/min

Subjects fasted the night before the study, until after the 4 hour blood sample was obtained. Blood samples were collected immediately prior to (zero hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48 and 60 hours after dosing. Additionally, a 72 hour sample was obtained from subjects assigned to Groups I and II. Urine samples from the following intervals were also collected: -12 to 0 (pre-dose), 0 to 12, 12 to 24, 24 to 48 and 48 to 72 hours. All samples were assayed for MDL 16,455.

Assay Performance

Data Analysis

Pharmacokinetic: C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$, CL_{po} , CL_R and A_e

Statistical: Only descriptive statistics are reported for this study.

Results Twenty-nine subjects (see Subject Demographics, Table 30) were enrolled and completed this study. Mean plasma concentration-time data for the mild-to-moderate, moderate-to-severely renally impaired and dialysis groups are presented in Figure 19. Plasma and urine pharmacokinetic parameters are presented in Tables 31 and 32, respectively.

Discussion Descriptive statistics of pharmacokinetic parameters are compared to normal volunteers in the Special Populations subsection of the Pharmacokinetics summary. Any conclusions reached from this comparison will be reported in that section.

Comment

It would have been preferable to include a control (non-renally impaired) study arm. Since no "normal" subjects for comparison were included in this study, a comparison across studies will be required to assess the effect of renal impairment on drug disposition.

Table 30. Subject Demographics

Gender	
Male % (N)	67 (19)
Female % (N)	33 (10)
Age (years)	
Mean ± SD	47 ± 13
Range	26–68
Race	
Caucasian % (N)	69 (20)
Black % (N)	17 (5)
Asian % (N)	14 (4)
Weight (kg)	
Mean ± SD	78 ± 20
Range	50–144
Height (cm)	
Mean ± SD	170 ± 8
Range	159–185
Frame	
Small % (N)	3 (1)
Medium % (N)	72 (21)
Large % (N)	24 (7)
Renal impairment	
Mild-to-Moderate	31 (9)
Moderate-to-Severe	34 (10)
Patients on Dialysis	34 (10)
Note: This table summarizes the demographics for all subjects that were dosed with MDL 16,455A. The demographics for subject PJS10013-0025, who was enrolled in the study but not dosed with MDL 16,455A, are not included in this table.	

Figure 19. Mean Plasma MDL 16,455 Concentration vs Time Profiles

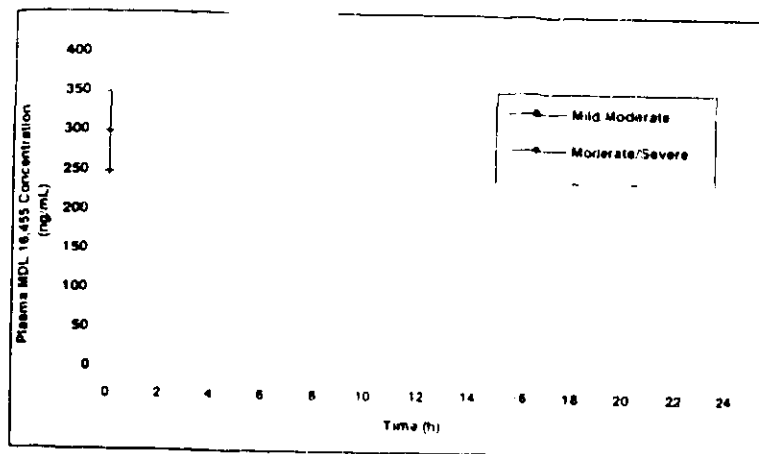


Table 31.

Mean Single Dose Plasma MDL 16 455 Pharmacokinetic Parameters in Patients with Renal Disease

Excretion Group	Parameter	Mild to Moderate (N=9)		Moderate to Severe (N=10)		Dialysis Patients (N=7)	
		Mean	%CV	Mean	%CV	Mean	%CV
Mild to Moderate (N=9)	Mean	10.14	2.43	11.27	2.43	11.85	2.85
	%CV	33.77	58.26	33.77	58.26	33.77	58.26
Moderate to Severe (N=10)	Mean	44.73	2.75	43.94	2.75	43.74	2.75
	%CV	32.63	53.57	32.63	53.57	32.63	53.57
Dialysis Patients (N=10)	Mean	38.06	2.25	33.77	2.25	34.56	18.85
	%CV	35.99	37.42	31.31	37.42	37.44	56.57

Note: In dialysis patients at site PJST0013 plasma samples were only collected for 48 hours. In dialysis patients at site PJST0012 plasma samples were collected for <60 hours.

Table 32.

Mean Single Dose Urine MDL 16 455 Pharmacokinetic Parameters

Parameter	Mean	Mild to Moderate (N=9)	Moderate to Severe (N=10)	Dialysis Patients (N=7)	
		Mean	%CV	Mean	%CV
Cumulative Amount Excreted (mg)	Mean	4.83	78.26	1.81	119.41
	%CV	78.26	119.41	119.41	201.37
Cumulative Percent of Dose Excreted (%)	Mean	6.55	78.26	2.44	119.41
	%CV	78.26	119.41	119.41	201.37
Renal Clearance (L/h)	Mean	2.46	82.39	0.53	132.05
	%CV	82.39	132.05	132.05	211.14
Urinary half-life (h)	Mean	10.25	80.27	8.01	29.41
	%CV	80.27	29.41	29.41	na
	(N)	(6)	(3)	(3)	(1)

Note: In all except three patients, MDL 16 455 was not quantifiable over the entire collection period. As a consequence, urinary half-life estimates were only obtained in a small number of subjects.

The Effect of Erythromycin on the Pharmacokinetics of MDL 16,455A

Study PJPR0018 Volumes 1.82-1.85

INVESTIGATOR AND LOCATION

OBJECTIVES Primarily to characterize the pharmacokinetics of MDL 16,455 when MDL 16,455A is given alone and in combination with multiple doses of erythromycin. Secondly, to examine the pharmacokinetics of erythromycin when administered alone and with MDL 16,455A and to characterize the effect on QTc when MDL 16,455A was given in combination with erythromycin.

FORMULATIONS MDL 16,455A: 60 mg capsules, Formula Number PJXCX5-001, Lot Number RH9411 (Full Production-Scaled lot); Erythromycin: 250 mg tablets (E-mycin[®], Lot No. 743 KP, Boots) commercially procured.

STUDY DESIGN This open-label, multiple-dose, randomized 3-period crossover study included 24 subjects. Subjects received each of the following three treatments separated by a washout period of at least 10 days:

Treatment A	MDL 16,455A (2 x 60 mg q12hr x 6.5 days)
Treatment B	Erythromycin (2 x 250mg q8hr x 6.33 days)
Treatment C	MDL 16,455A (2 x 60 mg q12hr x 6.5 days) with Erythromycin (2 x 250mg q8hr x 6.33 days)

Subjects began fasting after a snack at 2100 on Study Day -1. A fasting blood and urine sample was obtained and serial ECGs were performed on Day zero to establish a baseline. Beginning on Study Day 1, subjects began receiving their appropriate study medication. On Study Days 5 and 6, 0700 blood samples were collected for erythromycin and MDL 16,455 determinations. After a 2300 snack on Day 6, subjects began fasting. After the 0700 doses were administered on Day 7 serial (1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 hours after dosing) blood samples were collected. Serial (0, 2, 3, 4, 6, 8, 12, 24 and 36 hours after dosing) ECGs were also performed. Subjects continued fasting until after the 4 hour blood sample was obtained.

ASSAY PERFORMANCE

DATA ANALYSIS

Pharmacokinetic: MDL 16,455- $C_{max,ss}$, $C_{min,ss}$, $C_{max,ss}/C_{min,ss}$, T_{max} , $AUC_{0-12,ss}$, CL_{po} , CL_R , A_e and % of dose excreted

Erythromycin- $C_{max,ss}$, $C_{min,ss}$, T_{max} , $AUC_{0-8,ss}$, CL_{po}

Pharmacodynamic: QT interval from the serial ECGs were corrected using Bazzet's formula (QTc). Maximum QTc changes from baseline were compared between Treatment Groups.

Statistical: Between treatment comparisons for MDL 16,455 and erythromycin pharmacokinetic parameters were performed according to the 1992 FDA Guidance.

RESULTS Of the 24 subjects originally enrolled in the study, 18 completed all three treatment arms. Mean plasma concentration versus time profiles for MDL 16,455 and erythromycin are presented in Figures 20 and 21, respectively. Pharmacokinetic

¹²Based on n=2 replicates at each level

parameters are presented and compared in Tables 33 and 34. Urine data are presented in Table 35. A summary of the ECG data is presented in Table 36.

DISCUSSION While a significant increase in MDL 16,455A bioavailability is observed when given concomitantly with erythromycin, no significant pharmacodynamic interaction (QTc changes) are evident. MDL 16,455A appears to have no effect on the disposition of erythromycin. Increases observed in urinary clearance are roughly proportional to increases in bioavailability.

CONCLUSION Since there are no significant ECG changes associated with this pharmacokinetic interaction (as in the terfenadine-erythromycin interaction), this combination may be safe. This type of interaction (with a known cytochrome P450 3A4 inhibitor) is not expected with a drug which is mainly excreted unchanged. Therefore, further investigation is needed to identify the mechanism of this interaction.

COMMENTS

1. While the protocol does specify when meals will be served, it makes no mention of meal content or standardization.
2. Subject confinement during the course of the study is not addressed in either the study protocol or report. The sponsor is requested to clarify this issue.
3. In the MDL 16,455 urine assay, satisfactory precision and accuracy were not demonstrated at the sponsor-stated lower limit of quantitation (0.1 $\mu\text{g/mL}$). Since satisfactory assay performance was reported at the next highest concentration (0.2 $\mu\text{g/mL}$), urine data may be erroneously reported.

Figure 20.

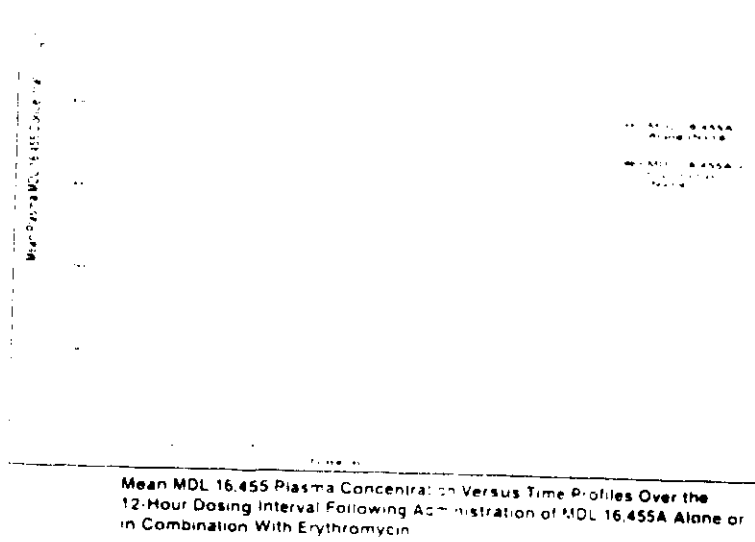


Table 33.

Mean Plasma Pharmacokinetic Parameters and Treatment Comparisons for MDL 16,455								
Parameter	Time	Mean	SD	CV (%)	Pairwise Comparison			
					Pair	Ratio (%)	90% CI	P Value
AUC _{0-12h} (ng/ml)	A	2421.52	28.07	11.59				
	C	5044.94	14.4	2.87	C/A	203.38	(181.9, 227.4)	<0.001
C _{0.5h}	A	40.36	14.15	34.9				
	C	24.75	15.1	60.9	C/A	49.17	(44.0, 55.0)	<0.001
C _{max} (ng/ml)	A	409.74	14.4	3.51				
	C	743.99	32.65	4.38	C/A	180.37	(159.7, 203.7)	<0.001
t _{max} (h)	A	2.2	42.63	1927				
	C	3.7	30.94	838	C/A	174.71	(143.1, 213.2)	<0.001

Treatment A=MDL 16,455A 120 mg Q12h
 Treatment C=MDL 16,455A 120 mg Q12h + Erythromycin 500 mg Q6h

Figure 21.

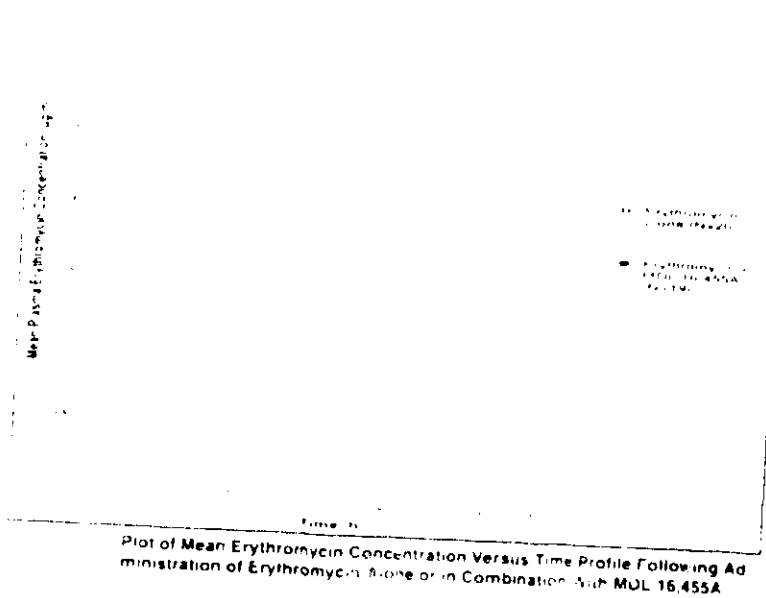


Table 34.

Mean Plasma Pharmacokinetic Parameters and Treatment Comparisons for Erythromycin								
Parameter	Time	Mean	%CV	Adjusted Mean	Pairwise Comparison			
					Pair	Ratio (%)	95% CI	P Value
AUC _{0-24h} (ng·h/ml)	B	23.44	17.21	21.46	C/B	94.00	(83.1, 106.3)	0.392
	C	23.85	46.91	20.18				
C _{max} (ng/ml)	B	24.95	53.14	23.30	C/B	100.38	(94.1, 120.3)	0.392
	C	24.65	37.88	24.78				
C _{min} (ng/ml)	B	4.21	28.70	4.01	C/B	87.13	(77.8, 97.5)	0.049
	C	3.88	41.85	3.49				
t _{max} (h)	B	4.85	32.96	4.48	C/B	109.10	(87.7, 135.4)	0.495
	C	5.21	24.43	4.89				

Treatment B = Erythromycin 500 mg Q6h
 Treatment C = MOL 16,455A 120mg Q12h + Erythromycin 500 mg Q6h

Table 35.

Mean and Maximum QTc Parameters and Treatment Comparisons for MDL 16 435						
Morganroth Read ECG Data						
Parameter	Treatment	N	Day 0 mean (SD)	Day 7 mean (SD)	95% CI	P Value
Mean QTc	A	18	331.1 ± 5.1	332.8 ± 5.6	(2.8 [1.1, 4.5])	<0.001
	M	19	331.1 ± 5.1	332.8 ± 5.6	(106.8 [11.7, 201.9])	<0.001

Table 36.

Table 325 Change From Baseline in Mean and Maximum QTc Morganroth Read ECG Data						
Mean QTc						
Treatment	N	Day 0 mean (SD)	Day 7 mean (SD)	Change from Day 0 to Day 7 mean (SE)	P Value	
M (n=19)	19	331.1 ± 5.1	332.8 ± 5.6	1.6 ± 2.1	0.385	
A (n=18)	18	331.1 ± 5.1	332.8 ± 5.6	1.7 ± 2.1	0.374	
Maximum QTc						
Treatment	N	Day 0 mean (SD)	Day 7 mean (SD)	Change from Day 0 to Day 7 mean (SE)	P Value	
M (n=19)	19	412.1 ± 4.1	412.0 ± 5.6	-0.1 ± 4.1	0.980	
A (n=18)	18	412.1 ± 4.1	412.0 ± 5.6	-0.1 ± 4.1	0.944	

1. 4 subjects began the study, 6 subjects withdrew prior to completion

2. P value from t-test or change from Day 0 to Day 7 equals 0

The Effect of Ketoconazole on the Pharmacokinetics of MDL 16,455A

Study PJPR0028 Volumes 1.86-1.88

INVESTIGATOR AND LOCATION

OBJECTIVES Primarily to characterize the pharmacokinetics of MDL 16,455 when MDL 16,455A is given alone and in combination with multiple doses of ketoconazole. Secondly, to examine the pharmacokinetics of ketoconazole when administered alone and with MDL 16,455A and to characterize the effect on QTc when MDL 16,455A was given in combination with ketoconazole.

FORMULATIONS MDL 16,455A: 60 mg capsules, Formula Number PJXCX5-001, Lot Number RH9411 (Full Production-Scaled lot); Ketoconazole: 200 mg tablets

STUDY DESIGN This open-label, multiple-dose, randomized 3-period crossover designed study included 24 subjects. Subjects received each of the following three treatments separated by a washout period of at least 10 days:

Treatment A	MDL 16,455A (2 x 60 mg q12hr x 6.5 days)
Treatment B	Ketoconazole (2 x 200mg qd x 7 days)
Treatment C	MDL 16,455A (2 x 60 mg q12hr x 6.5 days) with Ketoconazole (2 x 200mg qd x 7 days)

Subjects began fasting after a snack at 2100 on Study Day -1. A fasting blood and urine sample was obtained and serial ECGs were performed on Day zero to establish a baseline. Beginning on Study Day 1, subjects began receiving their appropriate study medication. On Study Days 5 and 6, 0700 blood samples were collected for ketoconazole and MDL 16,455 determinations. After a 2300 snack on Day 6, subjects began fasting. After the 0700 doses were administered on Day 7 serial (1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 hours after dosing) blood samples were collected. Serial (0, 2, 3, 4, 6, 8, 12, 24 and 36 hours after dosing) ECGs were also performed. Subjects continued fasting until after the 4 hour blood sample was obtained.

ASSAY PERFORMANCE

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DATA ANALYSIS

Pharmacokinetic: MDL 16,455- $C_{max, ss}$, $C_{min, ss}$, $C_{max, ss}/C_{min, ss}$, T_{max} , $AUC_{0-12, ss}$, CL_{po} , CL_R , A_e and % of dose excreted

Ketoconazole- $C_{max, ss}$, $C_{min, ss}$, $C_{max, ss}/C_{min, ss}$, T_{max} , $AUC_{0-24, ss}$, CL_{po}

Pharmacodynamic: QT interval from the serial ECGs were corrected using Bazzet's formula (QTc). Maximum QTc changes from baseline were compared between Treatment Groups.

Statistical: Between treatment comparisons for MDL 16.455 and ketoconazole pharmacokinetic parameters were performed according to the 1992 FDA Guidance.

RESULTS Of the 24 subjects originally enrolled in the study, 22 completed all three treatment arms. Mean plasma concentration versus time profiles for MDL 16,455 and ketoconazole are presented in Figures 22 and 23, respectively. Pharmacokinetic parameters are presented and compared in Tables 37 and 38. Urine data are presented in Table 39. A summary of the ECG data is presented in Table 40.

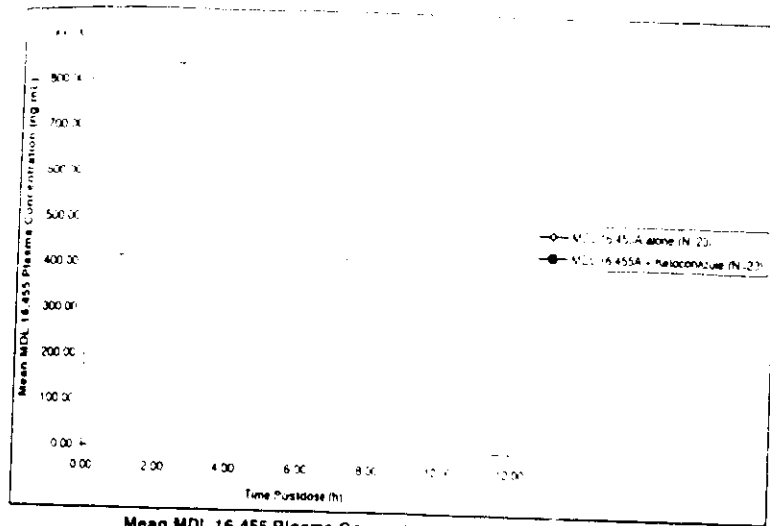
DISCUSSION While a significant increase in MDL 16,455A bioavailability is observed when given concomitantly with ketoconazole, no significant pharmacodynamic interaction (QTc changes) are evident. MDL 16,455A appears to have no effect on the disposition of ketoconazole. Increases observed in urinary clearance are roughly proportional to increases in bioavailability.

CONCLUSION Since there are no significant ECG changes associated with this pharmacokinetic interaction (as in the terfenadine-ketoconazole interaction), this combination may be safe. This type of interaction (with a known cytochrome P450 3A4 inhibitor) is not expected with a drug which is mainly excreted unchanged. Therefore, further investigation is needed to identify the mechanism of this interaction.

COMMENTS

1. While the protocol does specify when meals will be served, it makes no mention of meal content or standardization.
2. Subject confinement during the course of the study is not addressed in either the study protocol or report. The sponsor is requested to clarify this issue.

Figure 22.



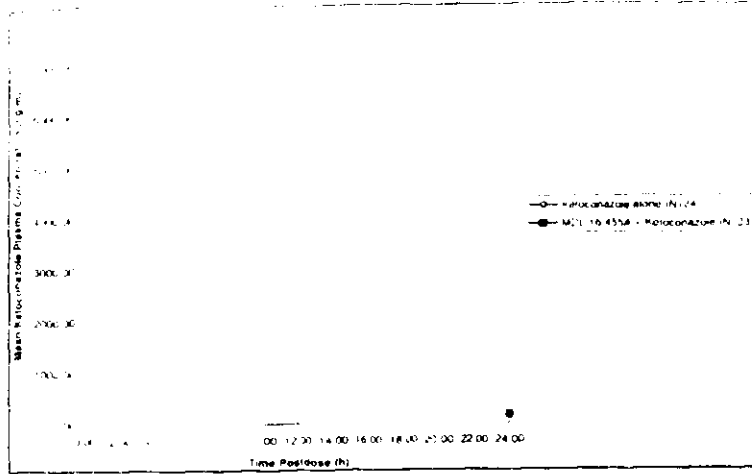
Mean MDL 16,455 Plasma Concentrations Over the 12-Hour Dosing Interval Following Administration of MDL 16,455A Alone or MDL 16,455A in Combination with Ketoconazole.

Table 37.

Mean Steady-State Plasma Pharmacokinetic Parameters and Treatment Comparisons for MDL 16,455								
Parameter	Trt	Mean	%CV	Adjusted Mean	Pairwise Comparison			
					Pair	Ratio (%)	90% CI	P value
AUC _{0-12h}	A	2099.67	33.31	2055.39	-	-	-	-
h*ng/mL	C	5547.24	24.86	5329.83	C/A	259.31	(231.4, 290.6)	<0.001
Cl _{po}	A	57.84	26.22	54.43	-	-	-	-
L/h	C	21.51	27.16	20.99	C/A	38.56	(34.4, 43.2)	<0.001
C _{max,ss}	A	388.41	40.88	376.85	-	-	-	-
ng/mL	C	913.9	29.54	866.23	C/A	229.86	(193.3, 273.3)	<0.001
t _{max,ss}	A	2.43	52.65	2.12	-	-	-	-
h	C	2.78	43.96	2.52	C/A	118.96	(94.5, 149.7)	0.207
C _{min,ss}	A	43.78	46.12	-	-	-	-	-
ng/mL	C	85.07	48.38	-	-	-	-	-

Treatment A=MDL 16,455A 120 mg Q12 h
 Treatment C=MDL 16,455A 120 mg Q12 h + Ketoconazole 400 mg QD

Figure 23.



Mean Ketoconazole Plasma Over the 24-Hour Dosing Interval Following Administration of Ketoconazole Alone or MDL 16,455A in Combination with Ketoconazole.

Table 38.

Mean Steady-State Plasma Pharmacokinetic Parameters and Treatment Comparisons for Ketoconazole								
Parameter	Trt	Mean	%CV	Adjusted Mean	Pairwise Comparison			
					Pair	Ratio (%)	90% CI	P value
AUC _{0-24 h}	B	61039.24	46.89	53247.01				
F (ng/mL)	C	60327.80	49.73	79529.62	C/B	93.02	(75.4, 114.7)	0.559
CL _{CR}	B	9.30	87.78	7.51				
L _{CR}	C	11.24	123.47	8.08	C/B	107.52	(87.2, 132.6)	0.556
C _{max,ss} (ng/mL)	B	8392.59	41.97	7495.41				
	C	7994.77	43.25	5629.27	C/B	86.44	(73.7, 106.2)	0.260
C _{min,ss}	B	2.25	43.96	2.06				
n	C	2.22	40.89	2.04	C/B	99.31	(79.0, 124.9)	0.959
C _{min,ss} (ng/mL)	B	128.06	85.10					
	C	140.59	77.56					

Treatment B=Ketoconazole 400 mg QD
 Treatment C=MDL 16,455* 120 mg Q12 h + Ketoconazole 400 mg QD

Table 39.

Mean Urine Pharmacokinetic Parameters and Treatment Comparisons for MDL 16 455							
Parameter	Group	Day 0		Day 7		P Value	P Value
		Mean	SE	Mean	SE		
A ₀₋₁₂ μg	A	7933.92	14.77	11373.7	13.37		
	C	18291.68	11.67	17261.39	12.04	C, A	256.13 (215.6, 304.2)
CL _{CR} L/h	A	3.83	4n.44	3.28			
	C	3.47	35.82	3.24		C, A	98.77 (182.6, 118.2)
% of Dose Excreted (0-12 h)	A	7.11	54.03				
	C	16.35	31.66				

Treatment A=MDL 16 455A 120 mg Q12h
 Treatment C=MDL 16 455A 120 mg Q12h + Ketoconazole 400 mg QD

Table 40.

Change from Baseline in Mean and Maximum QT _c - Morganroth-Read ECG Data					
Mean QT _c					
Treatment	N*	Day 0 mean ± se	Day 7 mean ± se	Change from Day 0 to Day 7 mean ± se	P Value†
MDL 16 455A	23	398.9 ± 3.1	394.3 ± 2.7	-4.7 ± 2.2	0465
Ketoconazole	24	396.9 ± 3.3	395.0 ± 2.7	-2.0 ± 2.3	3960
MDL 16 455A + Ketoconazole	23	395.9 ± 2.9	399.0 ± 3.2	3.1 ± 2.3	1812
Maximum QT _c					
Treatment	N*	Day 0 mean ± se	Day 7 mean ± se	Change from Day 0 to Day 7 mean ± se	P Value†
MDL 16 455A	23	423.8 ± 3.9	420.5 ± 3.9	-3.3 ± 4.4	4661
Ketoconazole	24	419.9 ± 4.1	417.1 ± 2.6	-2.8 ± 4.2	5194
MDL 16 455A + Ketoconazole	23	417.2 ± 3.6	425.2 ± 3.6	8.0 ± 4.0	0597

* N=24 subjects at the beginning of the study, 2 subjects withdrew prior to completion.
 † P Value from t test that the change from day 0 to day 7 is equal to zero

The *In Vitro* Binding of MDL 16,455 to Albumin,
 α -1-Acid-Glycoprotein and Human Serum Proteins

Project Report No. K-95-0195-D **Volume** 1.40

OBJECTIVES to determine the *in vitro* protein binding of MDL 16,455 in serum from normal healthy volunteers, and its binding to albumin and α -1-acid glycoprotein (AAG).

MATERIALS

- [¹⁴C]MDL 16,455A (lot 16), 14.5 μ Ci/mg (Marion Merrell Dow Research Institute)
- Blank human plasma
- Human albumin and α -1-glycoprotein :

CONCLUSION Since MDL 16,455 is not highly protein bound, changes in AAG or albumin due to stress or various disease states should not result in clinically significant changes in MDL 16,455 protein binding or subsequent changes in drug disposition.

Protein Binding of MDL 16,455 in Normal Healthy Volunteers and in Subjects with Renal or Hepatic Impairment

Project Report No. K-95-0208-D

Volume 1.40

OBJECTIVES to determine the protein binding of MDL 16,455 in plasma samples from normal healthy volunteers and subjects with renal or hepatic impairment.

MATERIALS

- Plasma samples were selected from each dose group (40 mg, 200 mg and 400 mg BID) in protocol PJPR0007 to represent normal subjects. The 1 and 12 hour samples were obtained from each subject to represent the peak and trough portions of the pharmacokinetic profile
- From protocol PJPR0013 (renal impairment study) the 2-hour post-dose plasma samples were taken for protein binding determination from subjects with mild, moderate and severe renal impairment
- The 2-hour postdose plasma sample was obtained from subjects participating in study PJPR0021 (hepatic impairment study) to represent subjects with mild (n=7) and severe (n=2) hepatic impairment.

METHODS & RESULTS One milliliter acrylic cells and membranes with a molecular cut off of 12,000 to 14,000 daltons were used for dialysis. Plasma was dialyzed against phosphate buffer in a rotating water bath at 37°C for 16 to 18 hours. Serum was assayed for albumin in order to account for volume shifts during dialysis. Buffer and plasma portions of each dialysis cell were assayed for MDL 16,455.

The percentage of MDL 16,455 (f_b) bound to plasma protein was calculated as follows:

$$f_b = 100 \times \frac{(C_{plasma} - C_{buffer})}{C_{plasma}}$$

Normal Healthy Volunteers (PJPR0007)- The samples selected for this study had plasma peak and trough MDL 16,455 concentrations ranging from _____ respectively. Mean protein binding was _____ with no substantial differences observed when subjects were sorted by dose administered, gender or time after dosing (peak versus trough).

Subjects with Renal Impairment (PJPR0013)- The average percent of MDL 16,455 bound to plasma proteins in renally impaired patients was No substantial differences were noted between the mild, moderate and severely impaired patients.

Subjects with Hepatic Impairment (PJPR0021)- The average percent of MDL 16,455 bound to plasma proteins in hepatically impaired patients was No substantial differences were noted between moderate and severely impaired patients.

CONCLUSION These study results support the hypothesis outlined in the *in vitro* protein binding study which predicted that disease states such as renal/hepatic impairment would not significantly influence the plasma protein binding profile of MDL 16,455.

Statistical Review of Fexofenadine Pivotal BA/BE Study
(Protocol PJPR0025), NDA20-625

Biopharm reviewer: Bradley Gillespie

A. Methods

1. Study Design and Models

To compare the bioavailability of the fexofenadine solutions (treatment C) with either scale-up (treatment A) or pilot capsules (treatment B), the sponsor carried out the study with a five-period replicated cross-over design where only the two capsule formulations were replicated for each individual. For this study, the sequence of the treatments were randomly assigned to each one of the five periods for any given individual subject. The statistical behavior of these PK parameters (AUC_{0inf} and C_{max}) from the cross-over experiment can be described by a linear model with treatment effect as random. In the model, a period effect was included to eliminate any potential bias. Furthermore, the model assumed the true individual treatment effects to be random in the population and quantified these random effects using between-subject variability for each treatment and correlation among the treatments. In the model, within subject variability can also be specified as treatment dependent. Note that non-replication for the solution treatment C would not affect the evaluation of the average bioequivalence (BE) among all three treatment groups, even though it introduced confounding of the between-subject variability and the residual errors within each individual for treatment C, i.e. these two sources of variability for treatment C can not be estimated separately.

Mathematical form of the model can be written as two-levels:

- a) At the **individual subject level**, treatment effects were assumed to be fixed across 5 different periods, and the observations (of either log AUC_{0inf} or log C_{max}) from the j-th period for I-th subject y_{ij} can be expressed as:

$$y_{ij} = T_i \mu_i + P_j \tau_j + \epsilon_{ij}, \quad \epsilon_{ij} \sim N(0, \sigma_{T_j}^2)$$

where T_i is the treatment assignment vector and P_i is the period assignment vector, both determined by the design and randomization schemes; $\mu_i = (\mu_i^A, \mu_i^B, \mu_i^C)$ is the individual treatment effect vector and is assumed to be fixed for the i -th subject; τ is the period effect vector, assumed to be the same for all individuals; ϵ_{ij} is the within subject variability and model mis-specification error, the average squared size of it is represented by $\sigma_{T_{ij}}^2$ which is assumed to be treatment dependent.

- b) At the **population level**, different individuals' treatment effects $\mu_i = (\mu_i^A, \mu_i^B, \mu_i^C)$, $i=1-24$, are assumed to be randomly distributed in the population.

$$\mu_i \sim N(\mu, G), \quad \mu = \begin{pmatrix} \mu_A \\ \mu_B \\ \mu_C \end{pmatrix}, \quad G = \begin{pmatrix} \omega_A^2 & \omega_A \omega_B \rho_{AB} & \omega_A \omega_C \rho_{AC} \\ \omega_A \omega_B \rho_{AB} & \omega_B^2 & \omega_B \omega_C \rho_{BC} \\ \omega_A \omega_C \rho_{AC} & \omega_B \omega_C \rho_{BC} & \omega_C^2 \end{pmatrix}$$

where $\mu = (\mu_A, \mu_B, \mu_C)$ is the average treatment effect in the population, and $(\omega_A, \omega_B, \omega_C, \rho_{AB}, \rho_{BC}, \rho_{AC})$ is the between subject variability parameter vector, which is one of the two major components of the variability observed in y_{ij} (the other component is the within subject variability vector $(\sigma_A, \sigma_B, \sigma_C)$).

From the distributional assumption made in the above model, the square-root of the variance parameters $(\omega_A, \omega_B, \omega_C)$ and $(\sigma_A, \sigma_B, \sigma_C)$ reflect approximately the **variabilities as percentages of the corresponding averages** in the untransformed PK parameter scales, due to between-subject variability and within-subject variability, respectively. Using AUC0inf as an illustrative example, if y represents $\log(\text{AUC0inf})$, then ω_A gives approximately the between-subject variability in AUC0inf expressed as a percentage of its average for treatment A. Whereas, σ_A gives approximately the within-subject variability in AUC0inf expressed as a percentage of individual average AUC0inf for treatment A. The analysis of variance equation relates the observed (marginal) variability in AUC0inf for treatment A to the two components in an additive form on the

squared scale: $var(y_{ij}) = (\omega_i^2 + \sigma_i^2)$, i.e., %CV (observed AUC0inf) = %CV (Between-subj) + %CV (Within-subj). Similar interpretations apply to treatments B and C. The correlation coefficients, $(\rho_{AB}, \rho_{BC}, \rho_{AC})$, describe a population trend of similarities of the individual mean AUC0inf between A and B, B and C, and A and C, respectively. A ρ_{AB} value close to 1 indicates a substantial reduction in the variability of the within-subject treatment differences when compared to the between-subject variabilities in either treatments. When this is the case, a cross-over design is more efficient than a parallel design.

Two statistical questions that will be discussed next are, based on the observation y_{ij} and the treatment-period assignment schemes,

- a) are the treatment effects equivalent to each other?
- b) what are the values for the variance components, i.e. inter- and intra- subject variability?

2. Bioequivalence Tests

Under the mixed effects model, the 90% confidence interval was estimated for the difference of the log-transformed AUC0inf or Cmax values between any pair of three treatments (A, B, or C). These differences correspond to the ratios of the corresponding pairs of treatment averages for either of the two bioavailability (BA) parameters, AUC0inf and Cmax. The lower and upper limits of these 90% confidence intervals for the ratios were compared with the regulatory bioequivalence limits of 80% and 125%, respectively, for the establishment of BE. Two analysis methods, restricted maximum likelihood method (also referred to as the method of moments), were used to estimate treatment differences and the corresponding confidence intervals. PROC MIXED and PROC GLM in SAS 6.10 were used calculate the confidence intervals corresponding to these two methods, respectively.

3. Variability Assessments

The replication of the measurements of the two capsule treatments for each individual allows the estimation of between-subject variability and within-subject variability separately for treatments A and B. For treatment C, between-

and within-subject variability were non-separable (or non-identifiable) due to the non-replication of that treatment. The restricted maximum likelihood method was used to estimate the various variance components by using PROC MIXED in SAS 6.10.

B. Results

Different assumptions (unstructured and compound symmetry, see the SAS manual for the definitions) the the between-subject variability were tried on the data set. Likelihood functions for some of them were not informative enough to generate meaningful estimates, as evidenced by non-convergence of the algorithm for finding the maximum likelihood solutions.

1. AUC0inf

For the full data set, the Mixed Effect Model (REML) with unstructured variance-covariance matrix for the between-subject variability resulted in the following ratios, with corresponding 90% CI's,

A/B: 105.34 (96.9,114.5)
A/C: 108.77 (96.9,122.1)
B/C: 103.26 (92.0,115.9)

For the data set excluding subjects with severe missing data (subject number 14, 17 and 21), GLM (ANOVA) resulted in the following ratios, with corresponding 90% CI's,

A/B: 104.28 (96.8,112.3)
A/C: 107.31 (98.1,117.4)
B/C: 102.91 (94.0,112.6)

Between-subject variability (%CV)

A: 27.1%; B: 29.0%; C: 28.7% (unidentifiable); correlation between A and B: ~ 1.

Within-subject variability (%CV)

A: 24.7%, B: 18.2%, C: (unidentifiable)

2. Cmax

For the full data set, the Mixed Effect Model (REML) gives

A/B: 104.18 (93.8, 115.7)

A/C: 102.45 (90.2, 116.4)

B/C: 98.34 (86.6, 111.7)

For the data set excluding subjects with severe missing data (subject number 14, 17 and 21), GLM results are

A/B: 103.09 (93.8, 113.3)

A/C: 100.54 (89.7, 112.7)

B/C: 97.53 (87.0, 109.4)

Between-subject variability (%CV)

A: 26.5%; B: 32.8%; C: 30.6% (unidentifiable); correlation between A and B: ~ 1.

Within-subject variability (%CV)

A: 36.9%, B: 25.35%, C: (unidentifiable)

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6 OF 7

C. Conclusions

For both AUC_{0inf} and C_{max}, the 90% CI for the difference of any pair of treatments lies within 80%-125% bioequivalent limits. Hence, any pair of treatments is bioequivalent with each other at 5% significant level for both AUC_{0inf} and C_{max}.

For AUC_{0inf}, the between-subject variabilities are 27.1%, 29.0% and 28.7% for treatment A, B, and C, respectively; and the within-subject variabilities are 24.7% and 18.2% for treatment A and B, respectively. Correlation between A and B is almost 1.

For C_{max}, the between-subject variabilities are 26.5%, 32.8% and 30.6% for treatment A, B, and C, respectively; and the within-subject variabilities are 36.9% and 25.35% for treatment A and B, respectively. Correlation between A and B is almost 1.

Guangrui Ray Zhu, Ph.D
Mathematical Statistician

3/4/96

Concur:

Stella Green Machado, Ph.D
Director, QMR

3/4/96

cc:

HFD-705

HFD-855 William Gillespie, Ph.D.

HFD-870 Bradley Gillespie, Ph.D.

SEP 1 1995

Fexofenadine HCl
(Terfenadine Acid Metabolite)

NDA 20-625

Hoechst Marion Roussel, Inc.
Kansas City, MO

Type of Submission:
IS: NDA, NME
Submission Date:
7/31/95
Reviewer:
Brad Gillespie, PharmD
Purpose:
Suitability for Filing

BACKGROUND The free-base of fexofenadine HCl (MDL 16,455A) was identified as an active metabolite of terfenadine. Terfenadine has been marketed worldwide for over ten years, and is indicated for the symptomatic relief of seasonal allergic rhinitis (SAR). While elevated terfenadine levels have been associated with QTc interval prolongation, its acid metabolite fexofenadine, in animal studies, has been found to demonstrate the favorable anti-histaminic properties of the parent drug, without the undesirable adverse cardiovascular side effects. As a result of these findings, the sponsor initiated clinical studies to determine the safety and efficacy of the drug product in humans.

COMMENTS

1. The sponsor has adequately described fexofenadine's physical and chemical properties.
2. Labeling claims in the proposed package insert are clearly referenced, identifying their source bio-studies. Based on the summary volumes, labeling modifications are likely. Labeling does not provide for dosage adjustments. However, since doses of approximately 11 times the recommended dose have been given for up to 1 month without the development of clinically significant adverse events, a single dose for all adult patients is probably appropriate.
3. The sponsor proposes to market a single 60mg capsule. Composition information for the to-be-marketed as well as the clinical and bio-lots have been detailed by the sponsor.
4. Range specifications for inactive ingredients are not included in the biopharmaceutics portion of the submission.
5. Six pivotal clinical safety and efficacy studies utilized a combination of 20, 40 and 60mg capsules. The composition of the granulation formulation was identical in all six studies, only the size of the capsule and the amount of fill differed. Four of the studies used pilot-sized batches (PJPR 0009: lots RN9323 & RA9404, PJPR 0010: lots RN9323 & RA9404, PJPR 0014: RA9404 & RB9434 and PJPR 0024: lots RB9434 & RF9422), while a fifth and sixth (PJPR 0023: RF9414; PJPR

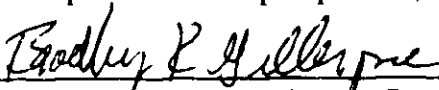
0017: RH9411) utilized production-sized batches. Two key drug interaction studies (PJPR 0018: erythromycin and PJPR 0028: ketoconazole) used lot RH9411, a production-scaled batch. The majority of the remaining clinical studies utilized an oral solution of fexofenadine in 1.5% glacial acetic acid and 98.5% propylene glycol. The pivotal bioequivalence study (PJPR 0025) compared this solution (lot 73048) to pilot- (lot RN9323) and full production-scaled (lot RF 9414) batches.

6. As in the clinical studies, the bio-studies mainly utilized a combination of oral solutions, pilot-sized capsule batches and 60mg production-scaled capsule batches. It should be noted that the same granulation formulation was used in both pilot- and production-scaled batches. Further, the pivotal bioequivalence study compared batches of both scales.
7. The sponsor performed a multiple-dose radiolabel study of terfenadine and fexofenadine to describe the ADME of fexofenadine and compare it to its parent, terfenadine. More than 70% of the unchanged drug was identified in the urine and feces. Only minor metabolic products were detected. Possible fexofenadine conjugates, terfenadine and its alcohol intermediate metabolite, MDL 17,523, were not detected.
8. The relative bioavailability of the to-be-marketed capsule formulation was assessed in the pivotal bioequivalence study.
9. The sponsor has evaluated the multiple-dose pharmacokinetics of this product in the to-be-marketed, 60mg twice daily regimen.
10. Single- and multiple-dose dose proportionality studies were performed covering the proposed dosage regimen.
11. The label does not specify whether the drug should be taken in a fed or fasting state. The sponsor has completed a single-dose study utilizing a production-sized batch (lot RF9422) to assess a possible food effect.
12. The sponsor has submitted the results of three separate PK/PD studies (wheal and flare and QTc interval prolongation).
13. Drug interaction studies with erythromycin and ketoconazole have been submitted. These interaction studies should be sufficient.
14. The sponsor has performed single-dose special population studies examining the use of fexofenadine in elderly, renally and hepatically impaired subjects. These studies adequately cover the populations described in the labeling. Studies were also performed that are capable of assessing any gender effect.

15. Plasma protein (albumin and α -1-acid glycoprotein) binding was assessed in healthy, renally and hepatically impaired subjects. The sponsor has also compared drug distribution in plasma, whole blood and saliva.
16. The sponsor has thoroughly described and validated the assay methods used in each bio-study. Further, the sponsor has adequately studied the stability of the analytes in all of the applicable biological matrices and under various experimental conditions. Lastly, the sponsor has conducted a cross-laboratory validation study across the three major analytical facilities utilized.
17. The data analysis and statistics performed meet the Division of Biopharmaceutics criteria.
18. The sponsor has optimized a dissolution method by performing dissolution testing in multiple media. Their final dissolution method is adequately described.
19. On its face, the biopharmaceutics section of NDA 20-625 is organized, paginated and is adequately legible to allow substantive review.

Recommendation

The Division of Biopharmaceutics has reviewed NDA 20-625 for the purpose of suitability for filing. Overall, from a biopharmaceutic perspective, this submission is fileable.


Bradley K. Gillespie, Pharm.D.

FT Mehta 9/1/95
Mehul Mehta, Ph.D., Section Head

cc:

HFD-155 (NDA 20-625)
HFD-155 (Divisional File)
HFD-155 (Lee)
HFD-155 (Sevka)
HFD-426 (Mehta)
HFD-426 (Fleischer)
HFD-426 (Chron)
HFD-426 (Reviewer File)
HFD-426 (Gillespie, Bradley)
HFD-340 (Viswanthan)
HFD-019 (FOI)

JUN 24 1996

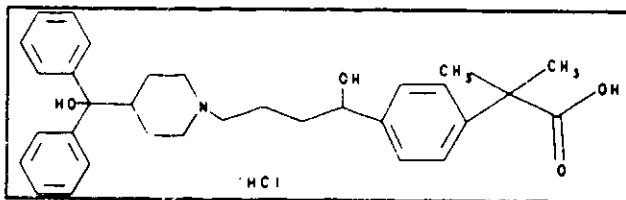
**DIVISION OF PULMONARY DRUG PRODUCTS
EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
REVIEW**

NDA 20-625**Date of Submission:** 7/31/95**Information to be Conveyed to Sponsor:** YES (X), NO ()**Reviewer:** Lawrence F. Sancilio, Ph.D.**Date Review Completed:** 6/24/96

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Drug Name: Fexofenadine HCl, MDL 16,455A, TAM (terfenadine active metabolite)
MDL 9,918 (terfenadine)

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)-1-piperidiny]butyl'- α,α -dimethyl-, hydrochloride salt $\pm$

Structure:**Molecular Weight:** 538.13, C₃₂H₃₉NO₄·HCl**CAS No.:** 138452-21-8**Related INDs and NDAs:** IND (fexofenadine HCl), NDA 18-849 (terfenadine)**Pharmacological Class:** H1 receptor blocker

Indication: Treatment of Seasonal Rhinitis

Route: Oral

Formulation: 60 mg capsule containing croscarmallose sodium, gelatin, lactose, microcrystalline cellulose and pregelatinized starch.

Amended Reviews, Reviewer Dates:

NDA 19-949, Terfenadine, C. G. Oberlander. 4/28/83

Com

IND

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IND

Background

Fexofenadine is the active metabolite of terfenadine, a marketed H₁ receptor blocker with little or no sedative properties. The uniqueness of fexofenadine is that unlike terfenadine, fexofenadine does not prolong QT_c intervals or inhibit the delayed rectifier potassium current channel. Consequently, fexofenadine is unlikely to produce Torsades de point, a cardiac arrhythmia seen in terfenadine patients under certain conditions.

List of Unpublished Reports and Pertinent Preclinical Articles Submitted

PHARMACOLOGY

The following were reviewed.

1. Mechanism of the cardiotoxic actions of terfenadine, JAMA 1993;269:1532-1536, vol. 16, p P174.
2. Interactions of the nonsedating antihistamines astemizole and loratadine with a voltage-dependent K⁺ channel cloned from human heart, No. C-94-0645-D, vol. 16, p 207.
3. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol. Immunotoxicol. 9:257-279, 1987, vol. 16, p 220.
4. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs, Ann Allergy 56:464-469, 1986, vol. 16, p 379.

The following were not reviewed since they were previously reviewed or were not relevant.

Second-generation H1-receptor antagonists, *Annals of Allergy* 1991; 66:5-19, vol. 15, p 79 .

Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: *The Pharmacological Basis of Therapeutics*, 7th ed., Gilman AG, Goodman LS, Rall TW, and Murad F, ed. MacMillan Publishing Co., New York, 1985, vol. 15, p 95.

Cardiotoxic effects with convulsions in terfenadine overdose, *Br Med J*. 1989:298, vol. 15, p 133.

Pharmacokinetics and biotransformation studies of terfenadine in man, *Arzneim-Forsch/Drug Res*. 1982,32: 1185-1190, vol.15 p 133.

Effects of intravenous infusion of terfenadine and MDL 16,455A on QTc interval in anesthetized rabbits, N. C.-93-0235-R, vol. 15, p 140.

Effect of intravenous terfenadine infusion on QTc interval in anesthetized dogs, No. C-93-0234-R, vol. 16, p 180.

Effect of repeated ascending doses of terfenadine and MDL 16,455A, the acid metabolite of terfenadine, on the electrocardiogram of dogs, No. C-93-0248-R, vol. 15, p 164.

Effect of terfenadine, MDL 16,455A, and the stereoisomers MDL 15,171 and MDL 15,172 on action potential and membrane currents in guinea pig ventricular cells, No. C-91-0084-R, vol. 15, p 193.

Time course of the antihistaminic effects of MDL 16,455A and terfenadine on histamine skin wheals in guinea pigs, No. C-93-0145-R, vol. 15, p 206.

Oral effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. C-84-0054-R, vol. 15, p 218 .

The effects of MDL 16,455A on the vascular effects of histamine and phenylephrine in the dog hindlimb preparation, No. C-84-0068-R, vol. 15, p 233.

The effects of terfenadine or chlorpheniramine on the vascular effects of phenylephrine and histamine in the dog hindlimb preparation, No. C-83-0054-R, vol. 15, p 245.

Antagonism of histamine-induced bronchoconstriction by MDL 9,918 and MDL 16,455A in anesthetized guinea pigs, No. C-93-0215-R, vol. 15, p 260.

Competitive receptor binding studies with MDL 16,455A and its enantiomers to rat brain

histamine-H1 receptors, No. C-93-0247-R, vol. 15, p 271.

Antihistaminic effect of MDL 16,455A, a major metabolite of terfenadine, No. C-84-0066-R, vol. 15, p 279.

Primary CNS evaluation of MDL 16,455A, No. C-93-0233-R, vol. 15, p 1.

General pharmacology of an antiallergic drug terfenadine, No. J-92-0010-R, vol. 16, p 11.

Effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. C-84-0067-R, vol. 16, p 121.

Effect of MDL 16,455A on the isolated guinea pig ileum, No. C-77-0015-R, vol. 16, p 132.

Effect of RMI 16,218A on the isolated guinea pig ileum. A comparison with terfenadine, No. C-77-0014-R, vol. 16, p 146.

Block of a human delayed rectifier K⁺ channel by terfenadine and its metabolites, No. C-93-0182-R, vol. 16, p 165 .

Cumulative dose-response curves: Technique for the making of dose-response curves in isolated organ and the evaluation of drug parameters. Arch Int Pharmacodyn Ther 1963;143:299-330, vol.15, p 304.

PHARMACOKINETICS

Absorption/Excretion

1. Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. J-91-0005-D, vol. 19, p 277.

Distribution

1. Tissue distribution of radioactivity in the rat following a single oral dose of [¹⁴C]MDL 16,455A, No. K-93-0668-D, vol. 16, p 244.

2. One-month dietary pharmacokinetic study of terfenadine in CD-1 mice (PK 206), No. K-93-0411-D, vol. 17, p 259

3. One-month dietary pharmacokinetic study of terfenadine in Sprague-Dawley rats (PK 233), No. K-93-0409-D, vol. 17, p 275.

4. Terfenadine and fexofenadine plasma concentrations following a 10 mg/kg oral dose of terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol. 19-P123

Metabolism

1. Incubation of fexofenadine with rat and human hepatic microsomes, No. K-93-0186-D, vol. 20, p 202.

The following were not reviewed since they were previously reviewed or were not relevant.

Plasma concentrations of MDL 16,455 in male and female Sprague-Dawley rats given a single 5 g/kg oral suspension doses of MDL 16,455A (PK-236), No. K-93-0364-D, vol. 17 p 86.

Acute oral toxicity of MDL 16,455A administered to dogs, No. C-90-0240-T, vol. 17, p 101.

Plasma concentrations of MDL 16,455 in female Beagle Dogs given a 500 mg/kg oral suspension dose of MDL 16,455A (PK-235), No. K-93-0370-D, vol. 17, p 114.

Plasma concentration of MDL 16,455 and terfenadine in Beagle dogs given 80 mg/kg/day capsule doses of terfenadine for one month (PK 234), No. K-93v0431-D, vol.17, p 292.

Maternal and fetal plasma concentrations of MDL 16,455 and terfenadine in Sprague-Dawley rats given daily 300 mg/kg oral doses of terfenadine (PK-251), No. K-94-0222-D, vol. 18, p 1.

Maternal and fetal plasma concentrations of MDL 16,455 and terfenadine in Dutch-Belted rabbits given daily oral 300 mg/kg doses of terfenadine (PK-250), No. K-94-0159-D, vol., 18 p 27.

MDL 16,455, MDL 17,523, and terfenadine in mouse plasma, No. WARS-2135V, vol.18, p 186.

The pharmacokinetics and oral bioavailability of MDL 16,455A in Sprague-Dawley rats, No. K-93-0442-D, vol. 19, p 54.

The bioavailability and urinary excretion of terfenadine acid metabolite (MDL 16,455A) and terfenadine in Sprague-Dawley rats, No. K-93-0071-D, vol. 19, p 80.

Terfenadine and Fexofenadine plasma concentrations following a 10 mg/kg oral dose of Terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol.19, p 123.

A comparison of the absorption and elimination of oral MDL 16,455A and terfenadine in Beagle dogs, No. K-93-0145-D, vol. 19, p 141.

Plasma concentrations of MDL 16,455 in Beagle Dogs given 90, 300, or 900 mg/kg/day oral doses of MDL 16,455A in a one-month toxicity study (TI93-033), No. K-93-0460-D, vol. 19, p 195.

Physiological parameters in laboratory animals and humans, Pharm Res. 10:1093-1095,1993, vol. 19, p 216.

Metabolism studies on terfenadine (II), No. J-94-0006-D, vol.19, p 220.

Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. 91-0005-D, vol. 19, p 277.

Protein binding of MDL 16,455 in serum of healthy, drug-free human subjects, No. C-88-0198-D, vol. 20, p 2i.

Metabolic disposition of terfenadine in laboratory animals.
Arzneim-Forsch/Drug Res. 32(11):1173-1178, 1982, vol. 20, p 11.

Pharmacokinetics, p 238. In: Drugs and the pharmaceutical sciences,
ed. James Swarbrick. 1975:vol 1, vol. 6, p 18.

Predicted human whole body and tissue exposures to radioactivity from an oral dose of ¹⁴C-labeled terfenadine, No. K-93-0470-D, vol. 20, p 46.

Metabolic studies on terfenadine (I): Absorption, distribution, metabolism and excretion in rats, No. J-94-0005-D, vol. 20, p 58.

Marion Merrell Dow Inc., No. K-93-0186-D, vol. 20, p 202.

Relative Bioavailability of MDL 16,455 from Two Oral Suspension Formulations in Dogs, No. K-95-0092-D, vol. 20, p 272.

Validation of a method based on liquid chromatography with fluorescence detection for quantification of fexofenadine and terfenadine in rat plasma, No. K-93-0634-D, vol. 20, p 295.

Validation of a method based, on liquid chromatography with fluorescence detection for quantification of fexofenadine and terfenadine in dog plasma, No. K-93-0500-D, vol. 20, p 327.

Validation of a method based on liquid chromatography with fluorescence detection for quantification of terfenadine in rat and dog urine, No. K-95-0441-D, vol. 20, p 361.

The pharmacokinetics and oral bioavailability of MDL 16,455A in Sprague-Dawley rats, No. 93-0442-D, vol. and page number not given.

TOXICOLOGY

Genotoxicity

1. MDL 16,455A: Mutagenicity test in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay, No.K-94-059-T, vol. 18, p 51.
2. MDL 16,455A: Evaluation of the Chinese Hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, No. K-94-0621-T, vol.18, p 80.
3. MDL 16,455A: Evaluation of an in vitro chromosomal aberration assay utilizing rat lymphocytes, No. K-9k-062-T, vol. 18, p 118.
4. MDL 16,455A: Evaluation in the mouse bone marrow micronucleus test, No. K-94-0635-T, vol. 18, p 151.

The following were not reviewed since they were previously reviewed or were not relevant.

Acute oral study with MDL 16,455, terfenadine metabolite I, in mice.
No. J-2-0020-T, vol. 17, p 54.

Acute oral toxicity of MDL 16,455A in mice and rats, No. C-90-0241-T, vol. 17, p 68.

Acute oral toxicity of MDL 16,455A administered to dogs. Project Report C-90-0240-T, vol. 17, p 101.

MDL 16,455A: Exploratory acute oral toxicity study in Beagle dogs No. -934046-T, vol. 17, p 129.

Fexofenadine: Two-week oral tolerance screen in Beagle dogs, No. 93-0048-T, vol. 17, p 143.

Fexofenadine: One-month oral toxicity study in Beagle dogs, 93-0051-T, vol.17 p 154.

REVIEW

PHARMACOLOGY

1. Mechanism of the cardiotoxic actions of terfenadine, JAMA 1993;269:1532-1536, vol. 16, p 174.

Episodes of Torsades de pointes in humans are the result of a quinidine like action. This was attributed to blockade of the delayed rectifier potassium current. Terfenadine like quinidine blocked the potassium current in isolated feline myocytes while its metabolite, fexofenadine, was inactive at concentrations up to 5 μ M which is up to 30 times higher than that of terfenadine which produces a half maximal inhibition of the delayed rectifier potassium current in isolated feline myocytes.

2. Interactions of the nonsedating antihistamines astemizole and loratadine with a voltage-dependent K⁺ channel cloned from human heart, No. C-94-0645-D, vol. 16, p 207.

Using a delayed rectifier K⁺ channel (fHK) cloned from the human heart, both astemizole and loratadine blocked the K⁺ channel fHK with an IC₅₀ of 1 μ M. However, the two drugs differed in their effect on current deactivation. Astemizole like terfenadine in a time dependent manner slowed current deactivation while loratadine did not affect the current deactivation.

3. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol. Immunotoxicol. 9:257-279, 1987, vol. 16, p 220.

The activity of terfenadine on immediate hypersensitivity reactions were compared with its 2 metabolites, fexofenadine and Metabolite II. The results are shown in the following table.

Model	Route	Potency (Terfenadine: 1)		
		Fexofenadine	Metabolite II	Ketotifen
Passive Cutaneous Reaction in Rats	p.o.			2
Antigen-Induced Bronchospasm in Guinea Pigs	p.o.	0.5	0.07	2.5
Histamine Release from Rat Mast Cells Induced by Compound 48/80	in Vitro	0.33	Inactive at 100 μ M	0.1

Model	Dose /Concentration Activity Was Noted	
	Terfenadine	Ketotifen
Antagonism of ^{45}Ca Uptake of Mast Cells Induced by Compound 48/80	2-10 μM	Not Tested
↑ Cyclic AMP Levels Rat Mast Cells	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
Guinea Pig Lungs	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
↑ Adenylate Cyclase Levels Rat Lung, Ex Vivo	5-20 mg/kg p.o.	Inactive at 20 mg/kg p.o.
Phosphodiesterase Activity Rat Lung, Ex Vivo	Inactive at 20 mg/kg p.o.	Inactive at 20 mg/kg p.o.

4. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs, Ann Allergy 56:464-469, 1986, vol. 16, p 379.

Terfenadine and fexofenadine and not Metabolite II at 10 μM inhibited Ca release from stored intracellular Ca. This was shown with mast cells who require Ca ions to release histamine. Consequently, in a calcium free media the Ca comes from released stored intracellular Ca. By blocking the release of histamine induced by Compound 48/40 in a Calcium free medium, terfenadine and fexofenadine thus exert their effect by inhibiting the release of stored Ca.

Summary of Pharmacology (Reviewed Reports/Articles)

Fexofenadine was different from terfenadine as it did not inhibit the delayed rectifier current in isolated feline myocytes at a concentration (5 μM) that was 30 times higher than an effective concentration of terfenadine. Terfenadine was similar to astemizole and different from loratidine on their effects on the voltage- dependent K⁺ channel cloned from the human heart. Although all 3 drugs inhibit this channel at 1 μM , terfenadine like astemizole slowed the current deactivation while loratidine showed no effect on the current deactivation.

Studies were conducted with terfenadine and its 2 metabolites, fexofenadine and Metabolite II. Orally, terfenadine was twice as potent as fexofenadine and 14 times as potent as Metabolite II in protecting guinea pig from anaphylactic shock. Terfenadine was 3 times as potent as fexofenadine in inhibiting Compound 48/80 induced release of histamine from rat mast cells. Metabolite II was inactive in this model. Studies showed that terfenadine inhibited the release

of histamine by terfenadine and fexofenadine by inhibiting the release of intracellular Ca^{++} . Terfenadine was different from ketotifen since it 1. antagonized the increased uptake of Ca^{++} of mast cells induced by Compound 48/80, 2. increased the cyclic AMP levels of rat mast cells and guinea pig lungs and 3. increased the adenylate cyclase levels of rat lungs ex vivo. Both terfenadine and ketotifen were not phosphodiesterase inhibitors.

PHARMACOKINETICS

Absorption/Excretion

1. Pharmacokinetics in Beagle dogs following oral administration of terfenadine, No. J-91-0005-D, vol. 19, p 277.

Method

M Beagle dogs (12-13 kg) were given a 60 mg tablet of terfenadine. Blood samples were drawn at 0.5, 1, 2, 3, 4, 6, 10, and 24 h. Urine and feces were collected at 24 h for 72 h.

Results

Plasma level for terfenadine was less than 50 ng/ml; no terfenadine was found in the urine and fecal excretion accounted for 0.8% of the dose. The results for the 2 major metabolites, fexofenadine and MDL 4829 (N-dealkylated terfenadine), are summarized in the following table.

Parameter	Fexofenadine	MDL 4829
C _{max} , ng/ml	1770	71
T _{max} , h	2.7	2.5
AUC _{0-24h} , ng.h/ml	13263	857
T _{1/2} , h	2.0	12.0
Excretion, % of Dose		
Urine	0-24 h, 3.7% 24-72 h, 0.4%	0-24 h, 6.8% 24-48 h, 1.6% 48-72 h, 0.3
Feces	0-24 h, 34% 24-48 h, 14% 48-72 h, 2%	0-72 h, 0.8%

Conclusion

In beagle dogs, approximately 5 mg/kg p.o. (1 x 60 mg tablet), of terfenadine was rapidly metabolized predominantly to fexofenadine and to minor degree to the N-dealkylated terfenadine. Very little or no terfenadine was found in the plasma, urine and feces. The primary excretory route for the metabolite, fexofenadine, was fecal in contrast to urinary for the N-dealkylated metabolite.

Distribution

1. Tissue distribution of radioactivity in the rat following a single oral dose of [14C]MDL 16,455A, No. K-93-0668-D, vol. 16, p 244.

Ten mg/kg of radioactive fexofenadine were administered by gavage as a single dose to M Sprague-Dawley and Long Evans rats. At various periods up to 72 h, animals were sacrificed and plasma levels and tissues were analyzed for radioactivity. In the Sprague-Dawley rat 23 tissues were examined while in the Long Evans rat levels were determined only in the plasma, eyes, skin (pigmented area) and erythrocytes. The results are summarized in the following table.

Parameter	Sprague Dawley Rat	Long Evans Rat
C_{max} , $\mu\text{g equiv./ml}$	0.019	0.049
AUC_{0-TF}^a , $\mu\text{g equiv.} \times \text{hr/ml}$	0.092	0.179
$T_{1/2}$, terminal, hr	13.3	1.42
Highest Concentration of Radioactivity		
AUC_{0-TF}^a $\mu\text{g equivalents} \times \text{hr/g}$		
Stomach	105	
Small Intestine	149	
Large Intestine	119	
Liver	9.8	
Excretion, 0-72 hr		
% of Radioactive Dose		
Urine	0.87	1.5
Feces	91.7	90.2

^a AUC from the time 0 to the last measurable C^{14} concentration

2. One-month dietary pharmacokinetic study of terfenadine in CD-1 mice (PK 206), No.K-93-0411-D, vol. 17, p 259

Method

Animals: M (26-32 g) and F (24-29g) CD mice were used.

Compound: Terfenadine (Lot No. Z 0575-007)

Formulation: Terfenadine was administered in the diet at a daily dose of 150 mg/kg; this dose was the HD in the carcinogenicity study.

Plasma Levels: Blood from 12 mice/sex was obtained at 4 h intervals from 8 PM on day 30 to 4 PM on day 31. Concentrations of terfenadine and 2 metabolites, fexofenadine and MDL 17523 were determined from the plasma by HPLC with fluorescence detection. The lower quantification limit for each compound was 25 ng/ml in a sample volume of 0.2 ml.

Results

The results are summarized in the following table.

Compound	C _{max} , ng/ml		AUC _{24h} ng.h/ml	
	M	F	M	F
Terfenadine	< 25	< 25	a	a
Fexofenadine	355	689	5,655	11,444
MDL 17523	< 25	< 25	a	a

^aCould not be determined due to undetectable levels

Conclusion

In a 30 day dietary administration of 150 mg/kg terfenadine to mice, no detectable levels of terfenadine or one of its metabolites, MDL 17523, was detected. Fexofenadine, another metabolite, was found in high levels. The C_{max} and AUC_{24h} in the F were approximately 2 x those found in M.

3. One-month dietary pharmacokinetic study of terfenadine in Sprague-Dawley rats (PK 233), No. K-93-0409-D, vol. 17, p 275.

Method

Animals: M (232-275 g) and F (159-201 g) CrI:CD (SD)BR (VAF/PLUS) rats were used.

Compound: Terfenadine (Lot No. 70733)

Formulation: Terfenadine was administered in the diet at a daily dose of 150 mg/kg; this dose was the HD in the carcinogenicity study.

Plasma Levels: Blood from 3 rats/sex was obtained at 4 h intervals from 8 PM on day 28 to 8 PM on day 29. Concentrations of terfenadine and its metabolite, fexofenadine, were determined from the plasma by HPLC with fluorescence detection. The lower quantification limits were 5 ng/ml for fexofenadine and 10 ng/ml for terfenadine in a sample volume of 0.5 ml.

Results

The results are summarized in the following table.

Compound	C _{max} , ng/ml		AUC _{24h} ng.h/ml	
	M	F	M	F
Terfenadine	96	152	1,175	^a
Fexofenadine	675	702	11,618	9,091

^a Could not be determined since the levels in many animals were not detectable.

Conclusion

In a 30 day dietary administration of 150 mg/kg terfenadine to rats, the plasma levels for fexofenadine were in both sexes markedly higher than those seen with terfenadine. The respective C_{max}s and AUC_{24h}s for fexofenadine were essentially similar in both sexes.

4. Terfenadine and fexofenadine plasma concentrations following a 10 mg/kg oral dose of Terfenadine in male Sprague-Dawley rats, No. K-93-0528-D, vol. 19, p 123.

Method

Terfenadine at 10 mg/kg was administered by gavage as a micellar solution to M Sprague-Dawley rats. Groups of 3 rats were sacrificed at 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 14, 18, and 24 h and the plasma assayed for terfenadine and fexofenadine.

The results are shown in the following table.

Parameter	Terfenadine	Fexofenadine
C _{max} , ng/ml	35.7	257
T _{max} , h	1.5	1.5
AUC _{0-∞} , ng.h/ml	61.3	683.8

Conclusion

In rats terfenadine was administered as a micellar solution at dose of 10 mg/kg p.o. It was

rapidly metabolized to fexofenadine since at 1.5 h, the plasma level of fexofenadine was approximately 7 x higher than the parent compound. In addition the AUC for fexofenadine was approximately 10 x higher that for terfenadine.

Metabolism

1. Incubation of fexofenadine with rat and human hepatic microsomes, No. K-93-0186-D, vol. 20, p 202.

Method

Fexofenadine (30 μ M) was incubated with microsomes from rats for 2 h and from humans 1 h. The rat microsomes were from untreated animals and from animals treated with dexamethasone to induce P-450 enzymes. Human microsomes were obtained from 2 normal volunteers. They were characterized for P-450 enzymes.

Results

The results are summarized in the following table.

Microsome Preparation	Results
Rat Untreated, naive (2 h incubation)	No change in fexofenadine substrate
Dexamethasone-treated (1 h incubation)	No change in fexofenadine substrate; Vehicle controls showed a chromatographic peak which co-eluted with MDL 4829 (N-dealkylated fexofenadine). Mass spectroscopy was not performed to confirm the presence of MDL 4829.
Human Untreated, naive (1 h incubation)	8% decrease in fexofenadine substrate; a small peak related to MDL 4829 was detected.

Conclusion

In human microsomes and possibly in rat microsomes, fexofenadine undergoes oxidative dealkylation at a very slow rate.

Summary of Pharmacokinetics

In Beagle dogs receiving approximately 5 mg/kg p.o. (1 x 60 mg tablet) of terfenadine, rapid and complete metabolism occurred since little or no detectable levels of parent compound were found. Two metabolites, fexofenadine and MDL 4829, *N*-dealkylated terfenadine, were found in the plasma, urine and feces. Fexofenadine was the prominent metabolite as its $AUC_{0-24\text{ h}}$ was 15 x higher than that for MDL 4829. Fexofenadine excreted mainly in the feces accounted for 50 % of the dose. Most of excretion of MDL 4829 which accounted for 8% of the dose was urinary.

Following the administration of a single dose of 10 mg/kg p.o. of radiolabeled fexofenadine to Sprague-Dawley and Long Evans rats, The C_{max} in the Long Evans rat was higher than that in the Sprague-Dawley rat; however, the reverse was seen with their AUCs. The terminal half life in the Sprague-Dawley rat was approximately twice that of the Long Evans rat. In distribution studies, the highest levels based on AUC, terfenadine was seen in the small intestine, large intestine, stomach and liver. None of the assayed tissues from the Long Evans rats showed any radioactivity indicating that fexofenadine was not distributed to any degree in the eyes, skin and erythrocytes. In both strains, excretion was predominantly in the feces as > 90% of the total radioactivity was found in the feces.

In Sprague-Dawley rats terfenadine was administered 10 mg/kg p.o. as a micellar solution. Terfenadine was rapidly metabolized to fexofenadine as the C_{max} and $AUC_{0-\infty}$ for fexofenadine were approximately 7 x and 10 x that of terfenadine, respectively.

Two dietary 30 day pharmacokinetics studies of terfenadine were conducted in mice and rats. Both species received a daily dose of 150 mg/kg p.o., the dose used in the carcinogenicity studies. In the mouse, terfenadine was metabolized predominantly to fexofenadine since no detectable levels of terfenadine and MDL 17523 were found in the plasma on day 30. F showed an $AUC_{24\text{ h}}$ and C_{max} that were approximately twice those in the M.

In rats, the plasma was assayed for terfenadine and fexofenadine. The C_{max} s for fexofenadine were similar in both sexes; they were approximately 5-7 x higher than terfenadine. However, the $AUC_{24\text{ h}}$ s of fexofenadine although similar in both sexes, were 10 x that for terfenadine in the M. However, the $AUC_{24\text{ h}}$ for terfenadine in the F could not be determined since in many animals, terfenadine levels were not detectable indicating the it was metabolized faster in the F than in the M.

TOXICOLOGY

Genotoxicity

1. MDL 16,455A: Mutagenicity test in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay, No.K-94-059-T, vol. 18, p 51.

GLP signed statement: Yes

Study Dates: 3/23/94-4/25/94.

Site the study was conducted: Hazelton Washington, Inc., Vienna, Va.

Method

Organisms: Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2uvrA. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor.

Positive Controls are listed in the following table:

Organism	With S9, Conc. ($\mu\text{g}/\text{plate}$)	Without S9, Conc. ($\mu\text{g}/\text{plate}$)
<u>Salmonella typhimurium</u>		
TA98	2-Aminoanthracene, (2.5)	2-Nitrofluorene (1.0)
TA100	2-Aminoanthracene, (2.5)	Na azide, (2.0)
TA1535	2-Aminoanthracene, (2.5)	Na azide, (2.0)
TA1537	2-Aminoanthracene, (2.5)	ICR-191 (2.0)
<u>Escherichia coli</u>		
WP2uvrA	2-Aminoanthracene, (25)	N-Nitroquinoline-N- oxide, (1.0)

With each organism the tests were conducted twice in triplicate for the test compound and in duplicate for the positive controls. The response to the positive control should be a 3-fold increase in the number of revertants per plate over that of the vehicle. A positive response and a valid assay were a reproducible dose response and ≥ 3 X increase in the number of revertant colonies with more than 1 dose.

Compound: Fexofenadine Lot No. 73038

Test for Cytotoxicity: For TA100 and WP2uvrA, 10 concentrations ranging from 6.67 μg - 5000 $\mu\text{g}/\text{plate}$ were tested. Cytotoxicity was seen at 3330 and 5000 $\mu\text{g}/\text{plate}$ (33-37%) in the absence of S9 and at 5000 $\mu\text{g}/\text{plate}$ (15%) in the presence of S9.

Concentrations: 100, 333, 667, 1000 and 3300 $\mu\text{g}/\text{plate}$ in the presence and absence of S9 mix for each organism.

Vehicle: Dimethylsulfoxide

Results

Fexofenadine, was not genotoxic in the presence and absence of S9 mcg/plate. The respective positive controls produced more than a 3 fold increase in the number of revertant colonies.

Conclusion

Fexofenadine was not mutagenic in the bacterial assay. This was a valid and acceptable assay.

2. MDL 16,455A: Evaluation of the Chinese Hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, No. K-94-0621-T, vol.18, p 80.

GLP signed statement: Yes; Fexofenadine sample was not audited.

Study Dates: 2/15/94-8/26/94.

Site the study was conducted: Health and Environmental Services, The Toxicology Research Laboratory, Midland, Michigan

Method

Chinese hamster CHO-K₁-BH₄ cell line was used. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor.

Vehicle: Dimethylsulfoxide

Test Compound: Fexofenadine (Lot No. 73038)

Positive Controls are listed in the following table:

With S9, Conc. ($\mu\text{g/ml}$)	Without S9, Conc. ($\mu\text{g/ml}$)
20-Methylcholanthrene, 4	Ethylmethane sulfonate, 621

An acceptable test was a statistical increase in the mutation frequency by the positive control, and the mutation frequency in the negative controls should be within the historical controls. Test compound is positive if it produces a statistical significant, dose related, reproducible increase in mutation frequency. Tests were conducted in duplicate whenever possible at each concentration.

Cytotoxicity Study: 200 cells/petri dish; concentrations tested, 218.75-3500 $\mu\text{g/ml}$ (5 concentrations with and without S9. No cytotoxicity was noted at the concentrations tested.

Results

The highest concentration, 3500 $\mu\text{g/ml}$, in the absence and presence of S9, showed a 10.3% and 24.2% of control cell survival. The test compound showed no mutagenicity under both conditions and the positive control showed a high number of revertant cells. This was a valid and acceptable assay.

Conclusion

Fexofenadine was not mutagenic in the Chinese Hamster (CHO/HGPRT) forward mutation assay.

3. MDL 16,455A: Evaluation of an in vitro chromosomal aberration assay utilizing rat lymphocytes, No. K-9k-062-T, vol. 18, p 118.

GLP signed statement: Yes; Fexofenadine sample was not audited.

Study Dates: 2/15/94-8/26/94.

Site the study was conducted: Health and Environmental Services, The Toxicology Research Laboratory, Midland, Michigan

Method

Lymphocytes were taken from M Sprague-Dawley rats, 13-15 weeks old. At each concentration the number of cells/assay were 200 for the test compound and 100/ positive

control. Liver microsomal enzyme reaction mix (S9 mix) was prepared from M Sprague-Dawley rats injected i.p. with Aroclor. Two complete assays were conducted, a preliminary and confirmatory test. In the preliminary test the cells were harvested at 24 h after treatment while in the confirmatory test, the cells were harvested at 24 and 48 h post treatment.

Vehicle: Dimethylsulfoxide

Test Compound: Fexofenadine (Lot No. 73038)

Positive Controls are listed in the following table:

With S9, Conc. ($\mu\text{g/ml}$)	Without S9, Conc. ($\mu\text{g/ml}$)
Cyclophosphamide, 6	Mitomycin, 0.5

An acceptable test was a statistical increase in the chromosomal aberration frequency by the positive control, and the chromosomal aberration frequency in the negative controls should be within the historical controls. Test compound is positive if it produces a statistical significant, dose related, reproducible increase in chromosomal aberration frequency. Each test was conducted in triplicate.

Mitotic Indexes were determined in both tests. Concentrations tested, Assay 1, 35, 116.7, 350, 1167 and 3500 $\mu\text{g/ml}$ with and without S9. Assay 2, 350, 1167, 3000 and 3500 $\mu\text{g/ml}$ with and without S9.

Results

Mitotic Index (MI): Assay 1: At 3500 $\mu\text{g/ml}$ the MI was reduced by 70% in the absence of S9 and 96.6% in the presence of S9. Assay 2: At 3500 $\mu\text{g/ml}$ the MI was reduced by 65% and 100% in the absence of S9 at 24 and 48 h, respectively. At 3000 and 3500 $\mu\text{g/ml}$ in the presence of S9, the MI was reduced by 100% at 24 and 48 h. At 1167 $\mu\text{g/ml}$, the MI was reduced by 13% at 24 and 36% at 48 h.

Chromosomal Aberration: Assay 1 and 2: No chromosomal aberration was noted in the absence of and presence of S9. In both tests the positive controls showed a marked increase in the number of chromosomal aberrations in the absence and presence of S9. The assay was valid and acceptable.

Conclusion

Fexofenadine was not clastogenic in the lymphocyte chromosomal aberration assay.

4. MDL 16,455A: Evaluation in the mouse bone marrow micronucleus test, No. K-94-0635-T, vol. 18, p 151.

GLP signed statement: Yes

Study Dates: 2/5/94-9/2/94

Site the study was conducted: Health and Environmental Services, The Toxicology Research Laboratory, Midland, Michigan

Method

Animals: 9 Week old M and F CD-1 Charles River mice (5/sex/group).

Test Compound: Fexofenadine (Lot No. 73038)
Positive Control: Cyclophosphamide

Formulation: Suspension containing 0.5% Methocel/ 0.5% Tween 80, 20 ml/kg for vehicle and fexofenadine treated animals and 10 ml/kg for reference treated animals.

Time of sacrifice: 24, 48 or 72 h for fexofenadine treated animals and 24 h for positive control group. 1000 cells from bone marrow of each animal were examined and the ratio of the number of micronucleated polychromatic erythrocytes (MN-PCE) to the number of normal polychromatic erythrocytes (NPE) was determined.

Doses: Vehicle (20 ml/kg by gavage), 625 mg/kg (LD), 1250 mg/kg (MD), 2500 mg/kg (HD). The HD was selected since a dose of 5000 mg/kg could not be given due to poor consistency of the suspension made it difficult to administer with a dosing needle. Reference: Cyclophosphamide: 120 mg/kg p.o.

Results

Dose ranging study: 2500 mg/kg was not toxic over a 4 day period.

At doses of 625, 1250 and 2500 mg/kg, fexofenadine produced no increase in the number of micronucleated polychromatic erythrocytes in M and F mice. Cyclophosphamide caused a marked increase in the frequency of abnormal erythrocytes (M, 28 vs 0.8; F, 40.3 vs 1.6). This a valid and acceptable study.

Conclusion

Fexofenadine was not mutagenic in the mouse micronucleus test.

Summary of Genotoxicity

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test.

OVERALL SUMMARY AND EVALUATION

Terfenadine is a non sedative H₁ receptor blocking drug. Terfenadine is metabolized to fexofenadine, a compound that possesses H₁ receptor blocking properties. Since the biotransformation to fexofenadine through the P450 system is fairly rapid in animals and in humans, the antihistaminic activity of terfenadine is attributed to a large degree to fexofenadine. The advantage of fexofenadine over terfenadine is that it does not possess the undesirable cardiac actions of terfenadine alone. Consequently, the potential for fexofenadine to produce Torsades de pointes, a potential fatal cardiac arrhythmia, is minimal. This cardiac action is seen with terfenadine in allergic patients especially those being treated with drugs like erythromycin that block the P450 enzymes thereby increasing the level of terfenadine.

The H₁ receptor blocking properties of fexofenadine in vitro and in vivo models are summarized in the following table. Its potencies relative to terfenadine ranged from 0.2 to 3.

Model	Activity
Binding Studies Rat Cerebral Cortex Membranes	2 x Potency of Terfenadine
Histamine-Induced Skin Wheal Test in Guinea Pigs	p.o., 0.4-0.6 x Potency of Terfenadine i.v., 3 x Potency of Terfenadine
Histamine-Induced Bronchoconstriction in Guinea Pigs	p.o., Equipotent to Terfenadine
Anaphylactic Shock in Guinea Pigs	p.o., 0.5 x Potency of Terfenadine
Histamine-Induced Contraction of Guinea Pig Ileum	0.3-1 x p.o., x Potency of Terfenadine
Histamine-Induced Vasodepression in Perfused Dog Hindlimb	i.v., Approximately equipotent to Terfenadine

Terfenadine may also exert its effectiveness in allergic diseases by inhibiting the release of histamine from mast cells. Compound 48/80 causes the release of histamine from rat peritoneal mast cells in a calcium free medium. This is due to a release of intracellular released calcium. Terfenadine, fexofenadine and disodium chromoglycate at 10 μ M inhibited the release of histamine induced by Compound 48/80; this indicates that these compounds may exert this effect by affecting intracellular calcium or by exerting a stabilizing effect on mast cell membrane.

Other properties that fexofenadine may possess since they were determined in vivo and ex vivo only for terfenadine. This is suggested since terfenadine is metabolized predominantly to fexofenadine. These properties observed at 5- 20 mg/kg p.o. were: 1. $\uparrow$ Cyclic AMP levels in rat mast cells, 2. $\uparrow$ Cyclic AMP levels in guinea pig lungs, and 3. $\uparrow$ Adenylate cyclase Levels in rat lungs.

The cardiac actions of terfenadine compared with fexofenadine are shown in the following table. The results show that fexofenadine possesses little or no effect on the heart; consequently, the potential for causing Torsades de pointes clinically in little or none at all.

Model	Activity	
	Fexofenadine	Terfenadine
In Vitro Studies		
Blockade of Human Delayed Rectifier K + Channel, fKH, EC ₅₀ , μM	214	0.367
Blockade of Delayed Rectifier K + Current in Feline Myocytes, EC ₅₀ , μM	Inactive at 5	0.17
Blockade of Delayed Rectifier K + Current Using Embryonic Kidney Cells Cloned from Human Heart, Potency	0.0017	1
In Vivo Studies		
Increased QTC Interval in Anesthetized Rabbits, Compound Infused i.v. over 1 h	No effect at 10 mg/kg	23.5% at 1 mg/kg
QTC Interval in Unanesthetized Dogs, Compound given p.o. twice daily for 5 days	No effect at 3 and 10 mg/kg; At 30 mg/kg ↓ QTC	10 mg/kg ↑ the QTC > 10% by day 3

in the general pharmacology studies involving the central nervous, cardiovascular, gastrointestinal, coagulating and renal systems, terfenadine possesses no potential clinical adverse effects.

In pharmacokinetics studies, fexofenadine at 30 mg/kg p.o. administered as a solution (98.5% propylene glycol-1.5% glacial acetic acid) to rats showed a 2.9% systemic bioavailability. This was attributed to 2 factors, poor absorption (24%) and high clearance (30 ml/min/kg). In dogs, receiving 8.7 and 27 mg/kg p.o. as a solution the absorption was 53.7 and 47.3%, respectively, showing greater absorption than the rat.

The following table compares the pharmacokinetics of a single dose p.o. fexofenadine in rats, dogs and humans. The dose in the rat (30 mg/kg) was slightly higher than that in the dog (27 mg/kg); both were higher than humans (2.4 mg/kg). In comparing dogs with rats, the dog showed a markedly higher C_{max}, AUC_{0-∞}, elimination half-life (initial and terminal phases) and a

much lower clearance. The t_{max} s and MRTs (mean residence time) were similar. The 17 fold difference in the clearance resulting in longer elimination half lives contributed to higher levels in the dog. With humans, the percent bioavailability fell between that of the dog and rat, and the clearance was much lower than either the rat or dog. When the data was normalized based on mg/kg, the AUC and C_{max} for humans fell between the rat and dog.

Parameter	Rats 30 mg/kg	Dogs 27 mg/kg	Humans 2.4 mg/kg
C_{max} , ng/ml	457	26,640	427
Normalized C_{max} , ng/ml	15	987	178
T_{max} , h	0.5	0.7	1-3
AUC _{0-∞} , ng.h/ml	436	107,505	2682
Normalized AUC _{0-∞} , ng.h/ml	15	3,982	1,118
Elimination Half-Life			
Initial Phase, h	0.4	1.96	
Terminal Phase, h	4.8	33.5	13
Cl_r , ml/min/kg	30	1.75	0.00079
MRT _b , h	2.7	4.0	
% Bioavailability	2.9	47.3-53.7	33

Distribution studies following the administration of 10 mg/kg p.o. fexofenadine were determined in Sprague-Dawley rats. Based on AUC_{0-TF}, fexofenadine was predominantly distributed in the stomach, small intestine, large intestine and to a lesser degree in the liver. In this study 91.7% and 0.87% of the radioactive dose was excreted in the feces and urine, respectively.

Following the administration of 300 mg/kg p.o. of terfenadine to pregnant animals, levels of fexofenadine were determined in the plasma levels of the dams and in the plasma levels of the fetuses. Fexofenadine was found in greater amounts in the plasma of the fetuses of the rabbits (477 ng/ml) than in the fetuses of rats (223 ng/ml); the AUC in the rabbits was approximately 9 x higher than that in the rat showing different pharmacokinetics. The dam/fetal ratio of the plasma levels in the rabbit was higher than rat (52 vs 4.1).

The following table compares the excretion pattern of fexofenadine in rats, dogs and humans. Humans, dogs and rats show similar excretory pattern, i.e., fexofenadine was excreted predominantly in the feces by way of the biliary tract and a small amount in the urine.

Species Dose, mg/kg	% of Dose Excreted	
	Feces	Urine
Rat		
10, p.o.	87.2	1.2
1, i.v.	82.4	11.1
1, portal vein	84.5	4.7
Dog		
1, i.v.	78.1	13.1
Human		
	80	11

In the excretion studies no metabolites were found in the rat (feces), dog (feces) and human (urine and feces). In an in vitro study, fexofenadine was incubated with rat microsomes alone, in microsomes from dexamethasone-treated rats to induce P-450 enzymes and in human microsomes. After 1 h incubation a small amount of the N-dealkylated fexofenadine was found. Thus, fexofenadine undergoes oxidative dealkylation in both species at a slow rate. Since this metabolite was not found in the primary excretory route of rats, dogs and humans, fexofenadine undergoes little or no metabolism in rats, dogs and humans.

In binding studies with plasma, the binding of fexofenadine to plasma proteins of rats and humans was similar and slightly lower than the binding to dogs. At concentrations from 0.1-0.8 $\mu\text{g/ml}$, the binding ranged from 88.4%-89.7% for rats, 88.9%-90.8% for humans and 93.0%-94.3% for dogs.

In toxicity studies fexofenadine was administered p.o. to rats, mice and dogs in single dose studies and in multidose studies up to 1 month in rats and dogs. The results from the reproductive and longer term toxicity studies for terfenadine were acceptable for fexofenadine since 1. terfenadine is predominantly metabolized to fexofenadine which contributes substantially to its antihistaminic activity, and 2. greater exposure to fexofenadine occurred when terfenadine was administered particularly in rats. The systemic bioavailability for fexofenadine in rats following p.o. administration of terfenadine was approximately 10 x higher (29% vs 2.9%) than when fexofenadine was administered.

The following compares the single dose p.o toxicity studies of fexofenadine and terfenadine in mice and rats. In rats and mice both fexofenadine and terfenadine were similar as their LD₅₀s were > 5000 mg/kg p.o. This may be attributed to poor absorption due to poor aqueous solubility. From this submission, poor systemic bioavailability in rats to fexofenadine also contributed to the low toxicity. Fexofenadine was also not toxic in dogs.

Compound Species	Doses, mg/kg, p.o.	Results
Fexofenadine Mice	4310 5146	No toxicity, LD ₅₀ > 5146 mg/kg p.o.
Rat	4310 5146	No toxicity, unabsorbed compound in feces LD ₅₀ > 5146 mg/kg p.o.
Dogs	1000 2000	Ataxia. LD ₅₀ > 2000 mg/kg p.o.
Terfenadine Mice		LD ₅₀ > 5000 mg/kg p.o.
Rats		LD ₅₀ > 5000 mg/kg p.o.

The results from multidose studies (10-14 days) in dogs with fexofenadine and terfenadine are summarized in the following table. Terfenadine was administered daily in single and/or divided doses. Terfenadine was more toxic than fexofenadine.

Compound	Doses, mg/kg, p.o.	Results
Fexofenadine	10, 30, 100, 300	No toxicity
Terfenadine	150, 500, 1000	At all doses, emesis, ↓ food consumption, ↓ body weight gained; 1000 mg/kg, pituitary, renal and cardiac changes were seen.

In a 3 month toxicity study in rats terfenadine was 10, 100 and 300 mg/kg were administered by gavage. Pharmacokinetics were not conducted in this study, but for a dose of 150 mg/kg from a 30 day dietary study, the AUC ranged from 9,091-11,618 ng.h/ml for F and M, respectively. This was 3.4-4.3 x the AUC for the clinical therapeutic dose. Thus, the AUC for the 300 mg/kg is higher than 4.3. At all doses the reticulocyte count was increased. The M showed an increase in the absolute and relative weights of the seminal vesicles at the 100 and 300 mg/kg p.o. At 300 mg/kg, there was a decrease in the absolute and relative weights of the heart and prostate. The F showed a dose related increase in the absolute and relative weights of the pituitary and thyroid and adrenal glands. Unabsorbed (?) terfenadine was found in 4 M and 9 F 300 mg/kg treated animals. No histopathology was noted.

No chronic toxicity studies was conducted on terfenadine in rats.

In a 1 month toxicity study in dogs, fexofenadine was administered 90, 300 and 900 mg/kg daily in 3 divided doses. The C_{max} s and AUCs were dose related, and the F showed higher AUCs than the M. No accumulation or decrease in plasma levels were seen. At 900 mg/kg salivation and emesis were seen; there was a dose related decrease in absolute and relative thymus weights at the MD and HD. No histopathology was seen. The NOEL was 90 mg/kg p.o. Based on the above results in the 10- 14 day studies, these results further support that in the dog fexofenadine was less toxic than terfenadine.

In dogs, the 2 year study with terfenadine was acceptable since terfenadine (80 mg/kg/day, LOEL) resulted in an exposure to fexofenadine based on AUCs that was 8.5-17.4 x the human exposure (2.4 mg/kg/day). In this study 30 and 100 mg/kg were dosed initially. The low dose was well tolerated. After 2-3 weeks due to toxicity, i.e., tremors, convulsions, impaired and death in 2/8 animals, the daily 100 mg/kg dose was reduced to 80 mg/kg after the treatment was temporarily stopped to allow for recovery. At this dose some central nervous system effects and constipation was seen during the latter part of the study; upon histological

examination, 2/2 M showed tubular atrophy in the testes at 80 mg/kg. The NOEL was 30 mg/kg.

In the carcinogenicity studies in mice and rats, 50 and 150 mg/kg of terfenadine were administered in the diet. No neoplasms were seen in the mice. In rats there was some increase in the incidence of adenocarcinomas in the uterus (C, 0/18, 50, 3/22, 150, 2/18) and mammary glands (C, 0/18, 50, 0/22, 150, 3/18); these were not considered significant to pursue when reviewed by one reviewer, C. Oberlander. When Dr. Taylor reviewed these data in 1990, two of his recommendation was: 1. to request the historical control data, and to request another carcinogenicity study if there are other findings that warrant this. This reviewer feels that since: 1. the incidence was not statistically significant when analyzed by the Fishers Exact test, 2. the incidence was low, and there was no dose relationship at least with the uterine neoplasm, 3. fexofenadine was not genotoxic, and 4. terfenadine has been on the market for a long period with no reported incidence or any indication of neoplasms, these findings are not considered clinically important. The following table shows that at the 150 mg/kg dose level, the AUC in F mice was twice that of the M while in rats, the AUCs were comparable, and that the ratio of the mice/rat AUC to the clinical dose AUC ranged from 2.1 to 4.3. The AUC for the lower dose was not reported. By today's standard, the MTD was not tested in the mouse. However, the ratios of the AUCs for the 150 mg/kg dose in mice and rats to the AUC for the human clinical exposure were 2.1 and 4.3. The above 4 factors were considered in conceiving this conclusion.

Parameter	Mice	Rats	Relative to Human AUC	
	150 A	150 A	A/B Mice	A/B Rats
AUC _{24h} , µg.h/ml, M	5.66	11.6	2.1	4.3
F	11.44	9.1	4.3	3.4
Human AUC _{0-∞} for 2.4 mg/kg dose: 2.682 µg.h/ml, B				

Fexofenadine was not mutagenic in the Salmonella-Escherichia coli/mammalian microsome reverse mutation, the (CHO/HGPRT) forward mutation and the rat lymphocyte chromosomal aberration in vitro assays and in the mouse bone marrow micronucleus in vivo test. This was further supported by studies in which terfenadine was inactive in the mouse bone marrow micronucleus in vivo test at 500, 1000 and 2000 mg/kg.

Based on reproductive toxicity studies with terfenadine in which significant exposure to

fexofenadine was achieved, no teratogenic effects were seen in mice, 50, 100 and 200 mg/kg p.o. by gavage, in rats, 50, 150 and 300 mg/kg p.o. by gavage or dietary administration and in rabbits, 30, 100 and 300 mg/kg p.o. by dietary administration. In rats administration of 50, 150 and 300 mg/kg in the diet did not affect fertility. At 150 and 300 mg/kg there was decreased food consumption and body weight gained in the dams and decreased body weight and survival of the fetuses. No AUC was reported in mice for 200 mg/kg p.o. However, in a month dietary study the AUC for 150 mg/kg the AUC_{24h} was 11,444 ng.h/ml. This was 4.3 x the human therapeutic exposure of 2,682 ng.h/ml for a daily dose of 160 mg. The AUC_{24h}s for the 300 mg/kg p.o. were 11,927 ng.h/ml for the rat and 101,631 ng.h/ml for the rabbit. They were 4.4 and 37.9 times the human therapeutic exposure.

Recommendation

Based on the preclinical data, there is no objection to approval of fexofenadine.

Comments for further studies: None.

Labeling

Changes were recommended in the submitted label. They are listed in **BOLD** under the Clinical Pharmacology (page 2), Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy and Overdosage Sections of the label which is appended.

Lawrence F. Sancilio 6/24/96

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

Chy Joseph June 24, 1996

cc. /Division File, NDA 20-625
/MSevka, HFD-570
/MHimmel, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/JSun, HFD-570

N:\NDA\20-625\Pharm\95-7-31.REV

Amendments:

NDA 19-949, Terfenadine, C. G. Oberlander, 4/28/83

Comments on carcinogenic studies with terfenadine, A. C. Taylor, Ph.D. 4/19/90
...

JAN 12 1994

SANCILIO

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

terfenadine
NDA 6
18949

Original, Serial No. 0

IND:

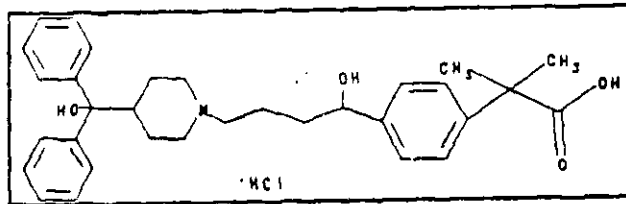
Reviewer: Lawrence F. Sancilio, Ph.D.
Date of Submission: 10/4/93
Date Assigned: 10/12/93
Date Initiated: 10/13/93
Date Completed: 1/3/94

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)--
1-piperidinyl]butyl'- α,α -dimethyl-, hydrochloride salt $\pm$

Name: MDL 16,455A, TAM (terfenadine active metabolite)

Structure:



Molecular Weight: 538.13

Molecular Formula: C₃₂H₃₉NO₄ · HCl

Pharmacological Class: H₁ receptor blocker

Indication: Allergic and Seasonal Rhinitis

Related Drugs: Terfenadine (NDA) see Amendment D for related structures

Related Compounds: See amendment A.

Formulation: MDL 16,455A

Proposed Clinical Study:

This is a double blind randomized, placebo controlled 4 period cross-over trial to determine in 40 normal M and F subjects, 1. the effect of MDL 16,455A on QT intervals, 2. the relationship if it exists between plasma levels of MDL 16,455A and changes in Qtc and 3. to characterize the multiple dose plasma and urine pharmacokinetics. Each subject will receive either placebo (vehicle, 98.5%:1.5% w/w, propylene glycol-acetic acid), 40 mg (0.8 mg/kg), 200 mg (4 mg/kg) or 400 mg (8 mg/kg) of MDL 16,455A twice daily for 6.5 days. There will be a 14-day wash out period between treatment.

Relationship Between MDL 16,455A and Terfenadine

Terfenadine is metabolized primarily to the acid metabolite, MDL 16,455A. Terfenadine undergoes 99% first pass metabolism resulting in low systemic bioavailability. The acid metabolite, MDL 16,455A, contributes substantially to the antihistaminic properties of terfenadine. Since the bioavailability of terfenadine was low the sponsor indicated that the toxicity of terfenadine reflected that of MDL 16,455A. Further, the bioavailability of MDL 16,455A in the rat following terfenadine administration was 10 X that when MDL 16,455A given (29% vs 2.9%). Thus, the rat receives greater exposure to MDL 16,455A when administered terfenadine. In view of this the toxicity studies conducted with terfenadine in rats and dogs were acceptable for those of MDL 16,455A.

Studies Submitted

Pharmacology

1. Competitive receptor binding studies with MDL 16,455A and its enantiomers to rat brain histamine -H1 receptors, No. C-93-0247-R, vol. 1.3, p 721.
2. Oral effects of terfenadine and MDL 16,455A on histamine skin wheals in guinea pigs, No. P84-14, vol. 1.3, p 669.
3. Time course of antihistaminic effects of MDL 16,455A and terfenadine on histamine skin wheals in guinea pigs, No. C-93-0145-R, vol. 1.3, p 657.
4. Effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, vol. 1.4, No. P84-05, p 904.

5. Antagonism of histamine-induced bronchoconstriction by MDL 16,455A and MDL 9,918 in anesthetized guinea pigs, No. C-93-0215-R, vol. 1.3, p 710.
6. Antihistaminic effect of MDL 16,455A, a major metabolite of terfenadine, No. P84-01, vol. 1.3, p 728.
7. Effect of MDL 16,455A on the isolated guinea pig ileum, No. P77-15, vol. 1.4, p 914.
8. Effect of RMI 16,218 on the isolated guinea pig ileum. A comparison with terfenadine, No. P77-14, vol. 1.4, p 927.
9. The effects of MDL 16,455A on the vascular effects of histamine and phenylephrine in the dog hindlimb preparation, No. P84-09, vol. 1.3, p 684.
10. The effects of terfenadine or chlorpheniramine on the vascular effects of phenylephrine and histamine in the dog hindlimb preparation, No. P83-04, p 695.
11. Block of a human delayed rectifier K⁺ channel by terfenadine and its metabolites, No. C-93-0182-R, vol. 1.4, p 946.
12. Effect of terfenadine, MDL 16,455A and the stereoisomers MDL 15171 and MDL 15,172 on action potential and membrane currents in guinea pig ventricular cells, No. C-91-0084-R, vol. 1.3, p 644.
13. Effects of iv infusion of terfenadine and MDL 16,455A on QTc interval in anesthetized rabbits. No. C-93-0235-R, vol. 1.3, p 591.
14. Effects of iv infusion of terfenadine on QTc interval in anesthetized dogs. No. C-93-0234-R, vol. 1.4, p 961.
15. Effect of repeated ascending doses of terfenadine and MDL 16,455A, the acid metabolite of terfenadine on the electrocardiogram of dogs. No. C-93-0248-R, vol. 1.3, p 615.
16. Primary CNS evaluation of MDL 16,455A, No. C-93-0233, vol. 1.4, p 787.
17. General pharmacology of an antiallergic drug, terfenadine, No. J-92-0010, vol. 1.4, p 797.

Summary of Pharmacology

Toxicology

Single-Dose

1. Acute po toxicity with MDL 16,455A terfenadine metabolite I in mice, No. J-92-0020-T, vol. 1.5, p 1017
2. Acute po toxicity of MDL 16,455A in mice and rats, T-90-07, vol.1.5, p 1031
3. Acute po toxicity of MDL 16,455A administered to dogs, T-90-05, vol. 1.5, p 1049
4. MDL 16,455A: Exploratory acute po toxicity study in dogs, I-93-0046-T, vol. 1.5, p 1062

Multi-Dose

1. MDL 16,455A: Two week po tolerance screen in beagle dogs, I-93-0048-T, vol. 1.5, p 1073
2. MDL 16,455A : One month po toxicity in dogs, I-93-0051-T, vol. 1.5, p 1087

Summary of Toxicology of MDL 16,455A and Terfenadine

Absorption, Distribution, Metabolism, Excretion

Rats

1. The pharmacokinetics and bioavailability of MDL 16,455A in Sprague-Dawley rats, No.K-93-0422-D, vol. 1.6, p 1278
2. The pharmacokinetics and po bioavailability of MDL 16,455A in Sprague-Dawley rats, No.K-93-0071-D, vol. 1.6, p 1304
3. Plasma concentration of MDL 16,455A in M and F Sprague-Dawley rats given a single 5 g/kg po suspension of MDL 16,455A, No. K-93-0364, vol. 1.6, p 1350
4. Plasma concentration of MDL 16,455A in M and F Sprague-Dawley rats given a single 5 g/kg po suspension of MDL 16,455A, No. K-93-0409-D, vol. 1.6, p 1350

Dogs

1. A comparison of the absorption and elimination of po MDL 16,455A and terfenadine in beagle dogs, No. K-93-0145-D, vol. 1.6, p 1410
2. A comparison of the absorption of MDL 16,455A in F beagle dogs

given a 500 mg/kg po suspension dose of MDL 16,455A.

3. Plasma concentrations of MDL 16,455A in beagle dogs given 90, 300 or 900 mg/kg of MDL 16,455A in a 1 month toxicity study, K-93-0460-D, vol. 1.6, p 1485

4. Plasma concentrations of MDL 16,455A and terfenadine in beagle dogs given 80 mg/kg/day capsules doses of terfenadine for 1 month toxicity study, K-93-0431-D, vol. 1.5, p 1226

5. Protein binding: Metabolism Studies on terfenadine, vol. 1.6, p 1547

Summary of Absorption, Distribution, Metabolism, Excretion

SUMMARY AND EVALUATION

Studies Reviewed

Pharmacology

1. Competitive receptor binding studies with MDL 16,455A and its enantiomers to rat brain histamine H₁ receptors, No. C-93-0247-R, vol. 1.3, p 721.

The results in the following table show that MDL 16,455A and its enantiomers, displaces mepyramine from its H₁ binding site to a greater degree than terfenadine and its enantiomers.

INHIBITION OF HISTAMINE BINDING TO
RAT CEREBRAL CORTEX MEMBRANES (H₁-RECEPTOR)

COMPOUND	K _i (nM)
MDL 913, TERFENADINE	317 ± 22
MDL 15171 (+)	410 ± 34
MDL 15172 (-)	330 ± 31
MDL 16455A	176 ± 26
MDL 16455A (+)	152 ± 9
MDL 16455A (-)	170 ± 6

Values are mean ± SEM of 4 to 5 separate determinations.

2. Oral effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, No. P84-14, vol. 1.3, p 669.

3. Effects of terfenadine and MDL 16,455A on histamine wheals in guinea pigs, vol. 1.4, No. P84-05, p 904.

4. Time course of antihistaminic effects of MDL 16,455A and terfenadine on histamine skin wheals in guinea pigs. No. C-92-0145-R, vol. 1.3, p. 657.

At 2 h pretreatment time the ED50 for MDL 16,455A and terfenadine for blocking the histamine wheal in guinea pigs was 11.1 and 5.2 mg/kg po, respectively. Terfenadine was 2.54 X (1.69- 4.52, 95% confidence intervals) more potent than MDL 16,455A in blocking the histamine response. The time course for the activity of 0.8 mg/kg for both compounds was similar; its peak effect and duration of action were 2 h and 6 h, respectively.

In the second study, at peak effect following iv administration, MDL 16,455A was 2.98 X (1.96-5.81) more potent than terfenadine. At 0.8 mg/kg iv MDL 16,455A produced a faster onset and a shorter duration of antihistaminic activity than a similar dose of terfenadine.

In the third study, terfenadine po was 1.57 X more potent than po MDL 16,455A. At equiactive doses (terfenadine, 1 mg/kg po; MDL 16,455A, 1.6 mg/kg po) both compounds produced similar onset (1 h), peak effect (2 h) and duration (6 h) of antihistaminic activity.

5. Antagonism of histamine-induced bronchoconstriction by MDL 16,455A and MDL 9,918 (terfenadine) in anesthetized guinea pigs. No. C-92-0215-R, vol. 1.3, p. 710.

Dose-ratio 2 values (the dose of antagonist required to produce a two-fold shift in the histamine dose response curve) were determined for iv or po MDL 16,455A and terfenadine at different pretreatment times. The following results indicate that iv MDL 16,455A was more effective than iv terfenadine; both were comparable by the po route in antagonizing the histamine-induced bronchoconstriction.

The dose-ratio 2 values for MDL 16,455A were:

0.03 mg/Kg at 10 minutes post iv administration,
0.07 mg/Kg at 30 minutes post iv administration,
and between 0.34 and 0.76 mg/Kg at 60 minutes post oral administration.

Under the conditions of the present experiment (compounds dissolved in 60% polyethylene glycol 400), the dose-ratio 2 values for MDL 9,918 were:

0.26 mg/Kg at 10 minutes post iv administration,
0.15 mg/kg at 30 minutes post iv administration,
and 0.38 mg/Kg at 60 minutes post oral administration.

MDL 9,918 (Terfenadine)

6. Antihistaminic effect of MDL 16,455A, a major metabolite of terfenadine, No. P84-01, vol. 12.3, p 728.

7. Effect of MDL 16,455A on the isolated guinea pig ileum, No. P77-15, vol. 1.4, p 914.

8. Effect of RMI 16,218 on the isolated guinea pig ileum. A comparison with terfenadine, No. P77-14, vol. 1.4, p 927.

Using histamine induced contraction of guinea pig ileum, the pA₂ values were 8.34 and 7.83 for terfenadine and MDL 16,455A, respectively for blocking the contraction induced by histamine. Based on these results MDL 16,455A was 0.31 (0.18- 0.53) as potent as terfenadine. In this model the rates of association and dissociation with histamine receptors by MDL 16,455A were more rapid than those of terfenadine.

Unlike terfenadine, MDL 16,455A was not spasmolytic; this action of terfenadine was attributed to its calcium channel blocking activity.

In a second study, the pA₂ for mg/kg and terfenadine were 7.61 and 8.05, respectively. Statistically, their relative potency were unity.

9. The effects of MDL 16,455A on the vascular effects of histamine and phenylephrine in the dog hindlimb preparation, No. P84-09, vol. 1.3, p 684.

10. The effects of terfenadine or chlorpheniramine on the vascular effects of phenylephrine and histamine in the dog hindlimb preparation, No. P83-04, p 695.

MDL 16,455A, 0.3-3 mg/kg iv, terfenadine, 1.3 mg/kg iv and chlorpheniramine, 1, 3 mg/kg iv, did not affect the vasoconstrictor response to phenylephrine in the perfused dog hindlimb preparation.

At the same doses the 3 compounds blocked the vasodepressor response to histamine. The activity of MDL 16,455A and terfenadine were longer than chlorpheniramine.

11. Block of a human delayed rectifier K⁺ channel by terfenadine and its metabolites, No.C-93-0182-R, vol. 1.4, p 946.

Terfenadine and its metabolites MDL 16,455A, MDL 4829A and MDL 17,523 were tested for their ability to block a rapidly activating delayed rectifier K⁺ channel (fHK) cloned from human heart. Terfenadine inhibited fHK with an IC₅₀ of 367nM. Terfenadine's main effect was to accelerate fHK current inactivation suggesting blockade of the open channel state as its mechanism of action. MDL 17,513, MDL 4829A and MDL 16,455A were far less active at blocking fHK displaying IC₅₀ values of 18, 141 and 214 μM, respectively.

12. Effect of terfenadine, MDL 16,455A and the stereoisomers MDL 15171 and MDL 15,172 on action potential and membrane currents in guinea pig ventricular cells, No. C-91-0084-R, vol. 1.3, p 644.

At concentrations up to 10 mM, MDL 16,455A and its 2 enantiomers [(-) MDL 15,171, (+) MDL 15,172) unlike terfenadine had no effect at 10⁻⁵M on the action potentials and membrane currents. The activity of terfenadine are summarized in the following table.

EFFECTS OF TERFENADINE ON THE ACTION POTENTIAL DURATION AND MEMBRANE CURRENTS

Concentration (M)	% of Control								
	APD ₅₀	n	I _{Ca}	I _{K1}	I _{Na}	n	I _K	n	
10 ⁻⁸	100 ± 2	4	99 ± 2	99 ± 2	7	.	ND	.	ND
10 ⁻⁷	101 ± 3	4	99 ± 1	95 ± 3	6	.	ND	.	ND
10 ⁻⁶	110 ± 6	10	104 ± 9	86 ± 4	9	99 ± 2	10	98 ± 2	4
10 ⁻⁵	23 ± 12 ^a	12	0	75 ± 12	8	62 ± 13	12	0	8

13. Effects of iv infusion of terfenadine and MDL 16,455A on QTc interval in anesthetized rabbits. No. C-93-0235-R, vol. 1.3, p 591.

Infusion of 3 and 10 mg/kg/h iv of MDL 16,455A to anesthetized rabbits did not alter the QTc intervals, heart rate or blood pressure. At these doses plasma levels of 2.891 (5.76 uM) and 9.777 (19.48 uM) u/ml of MDL 16,455A were achieved.

Terfenadine at 1 mg/kg/h iv increased maximally the QT interval by 18.29%, and the QTc interval by 23.51%. There was a decrease in systolic blood pressure and no effect on heart rate, diastolic blood pressure and mean blood pressure. At this dose plasma levels of 135 ng/ml (0.29 uM) of terfenadine and 139.8 ng/ml (0.28 uM) of MDL 16,455A were observed.

b

14. Effects of iv infusion of terfenadine on QTc interval in anesthetized dogs. No. C-93-0234-R, vol. 1.4, p 961.

In anesthetized dogs, terfenadine was infused iv for 1 h doses of 0.3, 1 and 5 mg/kg. At 1 mg/kg QTc interval was increased by 7-10%; at this dose plasma levels of 245.5 ng/ml. At 5 mg/kg 2/4 dogs died apparently due to severe hypotension and bradycardia.

15. Effect of repeated ascending doses of terfenadine and MDL 16,455A, the acid metabolite of terfenadine on the electrocardiogram of dogs. No. C-93-0248-R, vol.1.3, p 615.

In one group of unanesthetized dogs MDL 16,455A was given po 1, 3 and 10 mg/kg bid for 5 days; the second and third dose was given following a 1 week washout period. In a second group of dogs under similar conditions doses of 3, 10 and 30 mg/kg were given bid for 5 days. MDL 16,455A at the 30 mg/kg dose decreased the QTc interval up to 15 msec. At this dose the plasma level was 4.382 ug/ml.

Terfenadine at 10 mg/kg bid/day by day 3 increased the QTc interval more than 10% (21-23 msec). In these dogs the plasma levels of terfenadine were 128 ng/ml.

16. Primary CNS evaluation of MDL 16,455A, No.C-93-0233, vol. 1.4, p 787.

The results summarized in the following table show that MDL 16,455A manifested no CNS effects.

Table 17. Primary CNS Evaluation of MDL 16,455A in Mice		
Test	Dose mg/kg, i.p.	Activity Number Affected/Total
Gross Effects	400, 800 200, 100, 50	Slight reduc. SMA, Slight reduc. resp. rate No observable effects. LD ₅₀ >800 (acute) LD ₅₀ 200-400 (24-hr to 7 days)
Analgnesia	800	0/3
Hot Plate	800	0/3
HAc writhing	200 (sc)	0/5
Anticonvulsant		
MES	200	0/5
Pentylentetrazole	200	0/5
Strychnine	200	0/5
3-MPA	200	0/5
Antidepressant		
Roa-1284 Hypothermia	50	1/5
	25	0/5
	200	0/5
Roserpine Ptosis		
Dopamine Antagonist		
Amphet. Toxicity	25	0/4
5-HT ₂ Antagonist	200	0/5
DMT		
reduc.: reduction	MES: metrazole	
SMA: spontaneous motor activity	3-MPA: 3-mecapropionic acid	
resp. rate: respiratory rate	DMT: 5-methoxy-N,N-dimethyltryptamine	
HAc: acetic acid		
Supporting Data:		Vol Page
Ref P18		1.4 787

17. General Pharmacology of an Antiallergic Drug, Terfenadine,
No. J-92-0010, vol.1.4, p 797.

The following tables summarizes the pharmacological properties of terfenadine and MDL 16,455A.

Table 14 (Page 1 of 8) General Pharmacology Studies						
Species	Mode of Administration	Doses	Duration	Purpose	Comments	References
Mouse	i p	MDL 16,455A 50-800 mg/kg	Single Dose	Gross Behavior	Slight reduction in SMA and resp rate at 400-800 mg/kg LD ₅₀ > 800 (acute) LD ₅₀ 200-400 (24 hrs to 7 days)	P16 Vol 14 Page 787
	i p	MDL 16,455A 400-800 mg/kg	Single Dose	Analgesia	No effect	P16 Vol 14 Page 787
	i p	MDL 16,455A 200 mg/kg	Single Dose	Anticonvulsant	No effect	P16 Vol 14 Page 787
	i p	MDL 16,455A 25-200 mg/kg	Single Dose	Antidepressant	Re 4-1284 hypothermia 25 mg/kg 0/5 50 mg/kg 1/5	P16 Vol 14 Page 787
	i p	MDL 16,455A 200 mg/kg	Single Dose	Dopamine Antagonism	No effect	P16 Vol 14 Page 787
	i p	MDL 16,455A 200 mg/kg	Single Dose	5-HT ₂ Antagonism	No effect	P16 Vol 14 Page 787
Rat	i p	MDL 16,455A 10, 30, 100, 300 mg/kg	Single Dose	General Behavior	MDL 16,455A (in rats) no effect at low dose; at 300 mg/kg whitening of Pinnae, hypothermia, writhing, suppressed weight gain at 100, 300 mg/kg	P17 Vol 14 Page 797
Rat	p o i p	Terfenadine 1000, 3000 10, 30, 100, 300, 1000 mg/kg	Single Dose	General Behavior	Terfenadine (in rats) no effect p.o. on general behavior; at 3000 and 1000 mg/kg inhibited body weight gain, no effect i.p. at low dose, at 300, 1000 mg/kg i.p. hypothermia and several other changes	
Mouse	i p	MDL 16,455A 3, 10, 30 mg/kg	Single Dose	Spontaneous Locomotor Activity	MDL 16,455A. No effect at 3, 10 mg/kg i.p.; at 30 mg/kg inhibited activity 20-70 minutes after treatment	P17 Vol 14 Page 797
		Terfenadine 30 mg/kg	Single Dose		Terfenadine. No effect at 30 mg/kg i.p.	
		MDL 4,829 30 mg/kg	Single Dose		MDL 4,829. No effect at ≤30 mg/kg i.p.	

Table 14 (Page 2 of 8) General Pharmacology Studies

Species	Mode of Administration	Doses	Duration	Purpose	Comments	References
Mouse	i.p.	MDL 18 455A 3, 10, 30 mg/kg Terfenadine 30 mg/kg	Single Dose Single Dose	Motor Coordination	No significant effect No effect	P17 Vol 14 Page 787
Rabbit	i.v. i.v.	Terfenadine 0.3, 1, 3, 10 mg/kg MDL 18 455A 0.3, 1, 3, 10 mg/kg	Single Dose	Spontaneous EEG	EEG. • MDL 18 455A, MDL 4 829 no effect at 0.3 and 3.0 mg/kg. • Terfenadine no effect at 0.3 and 1.0 mg/kg. Stimulated occurrence of high amplitude slow waves at 3.0 mg/kg, flattened EEG, hypotension, and heart arrest 10 mg/kg MAP (Mean arterial blood pressure) • MDL 18 455A, MDL 4 829 no effect at 0.3 to 3.0 mg/kg • Terfenadine Dose-dependent lowering HR (Heart Rate) • MDL 18 455A, MDL 4 829 had no effect at 0.3 to 3.0 mg/kg • Terfenadine Dose-dependent sustained bradycardia at 1 and 3 mg/kg	P17 Vol 14 Page 787
Mouse	i.p. i.p. i.p.	MDL 18 455A 3, 10, 30 mg/kg Terfenadine 10, 30 mg/kg MDL 4 829 3, 10, 30 mg/kg	Single Dose Single Dose Single Dose	Pentobarbital-Induced Sleep	• MDL 18 455A No effect at ≤30 mg/kg • Terfenadine No effect at ≤30 mg/kg • MDL 4 829 Prolonged duration at 30 mg/kg	P17 Vol 14 Page 787

Table 14 (Page 3 of 8) General Pharmacology Studies

Species	Mode of Administration	Doses	Duration	Purpose	Comments	References
Rabbit	Conjunctival Sec	MDL 18,455A 0.8, 1.6, 3.2%	Single Dose	Local Anesthetic Activity	- MDL 18,455A. No effect at 0.8, 1.6, or 3.2% - Terfenadine. No effect	P17 Vol 14 Page 787
Mouse	i.p.	MDL 18,455A 3, 10, 30 mg/kg	Single Dose	Pupil Size	MDL 18,455A. No effect	P17 Vol 14 Page 787
	p.o.	Terfenadine 100, 300, 1000 mg/kg	Single Dose		Terfenadine. No effect	
Rat isolated Fundus Ventricle Muscle	<i>In Vitro</i>	MDL 18,455A 10^{-7} to 10^{-6} M	Single Dose	Isolated Fundus Ventricle Muscle	MDL 18,455A - no effect on either prostaglandin F_{2α}- or arachidonic acid-induced contractions Terfenadine - no effect at 10^{-7}M - inhibited prostaglandin F_{2α}-induced contraction dose-dependently at 3×10^{-7}, 10^{-6}, 3×10^{-6}M - no effect on arachidonic acid-induced contractions at 10^{-7}M, inhibition at 3×10^{-7}M	P17 Vol 14 Page 787
Anesthetized Dog	i.v.	MDL 18,455A 0.3, 1, 3 mg/kg	Single Dose	Effects on blood pressure, heart rate, dp/dt _{max} , blood flow, respiration	MDL 18,455A - no effect Terfenadine - no effect at 0.3 mg - transient, dose-dependent effect at 1, 3 mg (decreased BF, increased HR, and dp/dt_{max}) - at 3 mg increased respiration, decreased respiration rate - no effect on blood flow	P17 Vol 14 Page 787

Table 14 (Page 4 of 8) General Pharmacology Studies						
Species	Mode of Administration	Doses	Duration	Purpose	Comments	References
Isolated Heart Guinea Pig	Intra Coronary	MDL 16,455A 30, 100, 300 µg	Single Dose	Effect on Isolated Guinea Pig Heart	MDL 16,455A • no effect at 30, 100, 300 µg on contractile force or heart rate. • increased coronary flow at 300 µg Terfenadine: • at >1 µg reduced contractile force, increased coronary flow, • slight increase in HR at ≥3 µg	P17 Vol 14 Page 787
		Terfenadine 1, 3, 10 µg	Single Dose			
Rat	ip	MDL 16,455A 3, 10, 30 mg/kg	Single Dose	Effects on Blood Coagulation	MDL 16,455A: no effect Terfenadine: no effect	P17 Vol 14 Page 787
	po	Terfenadine 30, 100, 300 mg/kg	Single Dose			
Rabbit	In Vitro	MDL 16,455A 10 ⁻⁶ , 10 ⁻⁵ , 10 ⁻⁴ M	Single Dose	Effects on Platelet Aggregation	MDL 16,455A: no effect Terfenadine: no effect	P17 Vol 14 Page 787
		Terfenadine 10 ⁻⁶ to 10 ⁻⁴ M	Single Dose			
Rat	ip	MDL 16,455A 3, 10, 30 mg/kg	Single Dose	Urine Volume, Electrolyte Excretion	MDL 16,455A: No effect at 3, 10 mg/kg, increased electrolytes excretion at 30 mg/kg Terfenadine: No effect at 30, 100 mg/kg, decreased Cl-excretion at 300 mg/kg	P17 Vol 14 Page 787
		Terfenadine 30, 100, 300 mg/kg	Single Dose			
Guinea Pig	iv	MDL 16,455A 3, 10 mg/kg	Single Dose	In situ Gastric and Intestinal Motility (Spontaneous)	• MDL 16,455A: No effect. • Terfenadine: No effect.	P17 Vol 14 Page 787
	iv	Terfenadine 1, 3 mg/kg	Single Dose			
Guinea Pig	iv	MDL 16,455A 3, 10 mg/kg	Single Dose	In situ Gastric and Intestinal Motility (Stimulated)	• MDL 16,455A: No effect at 3, 10 mg/kg • Terfenadine: No effect at 1 mg/kg, inhibition of gastric motility at 3 mg/kg	P17 Vol 14 Page 787
	iv	Terfenadine 1, 3 mg/kg	Single Dose			

Table 14 (Page 6 of 8) General Pharmacology Studies

Species	Mode of Administration	Doses	Duration	Purpose	Comments	References
Rat	IV	MDL 18,455A 3 mg/kg Terfenadine : 3 mg/kg	Single Dose	Spontaneous (Tern) Uterine Contractility <i>In Vitro</i>	• MDL 18,455A. No effect • Terfenadine. No effect at 1 mg/kg	P17 Vol 14 Page 787
Rabbit Isolated Ileum	<i>In Vitro</i> <i>In Vitro</i>	MDL 18,455A 10 ⁻⁵ to 10 ⁻⁴ M Terfenadine 2x10 ⁻⁷ to 2x10 ⁻⁶ M	Single Dose Single Dose	Motility in Isolated Ileum	• MDL 18,455A. No effect. at 10⁻⁴M slight decrease in amplitude of motility • Terfenadine. Dose-dependent inhibition of spontaneous motility	P17 Vol 14 Page 787
Rabbit Isolated Aorta	<i>In Vitro</i>	MDL 18,455A 10 ⁻⁵ to 3 x 10 ⁻⁴ M Terfenadine 10 ⁻⁷ to 3 x 10 ⁻⁶ M	Single Dose	Isolated Aorta	• MDL 18,455A. ≥10⁻⁴M slightly relaxed aorta • Terfenadine. ≥10⁻⁷M relaxed contracted aorta. ED₅₀ = 1.13 x 10⁻⁶M	P17 Vol 14 Page 787

Table 14 (Page 6 of 6) General Pharmacology Studies

Species	Mode of Administration	Doses	Duration	Purpose	Comments	References
Guinea Pig Isolated Tracheal Muscle	In vitro	MDL 16,455A 10 ⁻⁶ , 10 ⁻⁸ , 10 ⁻⁴ M	Single Dose	Isolated Tracheal muscle	MDL 16,455A • no effect on intrinsic tone at 10⁻⁶ to 10⁻⁸M; decrease tone (52%) at 10⁻⁴M • slight reduction in muscle tone contracted with KCl (10⁻⁵ to 10⁻⁴M) • no effect on muscle tone contracted with carbachol • shifted histamine dose response curve to right	P17 Vol. 14 Page 797
		Terfenadine 10 ⁻⁶ , 10 ⁻⁸ , 10 ⁻² M	Single Dose		Terfenadine • no effect on intrinsic tone. • dose-dependent decrease in muscle tone contracted with KCl (10⁻⁵ to 10⁻²M) • no effect at 10⁻⁶M on carbachol contracted muscle (10⁻⁵ to 10⁻²M). • inhibited histamine-induced contraction at 10⁻⁶ to 10⁻²M; dose response curve shifted to right. • inhibited the maximum response to histamine at 3 x 10⁻⁶M	

Summary and Conclusion

In various models in mice, rats and rabbits in which activity on the central nervous system was assessed, MDL 16,455A produced no significant effects; in rabbits and dogs there was no effect on the cardiovascular and respiratory systems. Unlike terfenadine at 30 mg/kg ip, MDL 16,455A did not prolong the duration of pentobarbital sleeping time in mice; this suggests that MDL 16,455A was not an enzyme inducer. MDL 16,455A did not affect gastrointestinal motility in the charcoal meal test; it was active at 10 and 30 mg/kg ip in inhibiting gastric secretion in pylorus ligated rats. In in vitro systems MDL 16,455A did not affect the response to arachidonic acid or prostaglandin F2 alpha. No effects were seen on platelets, blood coagulation and gastrointestinal and uterine motility; MDL 16,455A did not relax the resting tone of the isolated rabbit aorta or guinea pig trachea at 10⁻⁶ M. The latter showed that MDL 16,455A was not a bronchodilator. MDL 16,455A transiently (0-2 h) increased the urinary excretion of Na and Cl ions at 10 and 30 mg/kg po in rats; this was not accompanied by an increase in urine volume. Thus, the results in these studies show that MDL 16,455A is relatively free of any potential adverse effects.

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Summary of Pharmacology

MDL 16,455A is the active metabolite of terfenadine, a non sedative H1 receptor antagonist. Binding studies show MDL 16,455A and its enantiomers to be approximately twice as active (KI: 152-176 nM vs 313-410 nM) as terfenadine and its enantiomers in displacing mepyramine from its binding site in rat cerebral cortex membranes.

MDL 16,455A was compared with terfenadine to demonstrate similarities and differences in pharmacological activities. In the histamine induced skin wheal test in guinea pigs, terfenadine by the po route was 1.57-2.54 X more potent than MDL 16,455A in blocking the histamine response; however, by the iv route MDL 16,455A was 2.98 X more potent than terfenadine in suppressing the wheal response. At equiactive po doses (1 mg/kg of terfenadine and 1.6 mg/kg of MDL 16,455A), their onset (1 h), peak effect (2 h) and duration (6 h) of action were similar.

In dose-ratio 2 studies (the dose of antagonist required to produce a two-fold shift in the histamine dose response curve) MDL 16,455A was more potent by the iv route and equipotent to terfenadine by the po route in blocking the histamine induced bronchoconstriction in anesthetized guinea pigs.

In isolated guinea pig ileum, MDL 16,455A was 0.3-1 X as potent as terfenadine in antagonizing the contraction induced by histamine. In these studies the rates of association and dissociation with histamine receptors by MDL 16,455A were faster than those of terfenadine.

In the perfused dog hindlimb preparation both MDL 16,455A and terfenadine blocked the vasodepressor response to histamine; however, both compounds did not alter the vasoconstriction induced by phenylephrine.

Terfenadine at concentrations between $1 \times 10^{-6}M$ and $1 \times 10^{-5}M$ blocked the calcium, I_{K1} , and sodium and I_K channels in guinea pig ventricular cells. Its ED50 was 367 nM in blocking the rapidly activating delayed rectifier K ion channel cloned from human heart. The inhibition of the potassium ion channels contributed to the prolongation of the duration of the action potential on neonatal rat ventricular myocytes. Further, these effects reflected the increase in the QTc intervals seen in dogs (po or iv) and rabbits (iv). At $1 \times 10^{-5}M$ of either MDL 16,455A or its 2 enantiomers [(-) MDL 15,171, (+) MDL 15,172], the potassium ion channels were not affected. The ED50 for MDL 16,455A on the delayed rectifier K ion channel was 214000 nM which was 600 X higher than that for terfenadine. In dogs given 30 mg/kg po for 5 days of MDL 16,455A, the QTc interval decreased. In general pharmacologic in vitro and in vivo studies to assess

potential side effects, MDL 16,455A produced no significant effects in mice, rats, guinea pigs, rabbits or dogs on the central nervous, cardiovascular, gastrointestinal, respiratory, renal and coagulating systems. MDL 16,455A was not an enzyme inducer since it did not alter pentobarbital sleeping time in mice.

Toxicology

Single-Dose

1. Acute po toxicity with MDL 16,455A terfenadine metabolite I in mice, No. J-92-0020-T, vol. 1.5, p 1017
2. Acute po toxicity of MDL 16,455A in mice and rats, T-90-07, vol.1.5, p 1031
3. Acute po toxicity of MDL 16,455A administered to dogs, T-90-05, vol. 1.5, p 1049
8-20
4. MDL 16,455A: Exploratory acute po toxicity study in dogs, I-93-0046-T, vol. 1.5, p 1062

The results of single dose studies are summarized in the following table.

Species	Doses, mg/kg po	No. / Dose	Results
Mice* Crj-CD-1 (ICR)	2250, 4500	5 M 5 F	No toxicity; no gross pathology
Mice* ^a CD-1	4310, 5146	20 M 20 F	No toxicity: no gross pathology Whitish material in feces indicating poor po absorption
Rats* ^a CD (SD)	4310, 5146	20 M 20 F	No toxicity: no gross pathology Whitish material in feces indicating poor po absorption
Dogs** Beagle	1000, 2000	1 M	No toxicity; vehicle (98.5% propylene glycol/1.5% acetic acid, 6.7-13.3 ml/kg) produced ataxia AUC _{0-24h} , ug.h/ml: 1000 mg/kg, 477.8 2000 mg/kg, 816.3
Dogs* ^a Beagle	270, 450	2 F	Vehicle (0.5% methylcellulose in 0.5% Tween 20 in water) No toxicity

*Observation period, 14 days

**Observation period, 7 days

^a Conducted under GLP regulations

Multi-Dose

1. MDL 16,455A: Two week po tolerance screen in beagle dogs, I-93-0048-T, vol. 1.5, p 1073

The results of the 10 days to 2 week tolerance study in beagle dogs are summarized in the following table. The vehicle was a v/v mixture of 98.5% propylene glycol/1.5% acetic acid.

Days	Doses, mg/kg po	No./Dose	Results
10	10, 30	1 M 1 F	No toxicity
14	100, 300		No toxicity, Day 15 AUC0-24h, ug.h/ml: 100 mg/kg, M, 27.7 F, 237.7 300 mg/kg, M, 99.6 F, 245.4

Summary and Conclusion

In an exploratory 10-14 day study in dogs, no toxicity was seen at po doses of 10, 30 100 and 300 mg/kg. The AUC0-24h in F were higher than in the M suggesting greater absorption in the F. However, in the F absorption was apparently maximal at 100 mg/kg since the AUCs at 100 and 300 mg/kg were similar.

2. MDL 16,455A : One month po toxicity in dogs, I-93-0051-T, vol. 1.5, p 1087

The study was conducted under GLP regulations at Marion Merrell Dow Drug Safety Department in Indianapolis, Ind.

Animals and Method: M and F Beagle dogs weighing 7.0-11 kg were divided into 4 groups each containing : M and 4 F. They were given daily by gavage the vehicle (a v/v mixture of 98.5% propylene glycol/1.5% acetic acid,), 90, 300 and 900 mg/kg in 3 divided doses of MDL 16,455A (Lot No. 71707) for 4 weeks. The following parameters were determined.

Mortality

Clinical Observations: daily

Body Weight: weekly

Food Consumption: daily, determining the average consumed weekly

Heat Rate: Prior to and at end of treatment and end of recovery period

Electrocardiogram: prior to and on days 1, 15 and 29 of C and HD

Hematology and Clinical Chemistry: prior to and on days 15, 30, 45 and 57

Urinalysis: prior to and on weeks 2, 4, 6 and 8.

Organ Weights, Macroscopy and Microscopy: termination

Toxicokinetics: plasma levels were determined at various times on days 1 and 29.

The following organs were weighed:

Brain	Heart	Liver	Testes
Pituitary	Adrenals	Spleen	Ovaries
Kidneys	Thymus	Prostate	Uterus (uterus, cervix)
Thyroids/Parathyroids			

The following tissues were examined histologically.

Adrenal Gland	Lung	Skin/Subcutis
Aorta	Lymph Node, Mandibular	Spinal Cord
Brain	Lymph Node, Mesenteric	Spleen
Bone(sternal)	Mammary Gland	Stomach
Epididymis	Marrow(sternal)	Testis
Esophagus	Ovary	Thymus
Eye	Pancreas	Thyroid
Gallbladder	Parathyroid	Tongue
Heart	Peripheral Nerve	Urinary Bladder
Intestine, Large	Pituitary	Uterus
Intestine, Small	Prostate	Vagina
Kidney	Salivary Gland	
Liver	Skeletal Muscle	

Toxicokinetics: The Cmaxs and AUCs 0-8 h are presented in the following tables. At all doses the Cmaxs and AUCs in F were higher than in the M. MDL 16,455A does not accumulate upon repeated administration.

Mean^a Maximum Plasma Concentrations (Cmax)

Dose (mg/kg/day)	Day 1		Day 2 ^b	
	Sex	Cmax (ng/mL)	Sex	Cmax (ng/mL)
90	M	15404 ± 20361	M	9257 ± 1856
	F	28999 ± 14322	F	15420 ± 5920
300	M	19354 ± 15773	M	29332 ± 7979
	F	39339 ± 28788	F	34239 ± 5103
900	M	57526 ± 46402	M	65357 ± 10889
	F	100403 ± 16289	F	72895 ± 21590

^aMean ± SD (n=4 dogs/sex/dose).

Mean^a AUC₀₋₈

Dose (mg/kg/day)	Day 1		Day 2 ^b	
	Sex	AUC ₀₋₈ (ng h/ml)	Sex	AUC ₀₋₈ (ng h/ml)
90	M	55499 ± 22154	M	39107 ± 14742
	F	102675 ± 52942	F	53814 ± 12913
300	M	55403 ± 41529	M	93006 ± 30166
	F	129520 ± 84034	F	108440 ± 13449
900	M	234891 ± 248154	M	237641 ± 68812
	F	355667 ± 101039	F	370096 ± 100125

^aMean ± SD (n=4 dogs/sex/dose).

Results

Mortality: None.

Clinical Observations: M, F, HD, increased incidence of salivation and of emetic episodes.

Body Weight: No effect.

Food Consumption: No effect.

Heat Rate: No effect.

Electrocardiogram: No effect.

Hematology: No effect.

Clinical Chemistry: No effect.

Urinalysis: No effect.

Organ Weights:

Organ	% Change in Weight			
	MD		HD	
	Abs.	Rel.	Abs.	Rel.
Thymus Gland, M	-27 (1/3)	-28 (1/3)	-47 (3/3)	-47 (2/3)
F	0	0	0	0

() No. of animals with weights that were below the lowest weight in the control group.

Histopathology: No changes.

Summary and Conclusion

In a 1 month toxicity in beagle dogs MDL 16,455A was given po in 3 divided doses 90, 300 and 900 mg/kg/day. Increased episodes of emesis and salivation were seen at the HD. Decreased thymus weight was noted at the MD and HD; this was not accompanied by histopathology in the thymus. MDL 16,455A did not show accumulation upon repeated administration; on day 29 the AUCs were dose related and not dose proportional. The NOEL dose was 90 mg/kg.

Summary of Toxicology

MDL 16,455A

In single dose toxicity studies in mice and rats no toxicity was noted at po doses up to 5146 mg/kg. In both species whitish material in the feces indicated that MDL 16,455A was not completely absorbed since it was given as a suspension.

In M dogs MDL 16,455A was administered in one study as a solution in 98.5% propylene glycol and 1.5% acetic acid at 1 and 2 g/kg. No toxicity attributed to MDL 16,455A was seen. The AUCs were dose related. When administered to F as a suspension (270 and 450 mg/kg po) no toxicity was observed.

In a 10-14 day tolerance study at doses up to 300 mg/kg po administered in the 98.5% propylene glycol and 1.5% acetic acid mixture, no toxicity was seen. The AUCs in the F were higher than M. However, maximum absorption occurred at 100 mg/kg in the F since the AUC at 100 and 300 mg/kg were similar.

In the 1 month study in dogs, MDL 16,455A was given 3 times a day; the daily doses were 90, 300 and 900 mg/kg in 98.5% propylene glycol and 1.5% acetic acid. The only toxic symptoms noted were salivation and an increase incidence of emetic episodes at the HD. The M showed at the MD and HD a dose related decrease in the absolute and relative thymus weight. No histopathology was noted. MDL 16,455A did not accumulate upon repeated administration, but the F showed higher AUCs than the M.

Terfenadine

The single, multi-dose, reproductive and genotoxic data are excerpted from the reviews of by C. Oberlander and A. S. Taylor (see their reviews in amendments B and C).

Single Dose

Species	Route	LD50, mg/kg
Mouse	po	>5000
	ip	510
Rat	po	>5000
	ip	474
Rat, Newborn	po	438

Mature rats and mice tolerated terfenadine by the po route. New born rats were more sensitive since the LD50 was > 0.1 that seen in the mature rats. By the ip route intestinal adhesions contributed to the deaths; this was attributed to the insolubility of the terfenadine.

Multi-Dose, Days 7-12

Species	Study	Doses, mg/kg po	Results
<u>Rats</u> 5 M, 5 F/ Group	11-12 Days	150, 500, 1000	No significant toxicity was seen.
<u>Dogs</u> 2 M, 2 F/ Group 1; 1 M, 1 F Groups 2- 4	7-10 Days	100 (7 days) 150 daily or 75 bid; 500 daily or 250 bid; 1000 daily, days 5, 6, 7, 250 mg/kg bid	Emesis-all doses ↓ food consumption, top 3 doses High band erythrocytes, VHD, M ↑ SPGT, VHD, M No dose related hist- pathology
<u>Rabbits</u> 3 F/Group	10 Days	150, 300	Marked anorexia, HD

Multi-Dose, 90 Days

Species	Study	Doses, mg/kg po	Results
<u>Rats</u> 20 M, 20 F/ Group	90 Days	30, 100, 300	HD, 7% ↓ body weight M, All doses, ↑ reticulocytes, Organ Weights M, MD, HD, ↑ abs. and rel. seminal vesicles wt HD, ↓ rel. and abs. heart and ventral prostate wt; MD, ↓ rel. heart wt F, Dose related ↑ abs. and rel. pituitary, thyroid and adrenal wt Gross Pathology: unabsorbed (?) drug in the stomach of 1 M and 1 F MD and 4 M and 9 F HD No histopathology was noted NOEL Dose; 30 mg/kg
<u>Dogs*</u> 4 M, 4 F/ Group	2 Years	30, 100/ reduced to 80 on day 31	LD, no effect HD, tremors ataxia, impaired vision and convulsions; 2 M, 2 F were sacrificed; 2 deaths were related to effects of compound Histopathology, HD, 2/2 surviving dogs showed tubular atrophy in testes NOEL Dose: 30 mg/kg

*This review of the 2 yr study in dogs was made by this reviewer since a portion of the analysis was missing from the report.

Reproductive

Species/Study	Doses, mg/kg	Results
<u>Mice</u> Segment II 20 F/Group	50, 100, 200 by gavage	No effect on fetuses; proper staining techniques were not conducted to detect skeletal abnormalities
<u>Rats</u> Segment I 20 M/Group	50, 150, 300 in Diet to M for 63 days	No effect on fertility, ↓ food consumption and body weight at the HD
Segment I 15 M+ 30 F/ Group	50, 150, 300 in Diet, 81 days to M and 35 days to F	HD M, ↓ Body wt. gained M, No effect on fertility MD, Fo, ↓ no. live pups- related to ↓ body wt. gained and food consumption HD, Fo ↓ body wt. gained and food consumption causing ↓ no. of fetuses, survival rates at 21 days and implantation sites F1 from MD and HD Fo; body weight on day 22 were < controls, attributed to ↓ lactation in the Fo. F1, no effect on reproduction
Segment II 18-20 F/ Group	30, 100, 300 by gavage	No teratology
<u>Rabbit</u>		
Segment II 15 F/Group	30, 100, 300	Deaths, C, 4/19, HD, 9/15 No dose related effects on the fetuses were seen.

Carcinogenicity

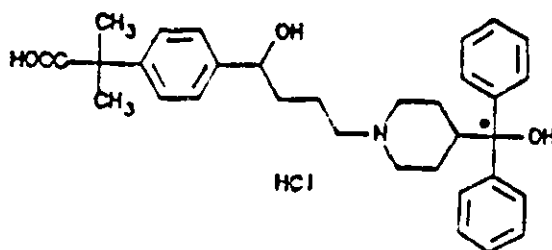
Species/Study	Doses, mg/kg po	Results
<u>Mice</u> 18 Months 50 M, 50 F/ Group <u>Rats</u> 2 Years 50 M, 50 F/ Group	50, 150 in Diet	No change in body weight No increased incidence of tumor or neoplasms Parovarian cysts, C 11/35, HD, 20/41 ↓ Body weight, HD, M, 9%, F, 11 F, uterine adenocarcinoma, C, 0/14, HD, 3/16 F mammary gland adenocarcinoma C, 0/14, HD, 2/16

Genotoxicity

Study	Doses, mg/kg or Concentration	Results
Microbial Plate Tests using Salmonella (TA1535, TA1536, TA1538, TA98, TA100) and Saccharomyces organisms	1-1000 ug/plate	500-1000 ug/plate toxic to organisms; concentrations ≤500 u were not mutagenic directly or in the presence of activated rat liver activated microsomal enzyme systems
E. coli	not stated	Labeling information indicated no mutagenic activity
Bone Marrow Micronucleus Test in mice	500, 1000, 2000 mg/kg q 24 h x 2	No bone marrow toxicity.

Absorption, Distribution, Metabolism, Excretion

Studies were conducted with radiolabeled [^{14}C]MDL 16,455 A with the position of ^{14}C shown in the following structure. Concentrations were determined using



Rats

1. The pharmacokinetics and bioavailability of MDL 16,455A in Sprague-Dawley rats, No.K-93-0422-D. vol. 1.6. p 1273

The following 3 studies were conducted in M Sprague-Dawley rats weighing 275-300 g in the first two studies and 325-350 g in the third study.

STUDY 1: MDL 16,455A was administered orally as a 30 mg/kg aqueous solution dose to groups of 3 fasted male Sprague-Dawley rats. Blood was collected at specified times and the plasma was analyzed for MDL 16,455.

STUDY 2: A 1 mg/kg MDL 16,455A dose was rapidly infused (1 minute) into the tail vein of groups of 3 rats. Blood was collected at specified times and the plasma was analyzed for MDL 16,455.

STUDY 3: A 30 mg/kg [^{14}C]MDL 16,455A oral dose was administered in a micellar solution to two groups of three bile duct-cannulated rats. Bile and urine were collected for 24 hours from one group of rats and for 72 hours from the second group. Blood was obtained at three times, including the terminal blood. Plasma was analyzed for MDL 16,455 and ^{14}C .

Results

Table 1: Pharmacokinetic Parameters of MDL 16,455A (free base) in fasted male Sprague-Dawley rats. The rats were administered a 30 mg/kg oral dose and a 1 mg/kg i.v. dose of MDL 16,455A micellar solution.

MDL 16,455 Parameters	1 mg/kg i.v. Dose	30 mg/kg Oral Dose
Bioavailability (%)		2.9
Cl_{ss} (ml/min/kg)	30.1	30
Elimination half-life		
Initial phase (h)	0.2	0.4
Terminal phase (h)	2.9	4.8
MRT_{ss} (h)	0.2	3.7
$AUC_{0-\infty}$ (ng-h/ml)	399	365
AUC_{0-24} (ng-h/ml)	449	433
AUMC (ng-h/ml)	1570	1811
V_d (L/kg)	0.93	
V_d (L/kg)	5.8	
C_{max} (ng/ml)	584	457
$t_{1/2\beta}$ (h)	0.000	0.5
Supporting Data		Vol Page
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Cl_{ss} = systemic clearance
 MRT_{ss} = mean residence time of oral and i.v. dose in the body
 $AUMC$ = area under the first moment curve
 V_d = volume displaced by MDL 16,455 before distribution to tissues
 V_d = estimated steady state volume of distribution

TABLE 2: Absorption of ^{14}C MDL 16,455A in bile duct-cannulated Sprague-Dawley rats given a 30 mg/kg oral micellar solution dose = 1.0

Animal Number	Collection		Absorbed Dose (%)		Unabsorbed Dose (%)
	Period (h)	Percent Dose as ^{14}C Bile	Urine	(Bile+Urine)	(Feces)
2	0-24	22.0	6.2	28.2	NA ^c
4	0-72	10.5	11.0	21.5	66.8 ^d
Mean	≤ 72	15.3	8.6	24.9	

Summary and Conclusion

Orally, MDL 16,455A was 24% absorbed; due to high clearance of 30 ml/min/kg which approached hepatic plasma flow, bioavailability was only 2.9% of the dose. 65% of the absorbed MDL 16,455A when administered as a micellar solution was taken up by the liver and excreted into the feces by way of the bile; the remaining absorbed MDL 16,455A was excreted in the urine. MDL 16,455A is poorly bioavailable by the po route.

2. The pharmacokinetics and po bioavailability of MDL 16,455A in Sprague-Dawley rats, No.K-93-09871-D, vol. 1.3, p 1304

This report presented the results of 4 studies involving M Sprague-Dawley rats (5-6 rats/dose). They were:

1. Rats were given 5 mg/kg iv of MDL 16,455A or terfenadine; over the following 120 h the urine was analyzed for MDL 16,455A or its conjugated form. Two weeks later the same rats received 10 mg/kg po of the compounds as an aqueous suspension and the urine analyzed for MDL 16,455A and its conjugated form.
2. Rats received 10 mg/kg po of MDL 16,455A in a 98.5% propylene glycol-1.5% acetic acid solution; over the following 120 h the urine was analyzed for MDL 16,455A or its conjugated form.
3. Rats received 10 mg/kg po of MDL 16,455A in a micellar solution; over the following 120 h the urine was analyzed for MDL 16,455A and total radioactivity. 24 h feces were prepared for radiochromatographic profile.
4. Rats received 1 mg/kg iv of MDL 16,455A as a solution in sterile water by the tail vein or portal vein; over the following 120 h the urine was analyzed for total radioactivity. Plasma levels were determined 5 and 10 min following administration. After 1 week these doses were crossed over in the same rats and similar analyses conducted.

Results

The data are summarized in the following tables. MDL 16,455A as the metabolite was 29% bioavailable when administered as terfenadine; when MDL 16,455A was given po, it was only 2.1% bioavailable. Plasma levels at the first sampling of MDL 16,455A following portal vein infusion were 56% lower than plasma levels seen following tail vein administration. Excretion was predominantly in the feces (>80% of the dose) by way of the biliary tract. No metabolites or conjugates were identified.

Table 1. Urinary excretion of MDL 16,455 following iv and oral doses of terfenadine. Bioavailability of MDL 16,455 from the oral dose. ^a (Mean ± SD)		
Percent terfenadine in urine as MDL 16,455		MDL 16,455 bioavailability (% dose)
5 mg/kg iv dose	10 mg/kg oral dose	
11.8 ± 1.2	3.4 ± 1.1	29 ± 10

^a Bioavailability of MDL 16,455 was determined from the ratio of percent dose excreted in the urine as MDL 16,455 after oral vs iv administration of terfenadine.

Table 3. Summary of mass balance for radioactivity 0-120 hours after a 10 mg/kg oral dose and 1 mg/kg single iv doses of [¹⁴C]MDL 16.455A were given to fasted male Sprague-Dawley rats.

Route	Dose (mg/kg)	Percent of dose as ¹⁴ C (mean ± SD)			
		Urine	Feces	Cage Wash	Total
Oral (Micellar)	10	1.18 ± 0.15	87.2 ± 0.5	0.38 ± 0.49	88.8 ± 0.3
Portal Vein	1	4.57 ± 1.25	84.5 ± 2.0	1.13 ± 0.61	90.2 ± 3.0
Tail Vein	1	11.10 ± 1.6	82.4 ± 3.8	1.75 ± 0.76	95.2 ± 2.5

Table 4. Bioavailability and percent dose absorbed in rats given single 10 mg/kg oral solution doses of [¹⁴C]MDL 16.455A (micellar solution) or of nonlabeled MDL 16.455A.

Formulation	Bioavailability ^a (%)	Absorption ^b (% dose)	Systemic availability of formulation ^c (% dose)
Micellar solution	3.2	26	11
Propylene glycol/ 1.5% acetic acid	2.8		
Aqueous solution	2.1 ± 0.9		

- ^a Determined by the ratio of urinary MDL 16.455, as percent of dose, after oral administration to that after a 5 mg/kg iv dose.
- ^b Estimated by the ratio of urinary radioactivity, as percent of dose, after oral administration to that after a 1 mg/kg portal vein administration.
- ^c Determined as in (b) except that the 1 mg/kg iv dose was given in the tail vein.

Summary and Conclusion

MDL 16,455A showed only 2.1% po bioavailability. In vivo bioavailability was increased to 29% when given as the parent compound, terfenadine. There was a substantial uptake of MDL 16,455A by the liver which contributed to its low bioavailability. MDL 16,455A was excreted unchanged predominantly in the feces by way of the biliary tract.

3. Plasma concentration of MDL 16,455A in M and F Sprague-Dawley rats given a single 5 g/kg po suspension of MDL 16,455A, No. K-93-0364, vol. 1.6, p 1350

In this study MDL 16,455A was given as a suspension 5 g/kg po to M and F Sprague Dawley rats. The vehicle was 0.5% aqueous methylcellulose in 0.5% Tween 20. Plasma levels of MDL 16,455A were determine at various intervals up to 72 h.

Results

The results are shown in the following table. Not all the compound was absorbed as whitish material was seen in the feces. The Cmaxs and AUCs 0-24h (M, 7179 ng.h/ml, F, 6931 ng.h/ml) were comparable in M and F and the AUCs0-24h

Plasma concentrations of MDL 16,455 in male and female Sprague-Dawley rats given single 5 g/kg oral suspension doses of MDL 16,455A		
Time (hr)	Concentration (ng/mL) (mean ± SD)	
	Male	Female
0.5	1043.9 ± 111.0	1215.4 ± 295.5
1	1353.1 ± 759.5	1184.3 ± 388.4
2	851.9 ± 193.8	1341.2 ± 228.1
5	194.7 ± 54.2	427.2 ± 348.0
8	208.9 ± 61.5	150.4 ± 52.7
12	149.6 ± 198.8	141.7 ± 114.9
16	277.1 ± 263.6	22.1 ± 5.6
24	38.8 ± 40.0	<22.3
48	<29.4	<LLQ*
72	<84.6	<LLQ*

* Concentration less than lower limit of quantification (5 ng/mL)

Summary and Conclusion

In rats a high dose of 5 g/kg of MDL 16,455A administered as a suspension was not completely absorbed. The Cmaxs and AUCs 0-24h were comparable in M and F.

Dogs

1. A comparison of the absorption and elimination of po MDL 16,455A and terfenadine in beagle dogs, No. F-93-0145-D, vol. 1.6, p 1410

Groups of 3 M beagle dogs received single doses of 8.7 and 27 mg/kg po of MDL 16,455A, 1 mg/kg iv of MDL 16,455A or 1 and 10 mg/kg po of terfenadine. For both compounds the vehicle was 98.5% propylene glycol and 1.5% acetic acid. Plasma levels were determined over 96 h. Excretion by the urinary and fecal routes were determined for this period.

Results

The results are summarized in the following tables. MDL 16,455A was approximately 50% bioavailable based on comparison of the po vs iv AUC or urinary excretion. The AUCs were dose related but not dose proportional. The systemic and renal clearances were low and the terminal half-life were long. This was confirmed by the low urinary excretion of the compound. Excretion was predominantly by the feces by way of the biliary tract. No metabolites were found in the feces.

Absorption of MDL 16,455 in fasted male beagle dogs administered oral doses of MDL 16,455A in a propylene glycol/1.5% acetic acid solution.		
Oral dose (mg/kg)	Percent dose absorbed	
	Plasma AUC ^a	Urine ^b
8.7	56.8 ± 8.4	53.7 ± 23.1
27	44.2 ± 4.3	47.3 ± 9.0

^a Calculated from ratio of oral to iv dose-normalized AUC.

^b Calculated from urinary excretion of MDL 16,455 after oral vs iv administration.

Pharmacokinetic parameters of MDL 16,455 in fasted male beagle dogs administered an 8.7 or 27 mg/kg oral dose of MDL 16,455A in a propylene glycol/1.5% acetic acid solution.		
Parameter	Dose	
	8.7 (mg/kg)	27 (mg/kg)
CL _r (mL/min/kg)	1.77 ± 0.45	1.75 ± 0.40
CL _t (mL/min/kg)	0.189 ± 0.103	0.247 ± 0.156
Elimination half-life		
Initial Phase (h)	1.54 ± 0.50	1.96 ± 0.50
Terminal Phase (h)	13.2 ± 1.9	33.5 ± 3.0
AUC (ng·h/mL)	45.197 ± 13.180	107.505 ± 13.110
AUMC (ng·h ² /mL)	172.452 ± 34.213	429.223 ± 38.147
MRT _t (h)	3.9 ± 0.4	4.0 ± 0.3
C _{max} (ng/mL)	10.503 ± 2.512	26.640 ± 3.516
t _{max} (h)	1.2 ± 0.8	0.7 ± 0.3
A _r (% dose)	2.65 ± 1.82	6.25 ± 4.02

14C materials balance (0-96 hours after a 1 mg/kg iv dose of 14C)MDL 16,455A in fasted male beagle dogs	
Sample	Percent dose as 14C (mean ± SD)
Urine	13.10 ± 7.5
Feces	78.10 ± 0.2
Cage Wash	4.50 ± 0.87
TOTAL	95.70 ± 6.7

When terfenadine was administered po the data for the pharmacokinetic profile for its metabolite, MDL 16,455A, are shown in the following table. The AUCs were dose related and dose proportional and the renal clearance and urinary excretion were low. However, the initial and terminal phase half lives for MDL 16,455A for 10 mg/kg po of terfenadine was similar to that observed for an equimolar dose (8.7 mg/kg po) of MDL 16,455A. Further, the MRT (Mean Residence Time) seen following 10 mg/kg po of terfenadine was more than 3 X that for 8.7 mg/kg po of MDL 16,455A. This indicates that when administered as terfenadine, MDL 16,455A was present in the plasma longer than when it was given as the parent drug.

Parameter	Dose	
	(values, mean ± SD)	
	1 mg/kg	10 mg/kg
C_{12} (mL/min/kg)	0.259 ± 0.032	0.224 ± 0.058
Elimination half-life		
Initial Phase (h)	1.48 ± 0.16	1.71 ± 0.08
Terminal Phase (h)	11.1 ± 2.0	13.5 ± 2.4
AUC (ng·h/mL)	2.665 ± 741	20.552 ± 10.672
AUMC (ng·h ² /mL)	21.311 ± 9.693	316.559 ± 199.503
MRT _h (h)	7.74 ± 1.77	14.7 ± 2.5
C_{max} (ng/mL)	506 ± 106	2.081 ± 1.043
t_{max} (h)	1.5 ± 0.5	2.7 ± 0.6
A_e (% dose)	3.45 ± 1.62	2.31 ± 0.89

Conclusion

In dogs MDL 16,455A was approximately 50% bioavailable; its pharmacokinetics (elimination half life, initial and terminal, systemic and renal clearances) were similar in animals receiving a molar equivalent dose of terfenadine. However, the AUC for MDL 16,455A was 2.5 X and the MRT 1/3 that seen in animals receiving a comparable molar dose of terfenadine.

2. A comparison of the absorption of MDL 16,455A in F beagle dogs given a 500 mg/kg po suspension dose of MDL 16,455A, No.K-93-0370-D, vol. 1.6, p 1468

In 4 F beagle dogs, the pharmacokinetics of 500 mg/kg po of a suspension of MDL 16,455A was determined.

Results

The data presented in the following table show the Cmax and AUC 0-24 were 53,380.7 ng/ml and 358,457 ng.h/ml, respectively.

Pharmacokinetic parameter values for MDL 16,455 in the plasma of female beagle dogs given single 500 mg/kg oral suspension doses of MDL 16,455A.	
Parameter	Values (mean $\pm$ SD)
C _{max} (ng/ml)	53,380.7 $\pm$ 12,897.4
t _{max} (h)	2
AUC ₀₋₂₄ (ng·h/mL)	358,457.0 $\pm$ 31,846

Summary and Conclusion

MDL 16,455A administered as a suspension was poorly absorbed in dogs when compared to administering it as a solution. The AUC for 27 mg/kg po of MDL 16,455A given po as a solution in 98.5 % propylene glycol/1.5% acetic acid mixture was 107.5 ug.h/ml as compared to 358.5 ug.h/ml for administering 19 x the dose (500 mg/kg) of MDL 16,455A as a suspension.

3. Plasma concentrations of MDL 16,455A in beagle dogs given 90, 300 or 900 mg/kg of MDL 16,455A in a 1 month toxicity study, K-93-0460-D, vol. 1.6, p 1485

In the 1 month po toxicity study in dogs, MDL 16,455A was given po as a solution using 98.5% propylene glycol/1.5% acetic acid daily in 3 divided doses (q 8 h) of 10, 100 and 300 mg/kg; the total daily dose was 30, 300 and 900 mg/kg. Plasma levels were determined on days 1 and 29.

Results

The data in the following table show the F show a higher AUC 0-8h than and a higher C_{max} than M at all doses on days 1 and 29. MDL 16,455A did not accumulate upon repeated administration.

Dose (mg/kg/day)	Day 1		Day 29	
	Sex	C _{max} (ng/mL)	Sex	C _{max} (ng/mL)
90	M	15404 ± 12361	M	9857 ± 1856
	F	28999 ± 14323	F	15400 ± 5930
300	M	19354 ± 15773	M	28332 ± 7879
	F	39359 ± 28788	F	34239 ± 9103
900	M	57528 ± 46402	M	65357 ± 10889
	F	100400 ± 16289	F	72885 ± 31599

Conclusion

In a 30 day po toxicity study in dogs, MDL 16,455A produced higher Cmaxs and AUCs in F than in M. MDL 16,455A does not accumulate upon repeated administration.

4. Plasma concentrations of MDL 16,455A and terfenadine in beagle dogs given 80 mg/kg/day capsules doses of terfenadine for 1 month toxicity study, K-93-0431-D, vol. 1.5, p 1226

In 3 M and 3 F dogs terfenadine was administered 80 mg/kg/day in capsules for 1 month. Plasma levels of MDL 16,455A and terfenadine were determined at various intervals on day 28.

Results

The data in the following table present the Cmaxs and AUCs of MDL 16,455A on day 28 and the Cmax and AUC ratios of the MDL 16,455A to terfenadine. The ratios for MDL 16,455A were 10-14 X times higher than terfenadine.

Table 18. Plasma concentrations of MDL 16,455 and terfenadine in beagle dogs given 80 mg/kg/day terfenadine for one month. N = 3 M, 3 F

Time (h)	MDL 16,455 (ng/mL) ^a		Terfenadine (ng/mL)	
	Males	Females	Males	Females
0.5	1.229 ± 37	1.39 ± 502	94 ± 35	199 ± 11
1	1.933 ± 434	2.011 ± 626	202 ± 183	319 ± 261
2	3.032 ± 1.177	4.986 ± 3.790	219 ± 196	419 ± 428
4	1.769 ± 277	4.162 ± 2.940	193 ± 161	380 ± 408
6	1.698 ± 60	3.167 ± 3.760	167 ± 145	312 ± 327
8	1.047 ± 61	2.667 ± 3.272	146 ± 97	252 ± 253
12	565 ± 77	1.146 ± 1.072	114 ± 80	199 ± 176
24	274 ± 131	71 ± 534	42.2 ± 29.4	65 ± 75

^a Data are shown as the mean ± SD

Table 19. Pharmacokinetic parameters for MDL 16,455 and unchanged terfenadine in beagle dogs.

Parameter	MDL 16,455		Terfenadine	
	Male	Female	Male	Female
C _{max} (ng/mL)	3.032 ± 1.177	4.986 ± 3.790	225 ± 191	428 ± 422
C _{max} Ratio ^a	21 ± 15	14 ± 6		
t _{max} (h)	2	2	<2	<2
AUC ₀₋₂₄ (ng·h/mL)	22.804 ± 2.681	46.644 ± 41.922	2.820 ± 2.139	5.100 ± 4.933
AUC ₀₋₂₄ Ratio ^b	11 ± 6	10 ± 2		

^a Ratio of C_{max} of MDL 16,455/C_{max} of terfenadine.

^b Ratio of AUC₀₋₂₄ of MDL 16,455/AUC₀₋₂₄ of terfenadine

Conclusion

In a 1 month study in dogs receiving 80 mg/kg/day terfenadine, the AUCs and Cmaxs of its active metabolite, MDL 16,455A, were 10-14 X higher than the parent compound.

5. Protein binding: Metabolism Studies on terfenadine, vol. 1.6, p 1547

The following table compares the binding properties of terfenadine and MDL 16,455A to the male plasma proteins of rats, dogs and human. The results show that MDL 16,455A at concentrations ranging from 0.1 to 0.8 ug/ml binds to a lesser degree than terfenadine to the plasma proteins of rats, dogs and humans. The binding capacity of MDL-4829 was much weaker than MDL 16,455A and terfenadine.

Table I Protein binding of Terfenadine and its metabolites (MDL-16455 and MDL-4829) in vitro method.

Sample		Ratio of Binding (%)		
		Terfenadine	MDL-16455	MDL-4829
Rat Plasma (male)	0.1 ug/ml	98.5 ± 1.0	80.4 ± 1.2	55.2 ± 0.7
	0.2	99.2 ± 0.3	88.3 ± 1.7	56.7 ± 0.6
	0.4	99.0 ± 0.1	89.7 ± 1.1	54.8 ± 0.8
	0.8	99.4 ± 0.0	88.2 ± 0.4	58.8 ± 0.2
Dog Plasma (male)	0.1 ug/ml	96.7 ± 1.2	93.9 ± 0.7	71.2 ± 1.0
	0.2	98.0 ± 0.3	93.8 ± 0.4	70.1 ± 0.9
	0.4	92.9 ± 0.2	94.0 ± 0.4	70.8 ± 0.1
	0.8	99.2 ± 0.1	94.3 ± 0.1	70.4 ± 0.2
Human Plasma (male)	0.1 ug/ml	99.5 ± 0.5	80.9 ± 0.6	63.1 ± 1.5
	0.2	99.1 ± 0.4	80.8 ± 1.0	65.0 ± 0.4
	0.4	99.0 ± 0.4	89.8 ± 0.4	64.8 ± 0.4
	0.8	99.2 ± 0.0	90.3 ± 0.2	65.1 ± 0.8

Data are expressed as the mean values ± S.E. for three samples.

Summary of Absorption, Distribution, Metabolism, Excretion

In rats MDL 16,455A was only 26%-29% absorbed; its bioavailability was reduced to 2.9% since its clearance was 30 ml/min/kg which approached hepatic plasma flow. Consequently, the compound was quickly taken up by the liver following first pass; it was then excreted in the feces unchanged by way of the bile. This was supported by studies whereby > 80% of the dose was excreted in the feces following portal vein or iv administration. Less than 10% of the dose was found unchanged in the urine. At 5000 mg/kg po poor absorption occurred since the Cmax was low (1.4 ug/ml vs 0.5 ug/ml for 30 mg/kg po) and whitish unabsorbed compound was found in the feces.

The bioavailability of MDL 16,455A was increased 10 fold to 29% when terfenadine was given.

In dogs the MDL 16,455A was approximately 50% bioavailable; unlike the rat its clearance was low (1.77 ml/min/kg). The dog was similar to the rat in that MDL 16,455A was excreted predominantly in the feces by way of the bile. Urinary studies indicated that MDL 16,455A was excreted unchanged. The elimination Terminal Half in the dog was 33.5 h in contrast to 4.8 h for a similar dose in rats indicating a potential longer duration of action.

The absorption of MDL 16,455A by the po route was dependent on the formulation. When given as a solution in 98.5% propylene glycol-1.5% acetic acid a dose of 27 mg/kg produced an AUC 107.5 ug.h/kg. When administering 500 mg/kg of MDL 16,455A as a suspension, the AUC was 358.5 ug/ml. Thus, the absorption of MDL 16,455A was greater when administered as a solution than when it was given as a suspension.

In the 1 month toxicity study in M and F dogs, the daily dose administered as a solution in 3 divided doses was 90, 300 and 900 mg/kg po. The F manifested a higher AUCs than the M and no accumulation occurred in either sex. In a similar study in dogs, terfenadine was given 80 mg/kg/day as a single dose in a capsule for 1 month. At the end of the study, the AUC for MDL 16,455A in animals receiving 80 mg/kg of terfenadine were 41% and 13% lower than those M and F dogs receiving 90 mg/kg/day of MDL 16,455A. Thus, levels of MDL 16,455A were higher in M dogs receiving MDL 16,455A than in M dogs receiving terfenadine. F dogs receiving MDL 16,455A or terfenadine manifested comparable plasma levels of MDL 16,455A.

In in vitro binding studies MDL 16,455A bound to the plasma proteins of rats, dogs and humans to a lesser degree than terfenadine. Indirect studies (pentobarbital sleeping time in mice) indicated that MDL 16,455A was not an enzyme inducer.

SUMMARY AND EVALUATION

MDL 16,455A, a metabolite of terfenadine, is primarily responsible for its antihistaminic activity in animals and in humans. In in vitro binding studies MDL 16,455A was approximately 2 X (KI was 313 nM for terfenadine as compared to 174 nM for MDL 16,455A) more potent than terfenadine in inhibiting the binding of pyrilamine, an H1 receptor blocker, to the rat cerebral cortex. In these studies both enantiomers of MDL 16,455A were equiactive to MDL 16,455A.

In the histamine-induced wheal test in guinea pigs, terfenadine was 1.57 X more potent than MDL 16,455A; 1 mg/kg po of terfenadine was equivalent to 1.8 mg/kg po of MDL 16,455A. In a similar antihistamine assay in humans, MDL 16,455A was tested at single po doses ranging from 10 mg to 360 mg; activity was seen at doses as low as 40 mg; peak activity occurred at 130 mg.

MDL 16,455A demonstrated antihistaminic activity against histamine induced: 1. bronchoconstriction in guinea pigs, 2. contraction of isolated guinea pig ileum and 3. vasodepressor response in dogs. In the dog hindlimb model MDL 16,455A did not alter the vasoconstriction response to phenylephrine. This indicates that clinically MDL 16,455A would not be expected to alter the decongestant response to phenylephrine.

Terfenadine blocked the potassium channels and prolonged the duration of the action potential in vitro, a property of cardiac drugs like quinidine. Consequently, terfenadine produced prolongation of the QTc interval in rabbits and dogs. In view of this patients receiving terfenadine have shown prolongation of QTc intervals and torsades de pointes, an abnormal cardiac rhythm. Further, in subjects receiving erythromycin and terfenadine, there was an accumulation of unmetabolized terfenadine since the antibiotic inhibited its metabolism. Some of these patients manifested a significant increase in their QTc intervals over those seen when given the erythromycin alone (Honig et al, Clin. Pharmacol. Ther. 52:231, 1992). This further supports the culpability of terfenadine for the prolongation of the QTc interval.

A clear advantage of MDL 16,455A over terfenadine is that MDL 16,455A does not block ion channels in particular the potassium channels. This was reflected in MDL 16,455A inducing no increase in the duration of the action potential and no prolongation of QTc intervals in dogs given up to 30 mg/kg bid for 5 days. These results suggests that there is little or no potential for MDL 16,455A to induce the cardiac arrhythmias seen with terfenadine in humans.

In the general pharmacologic models no activity was seen with MDL

16,455A to suggest potential adverse effects.

In rats and dogs MDL 16,455A was excreted unchanged predominantly in the feces by way of the bile. However, its total terminal half life in the rat was approximately 1/7 that of the dog indicating that MDL 16,455A remains in the plasma of the dog 7x longer than in the rat.

In acute toxicity studies on MDL 16,455A in mice and rats, MDL 16,455A was poorly absorbed as unabsorbed material was found in the feces. No toxicity was seen at doses as high as 5146 mg/kg po.

In single dose studies with MDL 16,455A in dogs, (1-2 g/kg in M dogs as a propylene glycol-acetic acid solution and 270 and 450 mg/kg as a suspension in F) no major toxicity was seen. In a 10-day- 2 week dose range finding study in dogs using doses of 10, 30, 100 and 300 mg/kg, the AUC at 100 mg/kg in the F was approximately 9 x higher than the M dogs receiving 100 mg/kg.

In the 1 month study in dogs 90, 300 and 900 mg/kg were given in 3 equally divided doses; the vehicle was 98.5% propylene glycol-1.5% acetic acid. This vehicle was used since it increased the bioavailability of MDL 16,455A as compared to giving MDL 16,455A as a suspension. Emesis and salivation occurred at the HD and the M manifested thymus atrophy at the MD and HD. At all doses F manifested a higher plasma levels than the M. The Noel Dose was 90 mg/kg po and the target organ was the thymus gland. No accumulation of MDL 16,455A occurred.

In rats MDL 16,455A was 2.1%, 2.8% and 3.2% bioavailable when administered in various formulations; this was attributed to high first pass clearance. This was not seen when terfenadine was administered since the availability of MDL 16,455A was increased approximately 10 fold. In dogs the bioavailability of MDL 16,455A was 57%; its first pass clearance was very low.

The following table present the ratios of the AUCs in dogs for MDL 16,455A given po or when plasma was analyzed for MDL 16,455A following the po administration of terfenadine to the AUC for the effective clinical dose of terfenadine (60 mg bid) and the highest reported for MDL 16,455A (200 mg) in humans. The doses from the animal studies were the highest dose of terfenadine tested in the carcinogenicity test in rodents in which no significant incidence of neoplasms were reported. In the 2 y^r study with terfenadine in dogs the HD tested initially was 100 mg/kg po. Due to tremors, ataxia, convulsions and impaired vision the dose was decreased to 80 mg/kg po on day 31. In the 1 month study with MDL 16,455A these toxicologic manifestations were not seen at daily doses of 90, 300 and 900 mg/kg given in 3 divided doses. Salivation and emesis were seen at the HD and decreased

thymus weight in M at the MD and HD. These effects seen in the terfenadine treated dogs were apparently due to the terfenadine and not to its metabolite, MDL 16,455A.

These results suggest that the long term toxicity data for terfenadine is acceptable for MDL 16,455A since 1. terfenadine is already a marketed drug, 2. the antihistaminic activity for terfenadine was due primarily to its metabolite, MDL 16,455A, 3. the AUC for 90 mg/kg of MDL16,455A in dogs was comparable to 80 mg/kg of terfenadine in the same species, 4. the bioavailability of MDL 16,455A in rats was 10 x higher when administered as terfenadine. Thus, the greater exposure of the rats to MDL 16,455A following the administration of terfenadine is preferable to evaluate its toxicity in the rat.

Study/Compound	Dose mg/kg po	AUC ug.h/ml ^a	AUC, Animal	
			AUC, Human TER.*	MDL.**
Terfenadine				
1 Month, Dog, capsule	80	M, 22.8 F, 46.6	6.2 12.6	3.8 7.8
1 Month, Rat, diet	150 _b	M, 11.6 F, 9.1	3.1 2.5	1.9 1.5
1 Month, Mouse, diet	150 ^b	M, 11.4 F, 5.6	3.1 1.5	1.9 0.9
MDL 16,455A				
1 Month, Dog, solution	30, tid	M, 39.1 F, 53.8		6.5 9.0

* 60 mg of terfenadine q 12 h.; AUC 0-inf. based on MDL 16,455A levels, 3.7 ug.h/ml (vol. 1.5, p 1002)

** Based on a single dose of 200 mg of MDL 16,455A ; the AUC 0-T was 6.0 ug.h/ml.

^a Based on MDL 16,455A

^b HD used in the carcinogenicity studies

The toxicity of terfenadine is summarized below since it reflects those of its active metabolite, MDL 16,455A .

In the 90 day po studies in rats (30, 100, 300 mg/kg), toxicity seen was at the MD and HD; there was increased seminal vesicles weight in the M and at all doses increased pituitary, adrenal and thyroid weights in the F. However, no histopathology was noted. Unabsorbed compound was seen in the stomachs of the MD and HD

animals.

In the 2 yr study in dogs (30 and 100 mg/kg po which was reduced to 80 mg/kg on day 31) toxicity was seen only at the HD; ataxia, convulsions and impaired vision were seen. Four animals were sacrificed; 2 were related to the compound. Two/2 surviving dogs showed atrophy of the testes which may have clinical significance. As indicated above none of these effects were seen in the 1 month study with MDL 16,455A at doses up to 900 mg/kg/day.

In the reproductive studies Segment I studies in M and F rats (50, 150, 300 mg/kg/day) terfenadine produced no effect on fertility and reproduction. Based on the doses, the studies were acceptable. In Segment II toxicity in F rabbits (30, 100, 300 mg/kg), no teratology was noted.

In carcinogenicity studies in mice (18 months, 50 and 150 mg/kg in the diet) and in rats (2 years, 50 and 150 mg/kg in the diet), no increase in the incidence of neoplasms were seen in the mice. The HD animals manifested an increased incidence of parovarian cysts (11/35 vs 20/41). In rats decreased body weight occurred in the HD M (-9%) and F (-11%); At the HD a low incidence of uterine adenocarcinomas (0/14 vs 3/16) and mammary gland adenocarcinomas (0/14 vs 2/16) was observed in the F. It was not clear that these results were compound related.

Terfenadine was not mutagenic directly or in the presence of rat activated rat liver microsomal systems in microbial assays and in the Bone Micronucleus test in mice. These studies were an adequate evaluation of the genotoxic effects of MDL 16,455A.

The following table presents the NOEL doses in the 1 month study with MDL 16,455A in dogs and in the 2 yr study in rats with terfenadine. The latter was used since it afforded greater exposure to MDL 16,455A when terfenadine was administered.

Species/Study	NOEL Dose mg/kg po	Supported Human Daily Dose, mg/kg (mg)
Rat, 2 yr Study with Terfenadine	50	5 (250)
Dog, 1 Month Study with MDL 16,455A	90	15 (750)

The proposed human daily doses are 30, 400 and 800 mg. The animal toxicity data in the dog support up to 750 mg daily. The rat data support doses up to 250 mg a day.

RECOMMENDATION

The toxicity based on the 2 year study with MDL 16,455A by way of the administration of terfenadine in the rat, support only the lowest proposed dose, 80 mg/day. The toxicity from the 1 month study with MDL 16,455A in the dog support all 3 doses. Since this is a 7 day study using escalated doses, I see no objection to using these doses in the manner proposed. The final decision to test the 400 and 800 mg must come from the Medical Officer. In a preliminary study using the histamine flare test single doses of 10, 20, 40, 80, 130, 200, 280 and 360 mg were administered to normal M volunteers. Inhibition of the wheal response was initially seen at 40 mg; peak effect occurred at 130 mg. No serious adverse effects were apparently seen as the study is still current and is being conducted on a blind basis.

The long term toxicity data in rats for terfenadine is acceptable for MDL 16,455A since greater exposure to MDL 16,455A occurred following the po administration of terfenadine than with MDL 16,455A.

Two year po toxicity in dogs will be needed if the daily clinical dose exceeds 5 mg/kg (250 mg); this dose is supported by the NOEL dose of 30 mg/kg observed in the 2 year toxicity study of terfenadine in dogs.

Lawrence F. Sancilio

Lawrence F. Sancilio, Ph.D.

cc: Orig.IND
HFD-150/Division File
✓ HFD-150/LSancilio
HFD-150/MSevka
HFD-151/CSO *MS*

Approved by ASTaylor

AUG 9 1994

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Review No. 3

IND:

Serial No. 20 Date of Submission: 5/13/94

Information to be Conveyed to Sponsor: YES (), NO (X)

Date Review Completed: 6/29/94

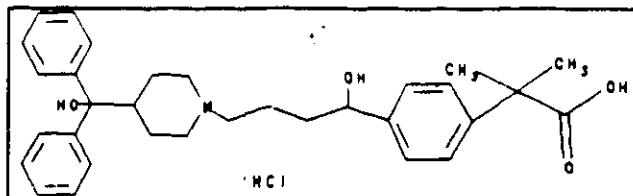
Reviewer: Lawrence F. Sancilio, Ph.D.

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Drug Name: MDL 16,455A, TAM (terfenadine active metabolite)

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)--
1-piperidinyl]butyl'- α,α -dimethyl-, hydrochloride salt $\pm$

Structure:



Molecular Weight: 538.13, $C_{32}H_{39}NO_4 \cdot HCl$

Related NDA: NDA 18-849, Terfenadine

Pharmacological Class: H1 receptor blocker

Indication: Allergic and Seasonal Rhinitis

Route: Oral

Previous Reviews, Dates, Reviewer:

1. 30-Day Review, 10/28/93, Lawrence F. Sancilio, Ph.D.
2. Original, Serial No. 2, Lawrence F. Sancilio, Ph.D.

Relationship Between MDL 16,455A and Terfenadine

Terfenadine is metabolized primarily to the acid metabolite, MDL 16,455A. Terfenadine undergoes 99% first pass metabolism resulting in low systemic bioavailability. The acid metabolite, MDL 16,455A, contributes substantially to the antihistaminic properties of terfenadine. Since the bioavailability of terfenadine was low the sponsor indicated that the toxicity of terfenadine reflected that of MDL 16,455A. Further, the bioavailability of MDL 16,455A in the rat following terfenadine administration was 10 X that when MDL 16,455A given (29% vs 2.9%). Thus, the rat receives greater exposure to MDL 16,455A when administered terfenadine. In view of this the toxicity studies conducted with terfenadine in rats and dogs were acceptable for those of MDL 16,455A.

Studies Reviewed:

1. Maternal and fetal plasma concentration of MDL 16,455 and terfenadine in Sprague-Dawley rats given daily 300 mg/kg po doses of terfenadine, No. K-94-0222-D, vol. 1.
2. Maternal and fetal plasma concentration of MDL 16,455 and terfenadine in Dutch-Belted rabbits given daily 300 mg/kg po doses of terfenadine, No. K-94-0159-D, vol. 1.

Review

1. Maternal and fetal plasma concentration of MDL 16,455 and terfenadine in Sprague-Dawley rats given daily 300 mg/kg po doses of terfenadine, No. K-94-0222-D, vol. 1.

Method

Compound, Terfenadine Lot No.: 70033
Vehicle and Volume: 0.5% methylcellulose/0.5% polysorbate 80 in water; the suspension was given by gavage (3ml/kg).

Species Strain No./ Group/	Weight Range, g	Daily Dose, mg/kg po	Duration of Dosing Days
Sprague- Dawley Primigravid Rats 6/group 2 groups	200-283	300	Day 7-16 of Gestation

Comments: Plasma levels of terfenadine and MDL 16,455 were determined by at 0, 1, 2, 3, 5, 8, 12 and

24 h after dosing in one group of 5 (1 animal aspirated from the gavage dosing and was sacrificed) on day 11 and another group on day 12; on day 16, a caesarian section was made 3 h after the last dose to access the fetal blood. Plasma from the fetuses of each dam was pooled.

Results

The results are presented in the following tables.

1, 2

On days 11 and 12 of gestation the plasma levels for MDL 16,455 and terfenadine were respectively similar; this allowed for their pooling. The plasma levels for terfenadine attained their peak faster than MDL 16,455 as the mean Tmax for terfenadine was 2.54 h as compared to 3.72 h ($P < 0.05$) for MDL 16,455. With one animal (#5305) the Tmax for MDL 16,455 occurred at 2 h in contrast to 3 h for terfenadine. A high level of MDL 16,455 may have been present prior to administration of the terfenadine to account for this finding. The mean Cmax for MDL 16,455 was 4.2 x higher than terfenadine. The AUCs for terfenadine could not be determined since the concentrations at 0 and 24 h were below the limit of quantification. The high AUCs for MDL 16,455 show greater exposure to the acid metabolite than the parent compound.

The plasma levels of MDL 16,455 in the fetuses in 10/12 animals were higher than those observed for terfenadine; in one dam no detectable level of terfenadine was found. The assay detected levels ≥ 100 ng/ml. The maternal/fetus plasma ratios for MDL 16,455 were 44% higher than the ratios for terfenadine. The sponsor proposes that this may be due to a slower maternofetal transfer of MDL 16,455. This is reasonable since MDL 16,455 is an acid and polar.

2. Maternal and fetal plasma concentration of MDL 16,455 and terfenadine in Dutch-Belted rabbits given daily 300 mg/kg po doses of terfenadine, No. K-94-0159-D, vol. 1.

Method

Compound, Terfenadine Lot No.: 70033
Vehicle and Volume: 0.5% methylcellulose/0.5% polysorbate 80 in water; the suspension was given by gavage (3 ml/kg). stated.

Species Strain No./ Group/	Weight Range, kg	Daily Dose, mg/kg po	Duration of Dosing Days
Dutch- BeltedDawley Primigravid Rats 6/group	1.8-1.9	300	Day 8-19 of Gestation

Comments: Plasma levels of terfenadine and MDL 16,455 were determined on day 11 of gestation at 0, 1, 2, 3, 5, 8, 12 and 24 h after dosing. On day 19 plasma levels were determined in the dams and fetuses at the Tmax previously determined on day 11. However, in one of the forthcoming tables, it was indicated that the samples were taken 5 h after the final dose on day 19.

Results:

The results are summarized in the following tables.

Three (No. 5112, 5113 and 5114) of 6 rabbits did not eat the food that was offered (data for degree of reduced food consumption and weight loss were not reported). No other clinical signs were seen. The plasma levels of the dams and their fetuses that did not eat were not different from the animals that did eat.

In the dams the Cmax and AUCs for MDL 16,455 was 88-135 x higher than those for terfenadine. The Tmaxs were generally earlier with terfenadine than with MDL 16,455 in the dams.

At day 19 when the fetuses were delivered by caesarian section, the mean plasma levels for MDL 16,455 in the dams were 19 -76 x higher than those found in the fetuses. The mean terfenadine levels in the dams were 0.03 times that for MDL 16,455. The maternal/fetus ratios of the levels ranged from 0.33 to 1.1; this was much than lower than those seen with MDL 16,455. Thus, terfenadine passes into the fetal circulation much more readily than the active metabolite.

Overall Summary and Evaluation

The antihistaminic activity of the marketed terfenadine, a non-sedative antihistamine, is attributed to its acid metabolite, MDL 16,455. In Segments II studies (ICH Stages C and D) in rats and rabbits, terfenadine was previously shown not to be teratogenic at 300 mg/kg, the highest dose tested.

In this submission 300 mg/kg po of terfenadine was given to pregnant rats and rabbits during the organogenesis period. These doses were previously used in assessing the teratogenic effects of terfenadine in NDA18-949. In those studies plasma levels of terfenadine and its metabolite, MDL 16,455 were not determined. The object of these studies were to determine the maternal and fetal plasma levels of terfenadine and its metabolite during organogenesis. Plasma levels of terfenadine and MDL 16,455 were measured in the dams and fetuses to determine the Cmax and/or AUCs ratios and maternal/fetal ratios for each compound.

The results showed that pregnant rats and rabbits differed in the pharmacokinetics of terfenadine. The rabbit manifested higher levels of MDL 16,455 in both the dams and fetuses than the rat.

Comparison of the results in the rats and rabbits are presented in the following tables.

Parameter	Terfenadine		MDL 16,455	
	Rat	Rabbit	Rat	Rabbit
Cmax, ng/ml	237	76	946	9313
AUC0-24h, ng.h/l	ND	1209	11927	101631

Parameter	MDL 16,455/Terfenadine Ratios of Plasma Levels	
	Rats	Rabbits
Cmax, ng/ml	4.2	135
AUC 0-24h, ng.h/l	ND	89

ND, not determinable since at 0 and 24, concentrations were below the limit of quantitation (100 ng/ml); consequently, AUC 0-24h could not be determined.

The Cmax for terfenadine in the rat was 3 x times higher than in the rabbit; however, the Cmax for MDL 16,455 in the rabbit was 10 x higher than the rat. Further, the rabbit showed a markedly higher MDL 16,455/terfenadine Cmax and AUC 0-24 h ratios than the rat. This indicates that pregnant rabbits were more exposed to the terfenadine and its metabolite than the pregnant rats.

In the fetuses the following table show that in the rat the plasma levels of terfenadine were in some fetuses higher than those observed in the rabbit fetuses. However, the opposite was seen with MDL 16,455. Higher plasma levels of the acid metabolite, MDL 16,455 were seen in the rabbit fetuses. The dam/fetus plasma levels in the rabbits for MDL 16,455 was >50 as compared to approximately 2 for terfenadine in the rat. The sponsor as well as this reviewer believe that the difference may be due to the lipid barrier by the rabbit placenta decreasing the passage of the more polar zwitterionic MDL 16,455 into the fetal circulation.

Parameter	Terfenadine		MDL 16,455	
	Rat	Rabbit	Rat	Rabbit
<u>Dam</u>				
Plasma Level, ng/ml	367	59	895	18741
<u>Fetus</u>				
Plasma Level, ng/ml	<171 (6/11)*	95	223	477
<u>Dam/Fetal Ratio</u>				
Plasma Levels	< 2.3	0.67	4.1	52

* No. of rats with levels of terfenadine that were above the highest level in the terfenadine treated rabbits

The data in the animals was related to human data. Plasma levels were obtained from volunteers receiving 60 mg b.i.d. (2.4 mg/kg) for 8 days. Comparisons of the pharmacokinetics are shown in the following table.

Species	AUC, 0-24 h, ng.h/ml		Species AUC/ Human AUC	
	Terfenadine	MDL 16,455	Ter.	MDL
Human 2.4 mg/kg	29	3212		
Rat 300 mg/kg	ND	11927	ND	3.6
Rabbit 300 mg/kg	1209	101631	42	31.6

ND not determinable

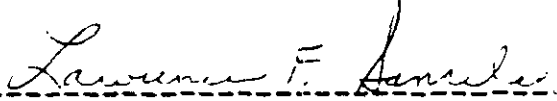
The data shown in the above table show that there was a good margin between the AUCs for MDL 16,455 in rats and rabbits and humans and between the AUC for terfenadine in rabbits and humans. Since the AUC 0-24 for terfenadine could not be determined in rats because the levels were undetectable at 0 and 24 h, there is a wide margin between the AUC for terfenadine in rats and in humans. Comparing the Cmaxs of terfenadine for rats and humans, the ratio was 119 (237 vs 2 ng/ml) which further support this wide margin.

The data presented in this submission indicate that the pharmacokinetics of terfenadine are quantitatively different in pregnant rats and rabbits. At 300 mg/kg the rabbit showed greater exposure to MDL 16,455 than the rat. Based on the plasma levels in the mothers and fetuses and those seen in humans, there is suggestion of a good margin of safety for terfenadine and its active metabolite, MDL 16,455. [Note: 300 mg/kg was the highest dose tested in the Segment II studies in both species, and it was not teratogenic; at the HD it was lethal in rabbits.] Further, since the rabbit shows at 300 mg/kg of terfenadine higher exposure to MDL 16,455 than the rat, the rabbit may be a better species to use in conducting future studies. In addition, the ratios of the AUCs for MDL 16,455 to dose based on mg/m² were similar in humans and rabbits; both were 4-5 X higher than the ratio for the rat (human, 36; rabbit, 28; rat, 6.7).

Recommendation

These results are acceptable as they show a margin of safety for MDL 16,455 based on exposure of pregnant rats and rabbits and their fetuses to a high dose (300 mg/kg pc which was not teratogenic in both species) of terfenadine.

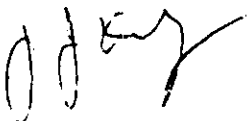
No letter to the Sponsor is necessary.



Lawrence F. Sancilio, Ph.D.

cc: Orig.IND
HFD-150/Division File
HFD-150/LSancilio
HFD-150/MSevka
HFD-151/CSO

Approved by JDeGeorge

 8/19/97

NOV 1 1993

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

30-Day Review

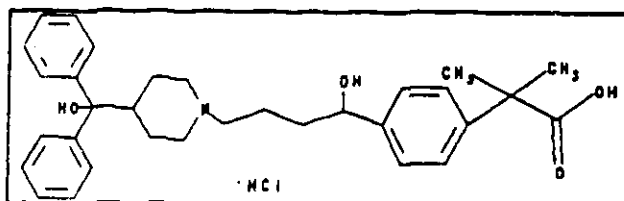
IND: Reviewer: Lawrence F. Sancio, Ph.D.
Date of Submission: 10/4/93
Date Assigned: 10/12/93
Date Initiated: 10/13/93
Date Completed: 10/28/93

Sponsor: Marion Merrell Dow Inc.
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Chemical Name: Benzeneacetic acid, 4-[1-(hydroxydiphenylmethyl)--
1-piperidiny]butyl'- α,α -dimethyl-, hydrochloride salt $\pm$

Name: MDL 16,455A, TAM (terfenadine active metabolite)

Structure:



Molecular Weight: 538.13

Molecular Formula: $C_{32}H_{39}NO_4 \cdot HCl$

Pharmacological Class: H1 receptor blocker

Indication: Allergic and Seasonal Rhinitis

Related Drugs: Terfenadine (NDA)

Proposed Clinical Study:

This is a double blind randomized, placebo controlled 4 period cross-over trial to determine in 40 normal M and F subjects, 1. the effect of MDL 16,455A on QT intervals, 2. the relationship if it exists between plasma levels of MDL 16,455A and changes in QTc and 3. to characterize the multiple dose plasma and urine pharmacokinetics. Each subject will receive either placebo (vehicle, 98.5%:1.5% w/w, propylene glycol-acetic acid), 40 mg (0.8 mg/kg), 200 mg (4 mg/kg) or 400 mg (8 mg/kg) of MDL 16,455A twice daily for 6.5 days. There will be a 14-day wash out period between treatments.

Pharmacology

Using the rat cerebral cortex membrane preparation, MDL 16,455A was more selective than terfenadine (K_i (nM), 176 vs 313) in displacing 3H mepyramine from its binding site. The activity for the + and - enantiomers for each compound were similar.

In ~~in vivo~~ po studies in guinea pigs, MDL 16,455A was 0.5-0.6 X as potent as terfenadine in reducing the skin response to histamine and in blocking the bronchoconstriction induced by antigen in sensitized animals.

MDL 16,455A produced no increase in Qtc interval in anesthetized rabbits when infused iv for 1 h at 10 mg/kg or given 30 mg/kg po bid for 5 days to conscious dogs. Under similar conditions terfenadine induced increase in Qtc interval at 1 mg/kg iv infused over 1 h in anesthetized rabbits or 10 mg/kg po bid for 5 days in conscious dogs.

Using guinea pig ventricular myocytes the approximate IC_{50} s for MDL 16,455A for prolonging the action potential and for inhibiting the Na, K (delayed rectifier current) and Ca channels were $> 10\mu M$.

The IC_{50} s for terfenadine were 5, 3 and 3.3 μM , respectively, for prolonging the action potential and inhibiting the K and Ca channels. In a delayed rectifier K current model using embryonic kidney cells with channels cloned from human hearts, MDL 16,455A was 0.0017 X as potent as terfenadine.

Absorption, Metabolism and Excretion

The results in the following indicate that the bioavailability of MDL 16,455A in the dog was 20 times that in the rat. When administered as terfenadine the bioavailability of MDL 16,455A in the rat was 10 times that for po administered MDL 16,455A. In both species MDL 16,455A was excreted approximately 80% in the feces via the bile and 12% in the urine. No metabolites were found in the feces of both species.

In a 1 month po toxicity study in dogs comparison of the AUCs on day 29 for MDL 16,455A following the po administration of 80

mg/kg terfenadine or 30 mg/kg tid of MDL 16,455A appears to be similar as seen in the following table. The AUCs in dogs were higher in the F than in the M.

Toxicology

Multi-dose studies were submitted only in the dog. In a 30-day study the NOEL dose was 300 mg/kg (100 mg tid). At 300 mg/kg tid only sporadic emesis and salivation were noted. At the NOEL dose the AUC ratios for dog to humans (based on an AUC of 2.351 ug.h/ml for a single dose of 80 mg) were 39.6 and 46.5 for M and F dogs, respectively. MDL 16,455A did accumulate upon repeated administration.

Stereoselective Isomeric Interconversion of Terfenadine

Dogs received po 10 mg/kg po of the +, - or ± terfenadine. Urine analysis revealed that in animals receiving the + or - enantiomer a 0.2%-2.5% of the + enantiomer was converted to the - enantiomer.

In dogs receiving the ± enantiomer, there was a preferential excretion of the - enantiomer within the first 8 h (62.2%-68.7% of the dose); by 48 h the ratio of + to - enantiomer was approximately 50%.

In 2 patients no interconversion of the enantiomers was seen upon examination of their urine.

SUMMARY AND EVALUATION

MDL 16,455A the metabolite of terfenadine is an H1 receptor antagonist. Its po potency was approximately 1/2 that of terfenadine in guinea pigs. In vivo studies in rabbits and dogs show that unlike terfenadine MDL 16,455A does not prolong Qtc interval. It is 2.9% and 57% bioavailable in rats and dogs. When administered as terfenadine the bioavailability of MDL 16,455A increases 10 fold. The AUCs in a 1 month study for MDL 16,455A administered as terfenadine or MDL 16,455A appeared to be comparable. The NOEL dose in dogs in a 1 month study was 300 mg/kg po. There were no targeted organs. In rats more exposure to MDL 16,455A was seen when terfenadine was given. Therefore, the toxicity of MDL 16,455A in rats is evaluated to greater degree by examining the toxicity profile of terfenadine. This was probably the reason the sponsor submitted a multi-dose toxicity in only the dog (Note: this is in my recommendation to the sponsor to justify submitting multi-dose toxicity for only 1 species). In a 3 and 6 month toxicity study in rats the NOEL dose was 30 mg/kg; the targeted organ was the liver which manifested vacuolization at 100 mg/kg in the 6 month study, and increased the thyroid, pituitary and gonad weights in the F in the 3 month study. In dogs the - enantiomer of terfenadine minimally interconverts to

the + enantiomer. No interconversion was seen in man.

The results from the 1 month toxicity study of MDL 16,455A in dogs and the 3 and 6 month toxicity studies of terfenadine in rats support clinical daily doses of 50 and 3 mg/kg, respectively. The doses proposed in the clinical study were 1.6, 8 and 16 mg/kg/day. Since, the data from both species support only the lowest dose, approval must come from the Medical Officer to utilize the 8 and 16 mg/kg doses.

Comparison of the Pharmacokinetics of MDL 16,455A in Rats and Dogs

Parameter	Rat	Dog
Absorption, % of Dose	25	57
Bioavailability, % of Dose	2.9 29*	57
CL _s , Systemic Clearance, ml/min/kg	30	1.8
t _{1/2} , h	0.5	0.7-1.2
Half Life, h		
Initial	0.4	1.5-2.0
Terminal	4.8	13.2-33.5

* When administered as terfenadine

Comparison of the AUCs (Day 29) Observed in the 1 Month Toxicity
in the Dogs Following PO Administration of Terfenadine or MDL
16,455A

Compound	Dose mg/kg/day po	AUC, ug.h/ml	
		0-8	0-24
Terfenadine	80 by capsule		M, 22.8 F, 46.6
MDL 16,455A	30 tid*	M, 39.1 F, 53.8	

* By capsule given as a solution in 98.5%-1.5% w/v propylene glycol-1.5% glacial acetic acid.

RECOMMENDATION

The results of the 1 month toxicity study in dogs (NOEL dose, 300 mg/kg po) support the proposed daily doses for 6.5 days of 80 mg (1.6 mg/kg), 400 mg (8 mg/kg) and 800 mg (16 mg/kg).

Since multi-dose toxicity data were submitted only for dogs, the sponsor was requested to justify not conducting a multi-dose toxicity in rats.

Lawrence F. Sancilio

Lawrence F. Sancilio, Ph.D.

cc: Orig. IND
HFD-150/Division File
✓ HFD-150/LSancilio
HFD-150/MSevka
HFD-151/CSO

aJL 11-1-93

Approved by ASTaylor

NDA 20-625

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

Addendum to Chem. Rev. #3 for NDA 20-625: Labeling Review

NDA #: 20-625

Date: 7/2/96

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel (HMR), Inc.
PO Box 9627
Kansas City, MO 64137

DRUG PRODUCT NAME

Proprietary: Allegra 60 mg Capsules
Nonproprietary/USAN: Fexofenadine HCl 60 mg capsules
Code Name/#: MDL 16,455A
Chem Type/Ther. Class: 1S

PHARMACOL. CATEGORY/INDICATION: Histamine H₁-receptor antagonist for treatment of seasonal allergic rhinitis

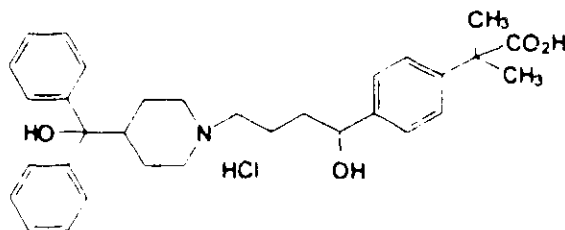
DOSAGE FORM: capsule

STRENGTHS: 60 mg per capsule

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: C₃₂H₃₉NO₄·HCl

Molecular Weight: 538.13

CONCLUSIONS & RECOMMENDATIONS:

The following conclusions regarding the labeling sections containing chemistry, manufacturing, and controls information should be reflected in the labeling:

- 1) Since the blister packaged drug product shows definite decreases in dissolution with concomitant increases in water content, and in the absence of any other data showing that these dissolution problems are not caused by the increased water content in the capsules, all packaging associated with the foil-backed

blister packaged drug product should include a statement indicating protection from excessive moisture

- 2) A statement indicating special storage conditions for the dosage form with respect to light has been deemed unnecessary
- 3) From a CMC standpoint the DESCRIPTION section statement is acceptable with the word "racemate" used to describe the drug substance as per the firm's proposal



Craig M. Bertha, Ph.D. Review Chemist

cc

Orig NDA 20-625

HFD-570/Division File

HFD-570/BRogers/7/2/96

HFD-570/CBertha/7/2/96

HFD-570/GStrange

HFD-570/GPoochikian

HFD-570/MSevka

HFD-510/Y-YChiu

R/D Init by GP 7/2/96

filename addendum cr3

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-625 **CHEM. REVIEW #** 3 **REVIEW DATE:** 6/14/96

RECOMMENDATION: APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7/31/95	8/1/95	8/6/95 (Reviewer 1)
ORIGINAL	7/31/95	8/1/95	2/5/96 (Reviewer 2)
Amendment (BC)	2/15/96	2/16/96	2/23/96 (Reviewer 2)
Amendment (BC)	3/1/96	3/4/96	3/4/96 (Reviewer 2)
Amendment (BC)	4/12/96	4/23/96	4/26/96 (Reviewer 2)
Amendment (AC)	4/26/96*	4/30/96	5/1/96 (Reviewer 1 and 2)
Amendment (BC)	4/29/96	5/13/96	5/20/96 (Reviewer 2)
Amendment (BC)	5/9/96	5/15/96	5/20/96 (Reviewer 2)
Amendment (BC)	5/15/96	5/16/96	5/20/96 (Reviewer 2)
Amendment (BC)**	5/31/96	6/3/96	6/7/96 (Reviewer 2)
Amendment (BC)**	6/6/96	6/10/96	6/11/96 (Reviewer 2)
Amendment (BC)**	6/7/96	6/10/96	6/10/96 (Reviewer 1 and 2)
Amendment (BC)**	6/14/96	6/17/96	6/14/96 (Reviewer 1 and 2)

*Submission date recorded incorrectly in Chem. Rev. #2 as 4/30/96 (see p. 11)

**Subject of this review.

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel (HMR), Inc.
 PO Box 9627
 Kansas City, MO 641344-0627

DRUG PRODUCT NAME
Proprietary: Allegra 60 mg Capsules
Nonproprietary/USAN: Fexofenadine HCl 60 mg capsules
Code Name/#: MDL 16,455A
Chem. Type/Ther. Class: 1S

PHARMACOL. CATEGORY/INDICATION: Histamine H₁-receptor antagonist for treatment of seasonal allergic rhinitis

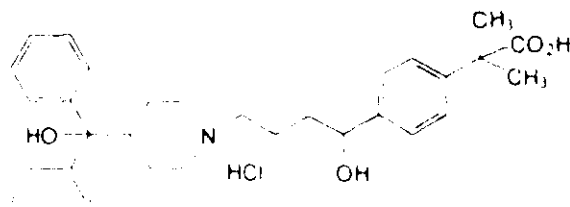
DOSAGE FORM: capsule

STRENGTHS: 60 mg per capsule

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula $C_{12}H_{17}NO_4 \cdot HCl$
Molecular Weight 538.13

SUPPORTING DOCUMENTS:

DMFS

DMF No	Holder Name	Subject	Status	Date Reviewed	Ref. in review

Type
IND
IND

applicable.

Subject

20625

7 OF 7

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	9/28/95	Acceptable	Found acceptable as of 5/15/96
Microbiology HFD-150	Not applicable		.
Biometrics HFD-715	5/13/96	Acceptable	Biometrics evaluation supports a 24 month expiry period (see p. 20)
Biometrics HFD-715	2/29/96	Acceptable	Statistical fill weight determination for capsules was evaluated
Environmental Assessment	EA was consulted to HFD-357 and the review was completed 5/8/96. Response to deficiencies was forwarded to HFD-357 on 6/7/96	Pending	
Methods Validation	Not forwarded		HMR has been requested, in the 6/14/96 Telecon, to submit the MV package by June 21, 1996
Labeling & Nomenclature Committee	12/12/95	Acceptable	Committee originally recommended against trademark under 21CFR201.10(c)(5) but reversed their decision

REMARKS/COMMENTS

CONCLUSIONS & RECOMMENDATIONS:

The application as amended is approvable from the standpoint of chemistry manufacturing and controls pending the approval of the EA consult by HFD-357. The PM should include in the

Remarks/Comments section below

cc:

Orig. NDA 20-625

HFD-570/Division File

HFD-570/BRogers/6/14/96

HFD-570/CBertha/6/14/96

HFD-570/GStrange

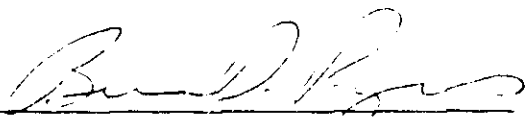
HFD-570/GPoochikian

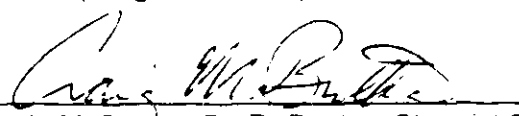
HFD-570/MSevka

HFD-510/Y-YChju

R/D Init by: AR 6/14/96

filename: 96-06-14.rev


Brian D. Rogers, Ph.D., Review Chemist 1
(Drug Substance)


Craig M. Bertha, Ph.D. Review Chemist 2
(Drug Product)

JUN 4 1996

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-625 **CHEM. REVIEW #** 2 **REVIEW DATE:** 5/31/96

RECOMMEND ACTION: NOT APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7/31/95	8/1/95	8/6/95 (Reviewer 1)
ORIGINAL	7/31/95	8/1/95	2/5/96 (Reviewer 2)
Amendment (BC)	2/15/96	2/16/96	2/23/96 (Reviewer 2)
Amendment (BC)	3/1/96	3/4/96	3/4/96 (Reviewer 2)
<u>Subject of this Review</u>			
Amendment (BC)	4/12/96	4/23/96	4/26/96 (Reviewer 2)
Amendment (AC)	4/30/96	4/30/96	5/1/96 (Reviewer 1 and 2)
Amendment (BC)	4/29/96	5/13/96	5/20/96 (Reviewer 2)
Amendment (BC)	5/15/96	5/16/96	5/20/96 (Reviewer 2)

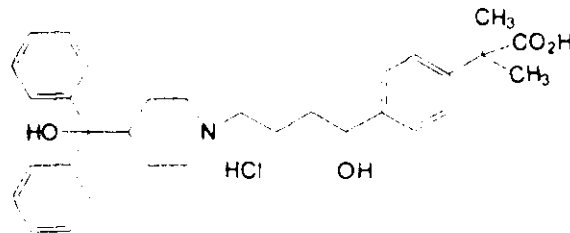
NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
 PO Box 9627
 Kansas City, MO 641344-0627

DRUG PRODUCT NAME
Proprietary: Allegra 60 mg Capsules
Nonproprietary/USAN: Fexofenadine HCl 60 mg capsules
Code Name/#: MDL 16,455A
Chem. Type/Ther. Class: 1S

PHARMACOL. CATEGORY/INDICATION: Histamine H₁-receptor antagonist for treatment of seasonal allergic rhinitis

DOSAGE FORM: capsule
STRENGTHS: 60 mg per capsule
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidiny]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: C₃₂H₃₉NO₄•HCl
 Molecular Weight: 538.13

SUPPORTING DOCUMENTS:

DMFS:

DMF No.	Holder Name	Subject	Status	Date Reviewed	Ref. in review

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			
IND			

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	9/28/95	Complete	Found acceptable on 5/15/96
Microbiology, HFD-160	Not applicable		
Biometrics, HFD-710	a) 5/13/96 b) 2/29/96	a) Pending b) Pending	a) Requested evaluation of expiration period in terms of stability of drug product (assay, degradants, and water content) b) Requested evaluation of the statistical fill weight determination for capsules
Environmental Assessment	EA was consulted to HFD-643 and the review was completed 5/8/96	Deficient	CSO has informed the firm of the deficiencies.
Methods Validation	Not requested; pending method issues resolution by applicant		An updated methods validation package will be requested from the applicant in the letter.
Labeling & Nomenclature Committee	12/12/95	Complete	Committee originally recommended against trademark under 21CFR201.10(c)(5) but reversed their decision.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls summarized in the attached draft letter to the applicant, chemistry portion. These deficiencies should be promptly forwarded to the applicant.

cc:

Orig. NDA 20-625
 HFD-570/Division File
 HFD-570/BRogers/5/31/96
 HFD-570/CBertha/5/31/96
 HFD-570/GStrange
 HFD-570/GPoochikian
 HFD-570/MSevka
 HFD-510/Y-YChiu
 R/D Init by: *AS* 6/4/96
 filename: 96-04-30.rev


 Brian D. Rogers, Ph.D. Review Chemist 1
 (Drug Substance)


 Craig M. Bertha, Ph.D. Review Chemist 2
 (Drug Product)

NDA 20-625

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-625 **CHEM. REVIEW #** 1 **REVIEW DATE:** 4/11/96

RECOMMEND ACTION: NOT APPROVABLE

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7/31/95	8/1/95	8/6/95 (Reviewer 1)
ORIGINAL	7/31/95	8/1/95	2/5/96 (Reviewer 2)
Amendment N(BC)	2/15/96	2/16/96	2/23/96 (Reviewer 2)
Amendment N(BC)	3/1/96	3/4/96	3/4/96 (Reviewer 2)

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
PO Box 9627
Kansas City, MO 641344-0627

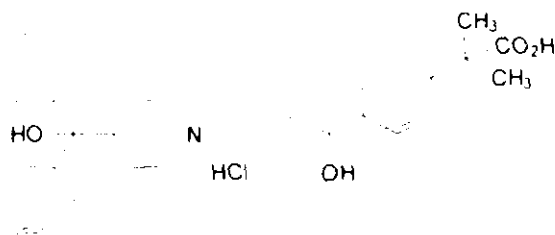
DRUG PRODUCT NAME

<u>Proprietary:</u>	Alliegra 60 mg Capsules
<u>Nonproprietary/USAN:</u>	Fexofenadine HCl 60 mg capsules
<u>Code Name/#:</u>	MDL 16.455A
<u>Chem. Type/Ther. Class:</u>	1S

PHARMACOL. CATEGORY/INDICATION: Histamine H₁-receptor antagonist for treatment of seasonal allergic rhinitis

DOSAGE FORM: capsule
STRENGTHS: 60 mg per capsule
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride (MDL 16,455A)

Molecular Formula: C₂₅H₃₁F₃O₅S
Molecular Weight: 500.57

RELATED DOCUMENTS (if applicable):

Type	Number	Owner	Subject
IND			
IND			

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	9/28/95	Pending	
Microbiology HFD-160	Not applicable		
Biometrics HFD-710	Not requested pending resolution of specification issues with applicant		
Environmental Assessment	EA was consulted to HFD-643 and review is pending	Pending	
Methods Validation	Not requested pending method issues resolution by applicant		
Labeling & Nomenclature Committee	12/12/95	Completed	Committee recommends against trademark under 21CFR201.10(c)(5)

CONCLUSIONS & RECOMMENDATIONS:

The application as submitted is not approvable from the standpoint of chemistry, manufacturing, and controls. Deficiencies are summarized in the attached draft letter to the applicant, chemistry portion. These deficiencies should be promptly forwarded to the applicant.

cc:

Orig NDA 20-625
 HFD-570/Division File
 HFD-570/BRogers/4/11/96
 HFD-570/CBertha/4/3/96
 HFD-570/GStrange
 HFD-570/GPoochikian
 HFD-570/MSevka
 HFD-510/Y-YChiu
 R/D Init by: CP 4/11/96
 filename: N20625.rev



Brian D. Rogers, Ph.D. Review Chemist 1
 (Drug Substance)



Craig M. Bertha, Ph.D. Review Chemist 2
 (Drug Product)

STATISTICAL REVIEW AND EVALUATION STABILITY STUDY

NDA#: 20-625
Applicant: Hoechst Marion Roussel, Inc.
Name of Drug: Allegra (Fexofenadine Hydrochloride or Fexofenadine)
Indication: Treatment of patients with seasonal allergic rhinitis
Documents Reviewed: June 3, 1996 Electronic data and documentation
Statistical Reviewer: B. Bono, M.S.
Chemist: C. Bertha, Ph.D.
Key words: linear regression, intercept, slope, 95% confidence interval, assay, water content, total degradation, degradation product

Summary of Review

- The sponsor proposes a 24 month expiry date based on 18-months of data.
- This review focuses on the clear blister packages, and the 30- and 3000-count bottles.
- The data support a 24 month expiry date for clear, blister packages, 30-count and 3000-count bottles.

I. Background

Hoechst Marion Roussel has submitted 18 month stability data (25 degrees Celsius and 60% relative humidity) on drum, foil, foil blisters, 30-, 100-, 500- and 3000-count HDPE bottles, clear and opaque PVC/PVDC blisters. It should be noted that the clear PVC/PVDC blisters and the 30-, 100-, 500- and 3000-count HDPE bottles are the only packaging types to be used with the United States marketed drug product. The applicant proposed a 24 month expiration period for all of these packages. The reviewing chemist, Craig Bertha, Ph.D., HFD-570, has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data for the clear blister packages and the 30- and 3000-count bottles for each of the following variables using the specifications listed below:

1. Assay (Potency)
2. Water Content
3. Total degradation
4. MDL 102.038 degradation product

II. Reviewer's Analyses

The statistical procedures described in the FDA Guidelines (February 1987) were applied to the stability data provided by the sponsor.

Poolability tests indicate that in the analyses of Assay, Total Degradation and Degradation Product, the data cannot be pooled to calculate common intercepts; and in the analysis of Degradation Product in the 30-count bottles, the data cannot be pooled to calculate a common slope (Table 1). Hence, different regression lines are fitted to the three different batches for all of the factors except water content (Table 2).

Table 1: Poolability Test Results

Factor	Packaging		
	Clear Blister	30-Count Bottles	3000-Count Bottles

Table 2: Regression Lines

Batch	Regression Line

For Assay and Water Content, the estimated expiry dating periods were calculated from the specification limits and the two-sided 95% confidence intervals of the regression lines. For Total Degradation and Degradation Product, the estimated expiry dating periods were calculated from the upper specification limit and the upper one-sided 95% confidence intervals of the regression lines. The estimated expiration dating periods for the three package types are given in Table 3.

Table 3: Estimated Expiry Dating Time

Container	Variable	Time (months)		
		Batch PE4089	Batch PE4092	Batch PE4093

The data for each variable are well within the specification limits, with 95% confidence, for 24 months. The estimated expiry dating period is based on data extrapolation beyond the range of storage time actually observed, which is valid under the assumption that the pattern of deterioration does not change significantly over the extrapolation period.

Figures are attached.

III. Conclusions

The proposed 24 month expiration date for clear blister packages, and 30- and 3000-count bottles is supported by the 18 month data the sponsor submitted. This is based on the specification limits of assay, water content, total degradation and the formation of the MDI degradant. However, the results are based on data extrapolation beyond the range of storage time actually observed. The sponsor should be requested to continue to collect data up to 24 months and reanalyze the data when new data become available.

Barbara A. Bono

Barbara A. Bono

Concur: Dr. Wilson
Dr. Lin

(CW) 7/9/96
KL 7/9/96

cc

Orig: NDA 20-625

HFD-570 - Division File

HFD-570 - GStrange

HFD-570 - CBertha

HFD-570 - GPoochikian

HFD-570 - Y-YChiu

HFD-570 - MSevka

HFD-715 - Division File, Chron

HFD-715 - ENevius, SWilson, KLin, BBono

bb: NDA 20625/STAT/95-07-31.CON

30 Pages

Purged

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
ALLEGRA®
(fexofenadine hydrochloride)
Capsules 60 mg BID
NDA 20-625**

**Division of Pulmonary Drug Products
(HFD-570)**

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FINDING OF NO SIGNIFICANT IMPACT

for

ALLEGRA®

(fexofenadine hydrochloride)

Capsules 60 mg BID

NDA 20-625

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 ALLEGRA®, Hoechst Marion Roussel, Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fexofenadine hydrochloride is a chemically synthesized drug which is administered as a 60 mg capsule BID in the treatment of seasonal allergic rhinitis. The drug substance is manufactured by the n. The finished dosage form is made by Marion Merrell Dow Inc., Kansas City, Missouri. The finished drug product will be used by patients throughout the United States.

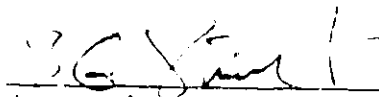
Fexofenadine hydrochloride is minimally metabolized. Chemical and physical test results indicate that fexofenadine hydrochloride will most likely be restricted to the aquatic environment and will not undergo significant hydrolysis, photolysis or biodegradation.

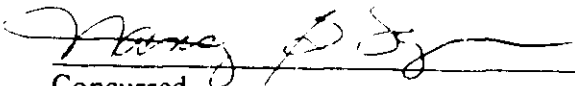
As fexofenadine hydrochloride is expected to persist in the aquatic environment for some time, the toxicity of the drug substance to aquatic organisms was characterized. Acute toxicity of fexofenadine to *Daphnia magna* showed a 48-hour EC_{50} of 780 mg/L and a 48-hour no observed effect concentration of 330 mg/L. In addition, the 96-hour LC_{50} to bluegill fish was >940 mg/L.

and the no observed effect concentration was 570 mg/L. These data show that fexofenadine is relatively non-toxic to aquatic organisms and will not have a significant environmental effect from use or disposal.

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 site. 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.

6/17/96 
DATE Approved
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

6/17/96 
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)

May 30, 1996

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Oncologic and Pulmonary Drugs (HFD-155)
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-2627
Telephone (816) 966-5000

Subject: NDA 20-625 ALLEGRA™
(fexofenadine HCl)

General Correspondence
Company Name Change

Madam/Sir

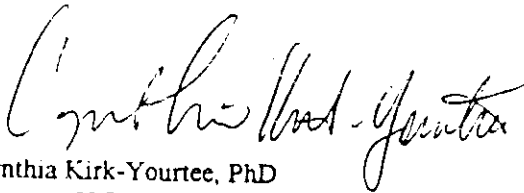
This is to inform you that as a result of the June 1995 acquisition of Marion Merrell Dow Inc. by the Hoechst Corporation, the company previously known as Marion Merrell Dow Inc. is now known as HOECHST MARION ROUSSEL, INC.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate. All investigators, protocols, and the direction of the INDs and/or NDAs has remained the same. Also, be advised that all investigators will be advised of the name change as appropriate.

If you should have any questions or comments concerning this submission, please contact the undersigned at:

HOECHST MARION ROUSSEL, INC
P.O. Box 9707
Kansas City, Missouri 64134-0707
(816) 966-7714

Sincerely,



Cynthia Kirk-Yourtee, PhD
Director, U.S. Regulatory Affairs

Hoechst Marion Roussel
A member of the Hoechst Group

Hoechst 

Marion Merrell Dow Inc.
Kansas City, Missouri 64134

NDA 20-625

S3-V1.12-P236

lexofenadine hydrochloride capsule

- 3. Chemistry, Manufacturing and Controls
- E. Environmental Assessment

Exhibit 13. MDL 16,455A Environmental Assessment FOI Copy

**REDACTIONS MADE
BY APPLICANT**

Marion Merrell Dow Inc
Kansas City, Missouri 64134

NDA 20-625

S3-V1.12-P237

fexofenadine hydrochloride capsule

- 3. Chemistry, Manufacturing and Controls
- E. Environmental Assessment - **FOI COPY**

E. Environmental Assessment

**REDACTIONS MADE
BY APPLICANT**

levofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment - FOI COPY

**REDACTIONS MADE
BY APPLICANT**

Introduction and Summary

This Environmental Assessment (EA) follows the content and format described in 21 CFR § 25.30, specifically, Format 1 as described in 21 CFR §25.31 a. *Appendix 15 (a), S3-V1.11-P36 (CONFIDENTIAL)* provides the summary data chart for MDL 16,455A and *Appendix 15 (b) i-xi, S3-V1.11-P38 through S3-V1.12-P58* the test reports (CONFIDENTIAL). Based on the information provided herein the applicant concludes it has submitted sufficient information to provide a basis for the agency's determination to prepare a Finding of No Significant Impact (FONSI).

MDL 16,455A labeling is indicated for use in the relief of symptoms of seasonal allergic rhinitis. MDL 16,455A is the hydrochloride salt of the acid metabolite of terfenadine, a non-sedating H₁ antihistamine which has been approved for use in the United States under the trade name Seldane®. The antihistaminic activity of Seldane is associated with the presence of MDL 16,455 in the plasma.

MDL 16,455A drug substance will be manufactured at The Dow Chemical Company, Midland, Michigan. MDL 16,455A 50 mg capsules will be manufactured and packaged by Marion Merrell Dow Inc., Kansas City, Missouri. Rejected, expired, or returned goods will be returned to Marion Merrell Dow Inc., Kansas City, Missouri for evaluation, and materials identified for disposal will be shipped to ENSCO Inc, El Dorado, Arkansas for incineration. The backup location for incineration is The Dow Chemical Company, Midland, Michigan. The manufacture of drug substance or drug product at each site will be conducted with sufficient controls to maintain compliance with applicable emissions requirements and will not impact compliance with emissions requirements at each site. There will be no significant impact on use of resources or energy at each site. The proposed action is not expected to have adverse effects on endangered or threatened species or historical sites near the Midland or Kansas City manufacturing sites.

MDL 16,455A is minimally metabolized. The methyl ester of MDL 16,455 (3.59% dose) and MDL 4,829 (1.47% dose) were the only potential metabolites of MDL 16,455 measured. Biliary and renal excretion are considered the principle routes of elimination for MDL 16,455.

MDL 16,455A is slightly soluble in water; is not expected to hydrolyze; has a low partition coefficient; has a low vapor pressure; and is not expected to photodegrade under normal environmental conditions. Based on these physical/chemical properties, environmental testing was conducted in Tier 1, Aquatic Compartment of the Environmental Assessment Technical Test Matrix.

Environmental fate testing included an aerobic biodegradation study in water. The study indicated MDL 16,455A will not significantly biodegrade (<4%) in water. Environmental effects testing included a microbial growth inhibition study, an acute toxicity study in *Daphnia magna* and an acute toxicity study in the bluegill fish (*Lepomis macrochirus*).

Marion Merrell Dow Inc
Kansas City, Missouri 64134

NDA 20-625

S3-V1.12-P239

terfenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment - **FOI COPY**

The Maximum Expected Emitted Concentration (MEEC) of MDL 16,455A is calculated assuming no metabolism or depletion due to biodegradation processes. The MEEC of (CONFIDENTIAL) of the lowest no-observed effect concentration for the environmental organisms tested. This percentage is (CONFIDENTIAL) orders of magnitude less than the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6). Therefore, the use of MDL 16,455A is not expected to have significant adverse effects in the environment.

The antihistaminic activity of the approved drug Seldane is associated with the presence of MDL 16,455 in the plasma therefore MDL 16,455 is already being excreted into the environment. The alternative to the proposed action is non-approval and the prevention of MDL 16,455A from being available for the use in the relief of symptoms of seasonal allergic rhinitis. Since the proposed action is not expected to have any significant adverse effects on human health or the environment, no alternatives are proposed.

NDA 20-625

S3-V1.12-P240

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment - **FOI COPY**

1. Date

July 31, 1995

**REDACTIONS MADE
BY APPLICANT**

2. Name of Applicant

Marion Merrell Dow Inc.

3. Address

9300 Ward Parkway
Kansas City, Missouri
64114-3321

4. Description of the Proposed Action

a. Description of Requested Approval/Need for the Proposed Action

The Applicant requests approval of a New Drug Application for MDL 16,455A for oral use in the relief of symptoms of seasonal allergic rhinitis. MDL 16,455A is the hydrochloride salt of the acid metabolite of terfenadine, a non-sedating H₁ antihistamine which has been approved for use in the United States under the trade name Seldane. The antihistaminic activity of Seldane is associated with the presence of MDL 16,455 in the plasma.

MDL 16,455A will be supplied in capsule form for oral administration. Capsules will be supplied in 60 mg strength, and the recommended dosage is 60 mg BID. The estimated annual production for the U.S. the first five years following approval of drug product is as follows:

Year	Capsules (000)
1997	(CONFIDENTIAL)
1998	(CONFIDENTIAL)
1999	(CONFIDENTIAL)
2000	(CONFIDENTIAL)
2001	(CONFIDENTIAL)

NDA 20-625

S3-V1.12-P241

fexofenadine hydrochloride capsule

- 3. Chemistry, Manufacturing and Controls
- E. Environmental Assessment - FOI COPY

REDACTIONS MADE
BY APPLICANT

b. Location Where Product Will Be Produced

i. Drug Substance

MDL 16,455A will be produced at The Dow Chemical Company, (CONFIDENTIAL), Midland, Michigan 48667. The Michigan Division of The Dow Chemical Company is situated on approximately 1900 acres in the Saginaw Valley of mid-Michigan. The Tittabawasee River runs through the Michigan Division site. The manufacturing site is adjacent to Midland, Michigan which has a population of approximately 35,000 people. Wastes from the manufacture of MDL 16,455A drug substance will be treated at the Michigan Division site of The Dow Chemical Company in Midland, Michigan.

ii. Drug Product

MDL 16,455A capsules will be produced and packaged at Marion Merrell Dow Inc. facilities located at 10236 Marion Park Drive, (CONFIDENTIAL), Kansas City, Missouri 64137. The plant site is located in the southern portion of Kansas City, Missouri which has a population of 1.6 million people. The site is approximately adjacent to Grandview, Missouri which has a population of approximately 25,000. The facility is about fourteen miles from downtown Kansas City and three to five miles from the business district of Grandview. The facility is located on 180 acres in a mixed use area comprising light industry, retail and wholesale establishments, and residential areas. Roughly half the site has been developed. Manufacturing facilities comprise approximately one-quarter of the developed area with the remainder comprised of Research and Development and general office facilities.

Marion Merrell Dow Inc., Kansas City does only minor chemical synthesis at this facility, the majority of the manufacturing operations are comprised of blending, formulation, compounding, and capsule production. MDL 16,455A drug substance will be produced at Midland, Michigan, and blending formulation, capsule production, and packaging will be done at Kansas City.

The Kansas City site is in rolling terrain with little undisturbed land remaining in this area. The site is located within one-quarter mile of the confluence of three major highways, US 71, Interstate 470 and Interstate 435, located to the west and south of the site.

NDA 20-625

S3-V1.12-P242

texotenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment - FOI COPY

REDACTIONS MADE
BY APPLICANT

c. Locations of Product Use and Disposal of Rejected/Returned Goods

MDL 16,455A will be used by patients with seasonal allergic rhinitis throughout the United States.

i. Drug Substance

Rejected, returned or expired drug substance (if not reprocessed) at the Midland, Michigan manufacturing site will be incinerated at the at The Dow Chemical Incineration Complex:

The Dow Chemical Company, (CONFIDENTIAL), Midland, Michigan 48667

EPA ID No.: MID 000724724

Permitted by: State of Michigan Department of Natural Resources

Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-83, 887-89, 441-88, 336-81A (no expiration)

Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)

Incinerator emission limits are given in *Exhibit 1. Incinerator Emission Limits, The Dow Chemical Company, Midland, Michigan, S3-V1.12-P124* (CONFIDENTIAL).

Rejected, returned or expired drug substance (if not reprocessed) at the Kansas City, Missouri manufacturing site will be incinerated at:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730

EPA ID No.: ARD069748192

Permitted by Arkansas Department of Pollution Control and Ecology

Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)

Construction and Operations Permit: 1009A (until terminated or modified)

NPDES Permit: AR0037800 (expiration October 31, 1995)

Incinerator emission limits are given in *Exhibit 2. Incinerator Emission Limits, ENSCO, Inc., El Dorado, Arkansas, S3-V1.12-P127* (CONFIDENTIAL).

ii. Drug Product

Rejected, expired or returned drug product (if not reprocessed) will be returned to Marion Merrell Dow Inc., 10236 Marion Park Drive, Park C, Kansas City, Missouri 64137 for evaluation and disposal. Materials identified for disposal will be shipped to the following facilities for incineration:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730

EPA ID No.: ARD069748192

Permitted by Arkansas Department of Pollution Control and Ecology

Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)

Construction and Operations Permit: 1009A (until terminated or modified)

NPDES Permit: AR0037800 (expiration October 31, 1995)

NDA 20-625

S3-V1.12-P243

terfenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
ii. Environmental Assessment - FOI COPY

**REDACTIONS MADE
BY APPLICANT**

Incinerator emission limits are given in *Exhibit 2. Incinerator Emission Limits, ENSCO, Inc., El Dorado, Arkansas, S3-V1.12-P127* (CONFIDENTIAL).

Back up location for incineration of drug product is:

The Dow Chemical Company, (CONFIDENTIAL), Midland, Michigan 48667

EPA ID No.: MID 000724724

Permitted by: State of Michigan Department of Natural Resources

Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-83, 887-89, 441-88, 336-81A (no expiration)

Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)

Incinerator emission limits are given in *Exhibit 1. Incinerator Emission Limits, The Dow Chemical Company, Midland, Michigan, S3-V1.12-P124* (CONFIDENTIAL).

5. Identification of Chemical Substances That Are the Subject of the Proposed Action

a. Drug Substance

Chemical Names:

Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]- α - α -dimethyl-, hydrochloride, ($\pm$)

2-(4-{Hydroxy-4-[4-(hydroxy-diphenyl)-methyl]-piperidin-1-yl}-butyl)-phenyl-2-methyl-propionic acid, hydrochloride salt

Generic Name: Fexotenedine hydrochloride

CAS Registry No: 138452-21-8

Code Number: MDL 16,455A

Synonyms: Terfenadine acid metabolite (TAM)
Terfenadine metabolite

Molecular Weight: 538.13

Molecular Formula: C₃₂H₃₉NO₄ • HCl

NDA 20-025

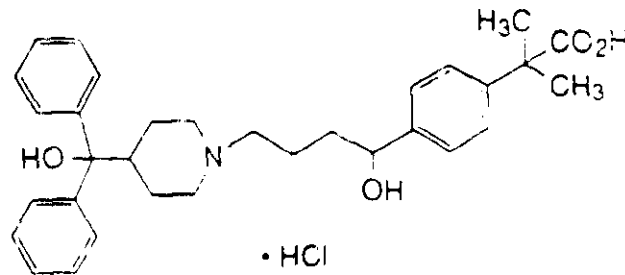
S3-V1.12-P244

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment - FOI COPY

REDACTIONS MADE
BY APPLICANT

Structure:



Physical Description: MDL 16,455A is a white to off-white crystalline powder.

A list of materials used in the preparation of the drug substance is included in *Exhibit 3. Starting Materials, Reagents, Solvents and Auxiliary Materials for MDL 16,455A, S3-V1.12-P136* (CONFIDENTIAL).

A list of drug substance impurities and degradation products is given in *Exhibit 4. Summary of Potential Impurities/Degradation Products in MDL 16,455A, S3-V1.12-P138* (CONFIDENTIAL).

b. Drug Product

Product Name: To be determined

A list of dosage form components is given in *Exhibit 5. Dosage Form Components of MDL 16,455A Capsules, S3-V1.12-P140* (CONFIDENTIAL).

6. Introduction of Substances into the Environment

a. Introduction from Manufacture of Drug Substance

MDL 16,455A will be produced at The Dow Chemical Company, (CONFIDENTIAL), Midland, Michigan, 48667. *Exhibit 6. Chemical Synthesis of MDL 16,455A, S3-V1.12-P142* (CONFIDENTIAL) describes the chemical synthesis of MDL 16,455A, and the chemical substances which may be expected to be emitted to the air, aquatic and terrestrial compartments of the environment as a result of the bulk drug substance manufacturing process. The following provides details of the emissions in the air, aquatic, and terrestrial compartments as a result of the manufacture of the drug substance; statement of controls exercised; citation of and statement of compliance with applicable emissions requirements; and effect of approval on compliance with current emissions requirements.

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S3-V1.12-P245

fexotenedine hydrochloride capsule

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REDACTIONS MADE
BY APPLICANT

i. Air Emissions

List of components of emitted streams:

Component	CAS #	Maximum Yearly Rate (lb/yr)*
CONFIDENTIAL	CONFIDENTIAL	CONFIDENTIAL
* CONFIDENTIAL		

Statement of controls exercised:

Process vent gasses are treated with a gas-fueled thermal oxidizer with minimum design efficiency of 99.9% organic destruction efficiency. Acidic process vent gasses are pretreated with a scrubber using 12 to 25 wt. % NaOH scrubbing fluid with a design efficiency of 90%.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Current air emissions are in compliance with the requirements set forth in The Dow Chemical Air Use Permit as granted by the State of Michigan Department of Natural Resources, Air Use Permit Nos. 1371-91. The thermal oxidizer is operated according to the requirements set forth by the State of Michigan Department of Natural Resources Air Use Permit No. 83-78. Ash from the combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, (CONFIDENTIAL), Midland, Michigan 48667.

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Exhibit 7. Statement of Compliance, The Dow Chemical Company, Midland, Michigan, S3-V1.12-P168* (CONFIDENTIAL).

levotetamide hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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Effect of approval on compliance with current emission requirements at production site:

Production of (CONFIDENTIAL) of MDL 16,455A will impact compliance with current emission requirements as emitted chemicals are not included in the current permit. A new air permit is currently being submitted to ensure compliance with emissions generated from the production of (CONFIDENTIAL) of MDL 16,455A.

ii. Aquatic Emissions

List of components of emitted streams:

Reference Waste Streams Nos. 4, 8, 14, 16 and 19 on MDL 16,455A Blockflow Diagram, Exhibit 8. MDL 16,455A Drug Substance Blockflow Diagram, Midland, Michigan, S3-V1.12-P170 (CONFIDENTIAL).

Component	CAS #	Maximum Yearly Rate (lb/yr)*
CONFIDENTIAL	CONFIDENTIAL	CONFIDENTIAL
* CONFIDENTIAL		

Statement of controls exercised:

The aqueous streams are discharged to The Dow Chemical Company Waste Water Treatment Plant (WWTP). The acids and bases are subsequently neutralized and are discharged as dissolved solids from the WWTP to the Tittabawassee River.

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fexofenadine hydrochloride capsule

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Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Aqueous discharge from The Dow Chemical Company Waste Water Treatment Plant is in compliance with the requirements set forth in the National Pollutants Discharge Elimination System (NPDES) Permit No. MI 40000868 for the Dow Chemical Waste Water Treatment Plant. Total Dissolved Solids daily maximum limit is 750 mg/L and total maximum monthly average is 500 mg/L.

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Exhibit 7. Statement of Compliance, The Dow Chemical Company, Midland, Michigan, S3-V1.12-P168 (CONFIDENTIAL)*.

Effect of approval on compliance with current emission requirements at production site:

Production of (CONFIDENTIAL) of MDL 16,455A will have no impact on compliance with current emission requirements.

iii. Terrestrial Emissions

List of components of emitted streams:

Reference Waste Streams Nos. 1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 15, 17, 18, 20, 21, and 22 on MDL 16,455A Blockflow Diagram, *Exhibit 8. MDL 16,455A Drug Substance Blockflow Diagram, Midland, Michigan, S3-V1.12-P170 (CONFIDENTIAL)*.

Component	CAS #	Maximum Yearly Rate (lb/yr)*
CONFIDENTIAL	CONFIDENTIAL	CONFIDENTIAL

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S3-V1.12-P248

fexofenadine hydrochloride capsule

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Component	CAS #	Maximum Yearly Rate (lb/yr)*
CONFIDENTIAL	CONFIDENTIAL	CONFIDENTIAL
CONFIDENTIAL		
CONFIDENTIAL	CONFIDENTIAL	CONFIDENTIAL
CONFIDENTIAL		

Statement of controls exercised:

These streams are incinerated at the Dow Chemical Company Incineration Complex. The thermal oxidizer operates at a minimum efficiency of 99.9%. Ash from the combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, (CONFIDENTIAL), Midland, Michigan 48667.

Citation of and statement of compliance with applicable emission requirements at federal, state and local levels:

The Dow Chemical Thermal Oxidation Unit Permit is operated according to the requirements set forth by the State of Michigan Department of Natural Resources in the Dow Chemical Incineration Complex Air Use Permit Nos. 336-81A, 93-73I, 471-79, 441-88 and State of Michigan Department of Natural Resources Hazardous Waste Facility Operating License EPA ID No. MID 000 724 724. The Dow Chemical Company Salzburg Landfill is operated according to the regu-

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S3-V1.12-P249

fexofenadine hydrochloride capsule

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lations set forth by the State of Michigan Department of Natural Resources, Hazardous Waste Facility Operating License EPA ID No. MID 890 617 435.

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Exhibit 7. Statement of Compliance. The Dow Chemical Company, Midland, Michigan. S3-V1.12-P168 (CONFIDENTIAL)*.

Effect of approval on compliance with current emission requirements at production site:

Production of (CONFIDENTIAL) of MDL 16,455A will have no impact on compliance with current emission requirements.

b. Introduction from Manufacture of Drug Product

MDL 16,455A 60 mg capsules will be manufactured and packaged by Marion Merrell Dow Inc., 10236 Marion Park Drive, (CONFIDENTIAL), Kansas City, Missouri 64137. These manufacturing operations are conducted according to current Good Manufacturing Practices and in compliance with applicable federal, state and local laws, regulations and permits.

MDL 16,455A 60 mg capsules will be packaged for commerce in 100 cc, 150 cc, 720 cc and 1 gallon high density polyethylene (HDPE) bottles and in unit dose blister packages. Each bottle will be secured with induction-sealed aluminum foil. A polypropylene, child-resistant closure will be used on the 100 cc and 720 cc bottles. A polypropylene non-child-resistant closure will be used for 150 cc and 1 gallon bottles. The unit dose-blister packaging will be used for commercial and sampling requirements.

The following provides details of estimated emissions in the air, aquatic and terrestrial compartments as a result of production of the drug product; statement of controls exercised; citation of and statement of compliance with applicable emission requirements; and effect of approval on compliance with current emissions limits.

i. Air Emissions

List of components of emitted streams:

Emission points are given in MDL 16,455A Drug Product Blockflow Diagram, *Exhibit 9. MDL 16,455A Drug Product Blockflow Diagram, Kansas City, Missouri. S3-V1.12-P177 (CONFIDENTIAL)*.

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S3-V1.12-P250

fexofenadine hydrochloride capsule

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Component	CAS #	Maximum Yearly Rate Kansas City (kg/yr)*	ENSCO† Incinerator (kg/yr)
MDL 16,455A	138452-21-8	CONFIDENTIAL	CONFIDENTIAL
Microcrystalline Cellulose	9004-34-6		
Lactose, Hydrous	63-42-3		
Pregelatinized Starch	9005-84-9		
Gelatin	9000-70-8		
Croscarmellose Sodium	74811-65-7		
Water, purified‡	7732-18-5		
* Quantities listed are after treatment and based on fifth year global drug product production.			
† Solid wastes are shipped to ENSCO, Inc. incinerator; quantities are emissions at El Dorado, Arkansas after treatment.			
‡ Removed during processing.			

Statement of controls exercised:

Compliance with air emissions is achieved by product design, process design, operating discipline limiting flow rates and concentrations of air streams to within regulatory limits or by engineered emission control systems for those streams exceeding regulatory limits at the process.

Air emissions from the MDL 16,455A capsule production process will consist of exhausted air containing water vapor, particulates and organic materials.

Compliance with particulate emission standards is achieved utilizing filters operating at 99% efficiency for particulate matter sized 10 microns and below and 99.9% for larger particulates. All process air streams are conveyed through the filters before being released to the environment. Particulate matter collected by the filters and used fabric filter media are disposed of by incineration.

There are no volatile organic emissions from the capsule production; however, such emissions are generated by the Quality Control Laboratory analysis processes. Quality control analytical work will include methodologies currently used for other existing products at this facility. No volatile organic solvents not currently in use will be utilized for this product. Assay, physical testing and stability testing will use small quantities and dilute concentrations of acetonitrile which may volatilize and be exhausted to the atmosphere. These laboratory operations are performed with local ventilation exhausts which do not employ emission control systems. Compliance with organic emission limits is achieved through engineering design and employment of Good Laboratory Practices procedures.

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S3-V1.12-P251

terfenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Marion Merrell Dow Inc. Kansas City facilities air emissions are currently regulated by permit from the Kansas City, Missouri Health Department Air Quality Section (#94/95-AQ-79). Kansas City has been delegated authority for implementation of Missouri state air laws and regulations, which implement the Federal Clean Air Act by the Missouri Department of Natural Resources; the facility is in full compliance with the city permit and state and federal laws.

A signed statement of compliance for drug product manufacture at the Kansas City facilities is included in *Exhibit 10. Statement of Compliance, Marion Merrell Dow Inc., Kansas City, Missouri, S3-V1.12-P179.*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have insignificant effects on compliance with the Kansas City facilities current regulatory requirements. No additional sources of volatile organic compounds will be established for MDL 16,455A and total particulate emissions will be increased by an amount equal to 1.3% or approximately 80 lb/yr vs. 1994 facility emissions of 6,100 lb. The facility will remain in full compliance with its permit and local, state and federal regulations.

ii. Aquatic Emissions

List of components of emitted streams:

Emission points are given in MDL 16,455A Drug Product Blockflow Diagram, *Exhibit 9. MDL 16,455A Drug Product Blockflow Diagram, Kansas City, Missouri, S3-V1.12-P177 (CONFIDENTIAL).*

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S3-V1.12-P252

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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Component	CAS #	Maximum Yearly Rate Kansas City (kg/yr)*
MDL 16,455A	138452-21-8	CONFIDENTIAL
Microcrystalline Cellulose	9004-34-6	
Lactose, Hydrous	63-42-3	
Pregelatinized Starch	9005-84-9	
Gelatin	9000-70-8	
Croscarmellose Sodium	74811-65-7	
Water, for cleaning	7732-18-5	
* Quantities listed are estimated from equipment cleaning operations at 0.001 x total amount processed based on fifth year drug product production. All emitted substances are sent to a city owned public treatment works (POTW). ** Estimated		

Statement of controls exercised:

The Kansas City facility discharges wastewater to a local publicly owned treatment works (POTW). Site discharges are regulated by a permit issued by the Kansas City, Missouri Water Pollution Control Department (expiration date January, 1998). Wastewater is treated at the Blue River Treatment Plant operated by Kansas City, Missouri. Discharges from the Blue River Treatment plant are to the Missouri River under an NPDES permit.

Wastewater from the MDL 16,455A capsule production will consist of cleaning solutions containing residual amounts of raw materials and coating solutions. All process discharges are neutralized and pH adjusted to a pH range of 6 to 10 pH units before discharging to the POTW system.

Citation of and statement of compliance with applicable emission requirements at federal, state and local levels:

Discharges to the POTW system are in compliance with a permit issued by the Kansas City, Missouri Water Pollution Control Department (expiration January, 1998), the State of Missouri, Law and Regulations (Department of Natural Resources) and with the Federal Water Pollution Control Act.

A signed statement of compliance for drug product manufacture at the Kansas City facilities is included in *Exhibit 10. Statement of Compliance, Marion Merrell Dow Inc., Kansas City, Missouri, S3-V1.12-P179* (CONFIDENTIAL).

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S3-V1.12-P253

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will have an insignificant effect on compliance with the Kansas City facility's compliance with its current permit and regulatory requirements.

iii. Terrestrial Emissions

List of components of emitted streams:

Component	CAS #	Maximum Yearly Rate Kansas City (kg/yr)*
MDL 16,455A	138452-21-8	CONFIDENTIAL
Microcrystalline Cellulose	9004-34-6	
Lactose, Hydrous	63-42-3	
Pregelatinized Starch	9005-84-9	
Gelatin	9000-70-8	
Croscarmellose Sodium	74811-65-7	
Water, purified‡	7732-18-5	
* Quantities are based on fifth year drug product production. † Excluded from landfilling/terrestrial emissions by Operating Procedures. Waste is incinerated and accounted for in ENSCO emissions under Section i, Air Emissions. ‡ Removed during processing.		

Statement of controls exercised:

Solid wastes from MDL 16,455A capsule manufacturing consist of small quantities of excipients from Quality Control area and associated wastes from manufacturing and processes. These wastes are collected, possibly recycled, or shipped off-site for incineration. Landfilling is precluded by procedures and would be utilized as emergency back up only.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Terrestrial discharges are in compliance with the Federal Resource Conservation and Recovery Act (Solid Waste Program: US EPA ID No. MOD-007119555) and Missouri Environmental Laws and Regulations (Missouri Hazardous Waste License No. 001603).

A signed statement of compliance for drug product manufacture at the Kansas City site is included in *Exhibit 10. Statement of Compliance, Marion Merrell Dow Inc., Kansas City, Missouri, S3-V1.12-P179* (CONFIDENTIAL).

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S3-V1.12-P254

lexofenadine hydrochloride capsule

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Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will not have a significant effect on compliance with the Kansas City facility's current regulatory requirements.

c. Employee Protection

Drug Substance Site:

Personnel in chemical production facilities are provided with appropriate personal protective equipment including safety glasses and goggles, safety shoes, protective gloves and clothing. Facilities and equipment are designed to minimize employee exposure to hazardous dust, fumes and vapors through engineering, work practices and administrative controls. Industrial hygiene monitoring of exposure to hazardous agents is routinely conducted at all production facilities. For certain non-routine or emergency situations, approved respiratory protection is provided to employees, and they are trained and fitted for use of the applicable respiratory protection device.

Employees are trained in the proper operation of equipment to minimize potential safety, health or environmental risks. Extensive safety training is mandated in all production facilities. Material Safety Data Sheets are available on-site for all chemicals handled in the production facilities.

Drug Product Site:

All associates receive extensive training for both normal and emergency situations as required to perform their respective operations. Associates receive general safety and chemical handling training as well as specialized training of the specific chemical hazards of the chemicals with which they work. Marion Merrell Dow Inc. provides worker protection by providing engineering controls wherever possible for potential hazards associated with noise, hazardous materials or ergonomic hazards. Associates are provided all necessary personal protective apparel to insure compliance with company requirements and that required by Occupational Safety and Health Act (OSHA), Hazard Communication Standard and Laboratory Standard. Also, emergency training and provisions are provided to respond in the event of injury, fire or chemical release to the air, water, or land as required under the applicable federal, state, and local laws.

Marion Merrell Dow Inc. has programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. Marion Merrell Dow Inc. has established emergency plans to be implemented in the event of an injury, spill or fire that may happen at any site or while material is transported around the world. In-plant operation, including distribution and waste management operations, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency operations. Any incident that would require additional specialized expertise, would be provided by local fire, rescue, medical and emergency authorities or emergency response contract specialists.

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S3-V1.12-P255

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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d. Introduction From Disposal of Drug Substance and Drug Product

Drug Substance

Rejected, returned or expired drug substance (if not reprocessed) at the Midland, Michigan manufacturing site will be incinerated at the Dow Chemical Incineration Complex:

The Dow Chemical Company, (CONFIDENTIAL), Midland, Michigan 48667

EPA ID No.: MID 000724724

Permitted by: State of Michigan Department of Natural Resources

Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-83, 887-89, 441-88, 336-81A (no expiration)

Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)

Incinerator emission limits are given in *Exhibit 1. Incinerator Emission Limits, The Dow Chemical Company, Midland, Michigan, S3-V1.12-P124* (CONFIDENTIAL).

Rejected, returned or expired drug substance (if not reprocessed) at the Kansas City, Missouri manufacturing site will be incinerated at:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730

EPA ID No.: ARD069748192

Permitted by Arkansas Department of Pollution Control and Ecology

Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)

Construction and Operations Permit: 1009A (until terminated or modified)

NPDES Permit: AR0037800 (expiration October 31, 1995)

Incinerator emission limits are given in *Exhibit 2. Incinerator Emission Limits, ENSCO, Inc., El Dorado, Arkansas, S3-V1.12-P127* (CONFIDENTIAL).

Drug Product

Rejected, expired or returned drug product (if not reprocessed) will be returned to Marion Merrell Dow Inc., 10236 Marion Park Drive, (CONFIDENTIAL), Kansas City, Missouri 64137 for evaluation and disposal. Materials identified for disposal will be shipped to the following facilities for incineration:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730

EPA ID No.: ARD069748192

Permitted by Arkansas Department of Pollution Control and Ecology

Hazardous Waste Management Permit: 10-H, CSN 70-0098 (expiration June 26, 1998)

Construction and Operations Permit: 1009A (until terminated or modified)

NPDES Permit: AR0037800 (expiration October 31, 1995)

Incinerator emission limits are given in *Exhibit 2. Incinerator Emission Limits, ENSCO, Inc., El Dorado, Arkansas, S3-V1.12-P127* (CONFIDENTIAL).

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S3-V1.12-P256

texofenadine hydrochloride capsule

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Back up location for incineration:

The Dow Chemical Company, (CONFIDENTIAL), Midland, Michigan 48667

EPA ID No.: MID 000724724

Permitted by: State of Michigan Department of Natural Resources

Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-82, 887-89, 441-88, 336-81A (no expiration)

Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)

Incinerator emission limits are given in *Exhibit I. Incinerator Emission Limits, The Dow Chemical Company, Midland, Michigan, S3-V1.12-P124* (CONFIDENTIAL).

Trial burns conducted at the incinerators established maximum emission rates under worst case conditions; 99.99% destruction and removal efficiency (DRE) was demonstrated for principal organic hazardous constituents. Destruction efficiencies are controlled by EPA regulations pertaining to Resource Conservation and Recovery Act (RCRA) guidance 40 CFR 264 Subpart O.

e. Introduction From Use of Drug Product

MDL 16,455A is administered orally and may be used by individuals throughout the United States. The estimated number of patients in the U.S. to be treated with MDL 16,455A capsules annually (CONFIDENTIAL) represents a small percentage (CONFIDENTIAL) of the U.S. population. The estimated market volume of MDL 16,455A capsules in the U.S. (based on 2001 projected sales), is estimated to amount to approximately (CONFIDENTIAL) MDL 16,455A. Excreted drug substance would be introduced into the environment primarily through municipal sewage treatment plants or septic tanks.

MDL 16,455A is minimally metabolized. The methyl ester of MDL 16,455 (3.59% dose) and MDL 4,829 (1.47% dose) were the only potential metabolites of MDL 16,455 measured. Biliary and renal excretion are considered the principle routes of elimination for MDL 16,455 (*Exhibit 11. Chromatographic Analysis of Radiolabelled Peaks in Urine, Feces and Plasma Samples From Humans Administered [¹⁴C]-MDL 16,455A, S3-V1.12-P181*) (CONFIDENTIAL).

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S3-V1.12-P257

terfenadine hydrochloride capsule

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7. Fate of Emitted Substances in the Environment

The maximum expected emitted concentration (MEEC) for the aquatic compartment (inlet to a typical WWTP) may be calculated by the following formula:

$$\text{ppm (in environment)} = (A) (B) (C) (D) (E) (F)$$

where A = pounds/year production
B = year/365 days
C = day person/150 gallons
D = 1/246 million persons (population of U.S., 1991)
E = gallons/8.34 pounds
F = one million

$$\text{ppm (in environment)} = \text{pounds/year production} \times 8.9 \times 10^{-9}$$

The MEEC for MDL 16,455A based on the projected annual production of MDL 16,455A in 2001 may be calculated as follows, assuming no metabolism or biodegradation:

$$\text{MEEC (ppm)} = \text{kg/yr} \times 2.205 \text{ lb/kg} \times 8.9 \times 10^{-9}$$

$$\begin{aligned} \text{MDL 16,455A MEEC} &= (\text{CONFIDENTIAL}) \text{ kg/yr} \times 2.205 \text{ lb/kg} \times 8.9 \times 10^{-9} \\ &= (\text{CONFIDENTIAL}) \end{aligned}$$

Physical/Chemical Properties

The physical and chemical properties of MDL 16,455A have been evaluated and are reported in detail in the *Chemistry, Manufacturing and Controls Section, S3-V1.2-P1* of the NDA document. Those data which are environmentally relevant are summarized here, and in a data summary chart in *Appendix 15 (a) MDL 16,455A Data Summary Chart, S3-V1.11-P36* (CONFIDENTIAL). Except where noted, all studies were conducted by Marion Merrell Dow Inc., Cincinnati, Ohio or Kansas City, Missouri.

Water Solubility

The solubility of MDL 16,455A in water is 2.44 mg/mL at 25°C (*Appendix 15 (b) i. Solubility of MDL 16,455A in Selected Solvents at 25°C, S3-V1.11-P38*) (CONFIDENTIAL).

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S3-V1.12-P258

levofenadine hydrochloride capsule

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Hydrolysis

MDL 16,455A is not expected to hydrolyze due to the absence of hydrolyzable groups such as esters, amides, etc. The estimated hydrolysis rate constant is $<10E-5$ /second.

Dissociation Constant

MDL 16,455A is a diprotic compound having both an acidic functional group and a basic functional group. The compound will be a cation at low pH (less than 3), a zwitterion at intermediate pH (between 5 and 9), and an anion at high pH (greater than 11). The dissociation constants were determined, using pH/solubility data, to be 4.25 and 9.53. (*Appendix 15 (b) ii. Solubility of MDL 16,455 as a Function of pH, S3-V1.11-P48*) (CONFIDENTIAL).

n-Octanol/Water Partition Coefficient

The n-octanol/water partitioning coefficients for MDL 16,455A, a diprotic zwitterionic compound was determined over the pH range 2 to 12. From the observed partitioning coefficients, the intrinsic partitioning coefficients were calculated for the positively charged, neutral and negatively charged species to be: $k_0 = 2.612$, $k_1 = 1.980$ and $k_2 = 5.49$, respectively. The partition coefficients were calculated to be 2.1, 2.0, and 2.8 (log k_{ow} (log P) of 0.32, 0.30 and 0.44) at pH 5, 7 and 9 respectively. (*Appendix 15 (b) iii. Partitioning Profile of MDL 16,455A in n-Octanol/Water, S3-V1.11-P58*) (CONFIDENTIAL).

Vapor Pressure

A study was conducted by The Dow Chemical Company, Midland, Michigan to measure the vapor pressure of MDL 16,455A by the Knudsen-Effusion/Weight Loss Method (*Appendix 15 (b) iv. Vapor Pressure of MDL 16,455A Measured by the Knudsen-Effusion/Weight Loss Method, S3-V1.11-P76*) (CONFIDENTIAL). The vapor pressure was found to be $< 5 \times 10^{-10}$ mmHg at 78.2 °C.

Melting Temperature

Upon heating, MDL 16,455A melts with decomposition at a DSC onset temperature above 190 °C (scan rate = 10^2 °C/min) (*Appendix 15 (b) v. MDL 16,455A - Melting Point Evaluation, S3-V1.11-P90*) (CONFIDENTIAL).

Ultraviolet -Visible Absorption Spectrum

MDL 16,455A shows UV absorbance maxima at 259 nm and 254 nm (*Appendix 15 (b) vi. MDL 16,455A - Analytical Evaluation of MDL 16,455A-048 as the Analytical Reference Standard, S3-V1.11-P99*) (CONFIDENTIAL).

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S3-V1.12-P259

texofenadine hydrochloride capsule

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Summary

Based on the above physical/chemical properties of MDL 16,455A, testing was conducted in Tier 1, Aquatic Compartment of the Environmental Assessment Technical Test Matrix.

Aerobic Biodegradation

An aerobic biodegradation study in water on [14C]-MDL 16,455A was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri (*Appendix 15 (b) vii. Aerobic Biodegradation of [14C] - MDL 16,455A in Water, S3-V1.11-P144*) (CONFIDENTIAL). No mineralization was observed during the 28-day test period. [14C]-MDL 16,455A was biotransformed slightly with a polar and non-polar degradate comprising 2.6% and 0.7%, respectively of the applied radioactivity.

Predicted Environmental Concentrations of MDL 16,455A

Air:

MDL 16,455A's low vapor pressure and solubility in water preclude the air compartment from being affected by volatilization of this substance at the public sewage treatment plant. Manufacturing controls would prevent significant releases to the air during the manufacturing process.

Freshwater, Estuarine, and Marine Ecosystems:

Since the majority of MDL 16,455A will be discharged to public sewage treatment plants as a result of patient usage, the majority of environmental transport and biotransformation processes will occur primarily in the aquatic compartment. As MDL 16,455A is soluble in water and is not expected to hydrolyze, photodegrade under normal environmental conditions, or biodegrade in water, aquatic toxicity testing was conducted in *Daphnia magna* and bluegill fish (*Lepomis macrochirus*) and is reported in Section 8 of the Environmental Assessment.

Terrestrial Ecosystems:

The n-octanol/water partition coefficient of MDL 16,455A at pH 7 is 2.0; log P (or log K_{ow}) is 0.30. The adsorption coefficient (K_{oc}) is calculated from the partition coefficient by the equation $\text{Log } K_{oc} = 0.554 \text{ Log } K_{ow} + 1.377$ and is 1.54. The K_{oc} and solubility in water predicts MDL 16,455A would be mobile and would not be expected to bioconcentrate or bind to soil.

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S3-V1.12-P260

fexofenadine hydrochloride capsule

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8. Environmental Effects of Released Substances

Expected Emitted Concentration

The Expected Emitted Concentration (EEC) of MDL 16,455A is calculated as follows:

EEC = MEEC - depletion due to biodegradation processes.

Assuming no biodegradation of MDL 16,455A, EEC = MEEC = (CONFIDENTIAL).

Nonclinical Toxicology Studies with MDL 16,455A

An acute oral toxicity study in mice and rats was conducted by the Merrell Dow Research Institute, Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio (*Appendix 15 (b) viii. Acute Oral Toxicity of MDL 16,455A in Mice and Rats, S3-V1.11-P223*) (CONFIDENTIAL). The approximate oral LD₅₀ of MDL 16,455A for mice and rats was > 5146 mg/kg. The toxicology of MDL 16,455A has been evaluated and is reported in detail in the *Section 5C. Toxicology, S5-V1.17-P1* of the NDA submission.

Microbial Growth Inhibition

A microbial growth inhibition study on MDL 16,455A was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri (*Appendix 15 (b) ix. Microbial Growth Inhibition with MDL 16,455A, S3-V1.11-P241*) (CONFIDENTIAL). No inhibition was observed for *Pseudomonas fluorescens*, *Bacillus megaterium*, *Azotobacter chroococcum*, *Aspergillus clavatus*, *Penicillium canescens* and *Chaetomium globosum* at any concentration of MDL 16,455A up to and including 1000 mg/L. Therefore the MIC for these species was > 1000 mg/L. The MIC for *Anabaena flos-aquae* was 400 mg/L.

The MEEC of MDL 16,455A represents (CONFIDENTIAL) of the MIC for *Anabaena flos-aquae*, the lowest MIC determined for the above microorganisms. This percentage is well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

Aquatic Toxicology Studies with MDL 16,455A

Daphnia magna

An acute toxicity study in *Daphnia magna* was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri (*Appendix 15 (b) x. Acute Toxicity of MDL 16,455A to Daphnia magna, S3-V1.12-P1*) (CONFIDENTIAL). The 48-hour EC₅₀ for MDL 16,455A was 780 mg/L. The 48-hour no-observed effect concentration was 330 mg/L.

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fexofenadine hydrochloride capsule

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The MEEC of MDL 16,455A represents (CONFIDENTIAL) of the acutely toxic level and (CONFIDENTIAL) of the NOEC in *Daphnia magna*. These percentages are well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

Freshwater Fish

An acute toxicity study in the bluegill fish (*Lepomis macrochirus*) was conducted by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri (*Appendix 15 (b) xi. Static Acute Toxicity of MDL 16,455A to Bluegill (Lepomis macrochirus), S3-V1.12-P58*) (CONFIDENTIAL). The 96-hour LC₅₀ for MDL 16,455A was > 940 mg/L. The 96-hour no-observed effect concentration was 570 mg/L.

The MEEC of MDL 16,455A represents (CONFIDENTIAL) of the acutely toxic level and (CONFIDENTIAL) of the NOEC in *Lepomis macrochirus*. These percentages are well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

Conclusion:

The MEEC of MDL 16,455A is calculated assuming no metabolism or depletion due to biodegradation processes. The MEEC of (CONFIDENTIAL) of the lowest no-observed effect concentration for the environmental organisms tested. This percentage is (CONFIDENTIAL) orders of magnitude less than the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6). Therefore, the use of MDL 16,455A is not expected to have significant adverse effects in the environment.

9. Use of Resources and Energy

a. Drug Substance

There will not be a significant impact on total usage of energy or utilities by the Michigan Division site of The Dow Chemical Company as a result of manufacture MDL 16,455A. The total steam and electrical power consumption for this purpose will be less than 1% of the overall site usage. No new land use will be required for the proposed new action.

The Michigan Department of Natural Resources Wildlife Division was contacted to determine if endangered or threatened species inhabit the area of drug substance manufacture. A search of the Michigan Natural Features Inventory database (Natural Heritage Program, Wildlife division) was conducted. The database indicated there are records of the threatened sedge *Carex serosa* in the Chippewa and Tittabawasee Rivers. The records documenting this species' presence are very old, and the Department of Natural Resources' assessment is the sedge should not be impacted by the manufacturing site.

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The National Register of Historic Places includes at least 17 listings of historical sites in Midland County, Michigan. Consultation with the Midland County Historical Society indicated the nearest historical site is approximately one mile from the plant's property. The proposed action is not expected to have a significant impact on these historical sites, as the controls on the manufacturing process should prevent any adverse effects to these sites.

b. Drug Product

The proposed action will not have a significant impact on total usage of energy or utilities by the Kansas City site. The manufacturing process for MDL 16,455A is expected to require an additional 10% utility requirements above the existing total site utilities usage. Site utility capacity is sufficient to provide this increased usage without need for expansion. No new land use will be required for the proposed new action.

The Missouri Department of Conservation lists the barn owl as a rare species in Jackson County. Consultation with the Department of Conservation indicated there are other species in the area also, but their experience indicated there are none in the immediate vicinity of the manufacturing site. Department staff examined map and computer files for federal and state threatened and endangered species, and determined that no sensitive species or communities are known to occur on the immediate site or surrounding area.

There are at least 134 historical sites in Jackson County, Missouri listed in the National Register of Historic Places. In addition, 13 sites in Jackson County are pending nomination in the Federal Register. The nearest historical site is located approximately one mile from the manufacturing site. The proposed action should not have a significant impact on these sites, as the controls on the manufacturing process will prevent any adverse effects to these sites.

10. Mitigation Measures

An emergency preparedness plan is in place both for the MDL 16,455A production unit and The Dow Chemical Company Michigan Division Site, which includes on-site fire and emergency response personnel. All storage vessels are equipped with secondary containment to prevent groundwater contamination. All operating personnel are trained on both proper industrial hygiene protocols and emergency response procedures.

Marion Merrell Dow Inc. has programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. Marion Merrell Dow Inc. has established emergency plans which are implemented in the event of an injury, spill or fire that may happen at any site or during transport around the world. All plant operations, including distribution and waste management, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency procedures. Material Safety Data Sheets for drug substance and drug product are available (*Exhibit 12. MSDS for MDL 16,455A Drug Substance and Drug Product, S3-V1.12-P226*) (CONFIDENTIAL). Any

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terfenadine hydrochloride capsule

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incident that would require additional specialized expertise would be provided by local fire, rescue, medical and emergency authorities or emergency response contract specialists. Additionally, the worldwide emergency response capabilities of The Dow Chemical Company are available under written agreement with Marion Merrell Dow Inc.

11. Alternatives to the Proposed Action

The antihistaminic activity of the approved drug Seldane is associated with the presence of MDL 16,455 in the plasma therefore MDL 16,455 is already being excreted into the environment. The alternative to the proposed action is non-approval and the prevention of MDL 16,455A from being available for the use in the relief of symptoms of seasonal allergic rhinitis. Since the proposed action is not expected to have any significant adverse effects on human health or the environment, no alternatives are proposed.

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S3-V1.12-P264

terfenadine hydrochloride capsule

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12. List of Preparers

Marion Merrell Dow Inc., Kansas City, Missouri

Don L. Krueger
Environmental Specialist
B.S. Chemical Engineering, University of Missouri, 1967
22 years experience

Vicki J. Selzer
Sr. Associate Scientist, Toxicology
D.V.M. Kansas State University College of Veterinary Medicine, 1985
B.S. Life Science and Physical Science, Kansas State University, 1980
9 Years Experience

Dhiren N. Shah
Director, Global Regulatory CMC
Ph.D. Physical and Industrial Pharmacy, Purdue University, 1979
M.S. Industrial Pharmacy, Columbia University, New York, 1971
B.Pharm Gujarat University, India, 1968
18 years experience

The Dow Chemical Company, Midland, Michigan:

Kirsten L. Lang
Sr. Production Engineer
B.S. Chemical Engineering, University of New Mexico, 1987
7 years experience

Ron M. Lacher
Sr. Process Specialist
B.S. Chemical Engineering, South Dakota School of Mines and Technology, 1972
M.S. Chemical Engineering, South Dakota School of Mines and Technology, 1977
8 years experience

Marion Merrell Dow Inc.
Kansas City, Missouri 64134

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fexofenadine hydrochloride capsule

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Persons and Agencies Consulted

Joan M. Fischer
Marion Merrell Dow Inc.
North American Business Development

State of Michigan Department of Natural Resources
Wildlife Division

Dennis Figg
Endangered Species Coordinator
Missouri Department of Conservation
Natural History Division

Kansas City Landmark Society

Midland County (Michigan) Historical Society

Chamber of Commerce
Kansas City, Missouri

Chamber of Commerce
Grandview, Missouri

U.S. Department of Commerce
Bureau of the Census
Population Division

Hoechst Marion Roussel, Inc.
Kansas City, Missouri, 64134

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S3-V1 BY APPLICANT

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Revised*

Lexofenadine hydrochloride capsule

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13. Certification

The undersigned officials of Hoechst Marion Roussel, Inc. certify that the information presented is true, accurate and complete to the best of the knowledge of Hoechst Marion Roussel, Inc.

Preparation of Environmental Assessment:

Signature: Vicki J. Selzer Date: 5/30/96
Vicki J. Selzer, D.V.M.
Sr. Associate Scientist, Toxicology

Review and Approval of Environmental Assessment:

Signature: Steven D. Barkyoumb Date: 5/30/96
Steven D. Barkyoumb, D.V.M., Ph.D.
Director, Global Drug Safety

Signature: Dhiren N. Shah Date: May 30, 1996
Dhiren N. Shah, Ph.D.
Director, Global Regulatory CMC

* Note the original certification found in Section 3, Volume 1.11 Page 33 was signed prior to the date references in item #1 of the Environmental Assessment. The date in item #1 was projected to correlate with the NDA submission date. The complete Environmental Assessment was officially signed off on June 29, 1995. As requested by FDA May 22, 1996, the sponsor can provide a certification reflecting today's date; however, the original certification is accurate.

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S3-V1.12-P267

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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14. References

The following references were used in the preparation of this Environmental Assessment and are generally available. Specific citations from these references may be obtained upon request.

8. 21 CFR Ch. 1 (4-1-93 Edition)
Part 25 Environmental Impact Considerations
Food and Drug Administration, HHS
9. 40 CFR Ch. V (7-1-93 Edition)
Part 1500 - 1508 Purpose, Policy and Mandate
Council on Environmental Quality
10. Environmental Assessment Technical Assistance Handbook
Food and Drug Administration
March 1987
11. Pharmaceutical Manufacturer's Association
Interim Guidance to the Pharmaceutical Industry for Environmental Assessment
Compliance Requirements for the FDA
July 1991
12. National Register of Historic Places
Volume 1, 1976
Volume 2, 1976
1966 - 1991
13. Federal Register
National Park Service
National Register of Historic Places
Volume 56, 1991
Volume 57, 1992
Volume 58, 1993
Volume 59, 1994

Marion Merrell Dow Inc.
Kansas City, Missouri 64134

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S3-V1.12-P268

terfenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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Attachments

Attachment 1. Dosage Form Components of MDL 16,455A Capsules S3-V1.12-P269

*Attachment 2. Statement of Compliance, The Dow Chemical Company, Midland, Michigan
S3-V1.12-P271*

*Attachment 3. Statement of Compliance, Marion Merrell Dow Inc., Kansas City, Missouri S
3-V1.12-P273*

Attachment 4. MSDS for MDL 16,455A Drug Substance and Drug Product S3-V1.12-P275

Attachment 5. MDL 16,455A Data Summary Chart S3-V1.12-P285

Marion Merrell Dow, Inc.
Kansas City, Missouri 64134

REDACTIONS MADE
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S3-V1.12-P269

lexofenidine hydrochloride capsule

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Attachment 1. Dosage Form Components of MDL 16,455A Capsules

Marion Merrell Dow Inc
Kansas City, Missouri 64134

REDACTIONS MADE
BY APPLICANT

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S3-V1.12-P270

fexofenadine hydrochloride capsule

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Dosage Form Components of MDL 16,455A Capsules:

Component	CAS No.	Molecular Weight	Empirical Formula	Physical Description
Tablet Core				
MDL 16,455A	138452-21-8	538.13	$C_{32}H_{39}NO_4 \cdot HCl$	Off-white powder
Microcrystalline Cellulose	9004-34-6	NS*	Cellulose	White to off-white
Lactose, Hydrated	63-42-3	342.34	$C_{12}H_{22}O_{11}$	White-creamy white crystalline masses
Pregelatinized Starch	9005-25-8	NS*	NS*	White fine powder
Gelatin	9008-70-8	NS*	NS*	Light amber to faint yellow trans- lucent sheets, shreds, flakes, powder or gran- ules
Croscarmellose Sodium	74811-65-7	NS*	NS*	White powder
Water, Purified ^{††}	7732-18-5	18	H ₂ O	Liquid
* Not specified				
† Removed during processing				

Marion Merrell Dow Inc.
Kansas City, Missouri 64134

REDACTIONS MADE
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S3-V1.12-P271

fexofenadine hydrochloride capsule

3. Chemistry, Manufacturing and Controls
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Attachment 2. Statement of Compliance, The Dow Chemical Company, Midland, Michigan



The Dow Chemical Company

E-1000-0000

LEXOLENADINE HYDROCHLORIDE DRUG SUBSTANCE ENVIRONMENTAL ASSESSMENT

Lexolenadine hydrochloride drug substance is manufactured at the Dow Chemical Company's Michigan division facilities, Midland, Michigan, in compliance with all applicable state and federal environmental regulations.

The unlawful release of contaminants to the environment is prevented by the use of appropriate emission control devices such as vent gas scrubbers, particulate filters, and activated waste water treatment.

The process to manufacture lexolenadine hydrochloride drug substance is covered by Air Use Permits issued by the State of Michigan (Air Quality Division of the Michigan Department of Natural Resources pursuant to the delegation of authority from the Michigan Air Pollution Control Commission - Act 348, P.A. 1965, as amended): Air Use Permit No. 1377-91A. The process is in compliance with these rules, which are consistent with and at least as stringent as applicable federal standards under the Clean Air Act.

This process is in compliance with the Resource Conservation and Recovery Act (RCRA) of 1976, Title II (Solid Waste Disposal) and the State of Michigan Public Act 64, the Solid Waste Management Act.

The process is in compliance with the Federal Water Pollution Control Act and the Michigan Water Resources Commission Act under the National Pollution Discharge Elimination System Permit No. MU4-000008.

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827 Building
The Dow Chemical Co.
Midland, MI 48667

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terfenadine hydrochloride capsule

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Attachment 3. Statement of Compliance, Marion Merrell Dow Inc., Kansas City, Missouri



FEXOFENADINE HYDROCHLORIDE DRUG PRODUCT -
ENVIRONMENTAL ASSESSMENT

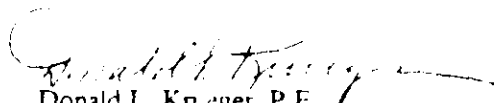
Fexofenadine hydrochloride drug products are manufactured at the Marion Merrell Dow Inc, Kansas City facilities in compliance with all applicable local, state and federal environmental regulations

The release of contaminants to the environment from the Kansas City facility is controlled by the use of appropriate emission control devices such as particulate filters, thermal destruction devices, wastewater treatment and by internal procedures and policies as necessary for compliance

The process to manufacture the fexofenadine hydrochloride drug products is covered by air permits issued by the City of Kansas City, Missouri, Health Department, Air Quality Section (Permit #502), under authority delegated to the City by the Missouri Department of Natural Resources and the US Environmental Protection Agency. The manufacturing process is in compliance with these permits and the underlying rules and regulations the permits and regulations are consistent with and at least as stringent as applicable federal standards under the Clean Air Act

The manufacturing process is in compliance with the Resource Conservation and Recovery Act (RCRA) of 1976, Title II (Solid Waste Disposal) and the State of Missouri Hazardous Waste Management Law and the Solid Waste Law, Title 16

The manufacturing process is in compliance with a wastewater discharge permit issued by the City of Kansas City, Missouri, Water and Pollution Control Department (expires January 1998). The wastewater discharge permit is consistent with and as stringent as applicable state regulations under title 10 of the Missouri Code of State Regulations and federal regulations under the Clean Water Act


Donald L. Krueger, P.E.
Environmental Specialist


Clive W. Bennett
Vice President, Operations
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Kansas City, Missouri 64134

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REDACTIONS MADE
BY APPLICANT

S3-V1.12-P275

fexofenadine hydrochloride capsule

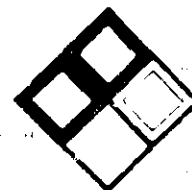
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Attachment 4. MSDS for MDL 16,455A Drug Substance and Drug Product



MATERIAL SAFETY DATA SHEET

S3-V1.12-P276



PREPARATION DATE: 25 January, 1994

SECTION 1: Chemical Product and Company Identification

Common Name: (used on the label) (Trade Name & Synonyms)	MDL16,455A Terfenadine Acid Metabolite TAM
Chemical Name:	Benzeneacetic acid, 4-[1-hydroxy- 4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]- alpha,alpha-dimethyl-hydrochloride
CAS Number:	138452-21-8
Manufacturer's Name: Address:	Marion Merrell Dow 10236 Marion Park Drive Kansas City, Missouri 64137
Emergency Telephone Number:	816-966 5000
Other Information Calls:	816-966-5592, 816-966-5755

SECTION 2: Composition/Information on Ingredients

Material:	MDL16,455A
% Weight:	100
Nature of Hazard:	MDL16455A is the acid metabolite of MDL9918, Terfenadine. Terfenadine is a non-sedating antihistamine. This pharmaceutical product is designed for the treatment of allergic conditions.

SECTION 3: Hazards Identification

Appearance and Odor: White solid

Acute Exposure: The approximate LD50 for mice and rats was > 5146 mg/kg.
Single oral doses of 1000 mg/kg and 2000 mg/kg in male dogs showed no
clinically apparent MDL16,455A related effects.

Chronic Exposure: Oral MDL16,455A was well tolerated clinically up to 300 mg/kg/day for 15
days, with only single sporadic episodes of emesis in dogs, given 300 mg/kg/day.

See Toxicological Information, Section 11.

PREPARATION DATE: 25 January, 1994

SECTION 4: First Aid Measures

Inhalation: Breathe fresh air.

Eyes: Flush thoroughly with water for 15 minutes, seek medical attention.

Skin: Remove contaminated clothing, wash affected area with soap and water.

Ingestion: If material is ingested, seek medical attention.

Note to physician: This material has comparable biological activity to Seidane.

SECTION 5: Fire Fighting Measures

Extinguisher Media: Carbon Dioxide, Dry Chemical Powder, Alcohol or Polymer Foam. Water may be effective for cooling.

Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with the skin.

Unusual Fire and Explosion Hazards: Hydrogen chloride gas and nitrogen oxides may be released.

See Section 9, Physical and Chemical Properties, for explosivity information.

Vapor Pressure: Not applicable.

Vapor Density: Not applicable.

Flashpoint: Not applicable.

Auto-ignition temperature: Not available.

SECTION 6: Accidental Release Information

Steps to be taken in case material is released or spilled: Sweep into suitable container and seal.

Waste Disposal Methods: Dispose according to local, state and/or federal regulations.

SECTION 7: Handling and Storage

Avoid contact with skin, or eyes.

Do not breathe the dust.

Incompatibility: Strong bases.

Hazardous decomposition products: Hydrogen chloride gas, nitrogen oxides.

Hazardous polymerization: Will not occur.

Conditions to Avoid: Temperatures > 190°C.

This material will rapidly dehydrate in a dessicator, or with a dry gas purge. After the material is dehydrated, it will rapidly rehydrate if any moisture is available. It appears that the material would best be stored at humidities between 40% and 60% Relative Humidity.

PREPARATION DATE: 25 January, 1994

SECTION 8: Exposure Controls/Personal Protection

Respiratory Protection: Atmospheric levels should be maintained below the exposure guideline. When respiratory protection is required, for certain operations, a NIOSH approved respirator, equipped with HEPA cartridges must be used.

Ventilation: Provide local exhaust ventilation to control airborne levels below the exposure guidelines.

Protective gloves: Use gloves impervious to this material.

Safety glasses must be used when handling this material.

Additional protective clothing and equipment: Disposable jump suit.

OSHA Permissible Exposure Limit: Not available.

ACG' H Threshold Limit Value: Not available.

Other exposure limits: Marion Merrell Dow Interim Industrial Hygiene Guide-1.0 mg/m³ of air.

This is based on a calculation using 300 mg/kg/day as a no observable effect level.

Chemical listed as a carcinogen or potential carcinogen: No.

National Toxicology Program: No.

I.A.R.C. Monographs: No.

OSHA: No.

SECTION 9: Physical and Chemical Properties

Appearance:	White solid.
Odor:	None.
Physical State:	Solid.
pH:	Not applicable.
Vapor Pressure:	Not applicable.
Boiling Point:	Not applicable.
Melting Point:	195°C-196°C
Specific Gravity:	Not applicable.
DSC:	Broad endotherms from 30°C to 150°C, corresponding to water loss.
TGA:	Samples lose approximately 10% weight to 150°C. Results suggest water content is extremely dependent upon storage conditions.

Solubility:	
Chloroform	0.5 mg/ml

PREPARATION DATE: 25 January, 1994

Hexane	0.1 mg/ml
Methanol	0.81 mg/ml
Tetramethylsilane	0.02 mg/ml
Propylene glycol	185 mg/ml at 25°C
Propylene glycol/acetic acid (98.5:1.5 v/v)	187 mg/ml at 25°C
Ethanol/water	Above 70% ethanol, maximum solubility > 87 mg/ml at 25°C.
Water	3.63 mg/ml at 25°C

Dust Explosivity Data

This dust explosivity data was generated for a sample of MDL16,455A in which 98% of the material went through a 200 mesh sieve. Indicating a particle size of 75µm. The dust explosion characteristics of a material are dependent on the particle size. This information should be considered when processing the drug.

Minimum Ignition Energy	150 millijoules at 0.045 oz/cuft.
Maximum Pressure	85 psig
Maximum Rate of Pressure Rise	15700 psi/sec
Explosion Severity	5.67-Classified as a "Severe" explosion hazard, based on the Bureau of Mines index.
Minimum Explosive Concentration	0.045 oz/cuft.
Volume Resistivity	2.06 x 10E+16 ohm-cm
Dielectric Constant	1.10
Relaxation Constant	2005 Seconds

Electrically, this material is classified as a non-conductor.

SECTION 10: Stability and Reactivity

Stability (Conditions to avoid): Temperatures >190°C

Incompatibility: Strong Bases

Hazardous decomposition products: Hydrogen chloride gas, and nitrogen oxides.

Hazardous polymerization: Will not occur

SECTION 11: Toxicological Information

The approximate oral LD50 for mice and rats was > 5146 mg/kg.

LD50, Single oral administration, mice, male and female > 4500 mg/kg

Dogs-Female-Single oral dose (2 dogs/dose) of 300 and 500 mg/kg-No clinical signs of toxicity or adverse effects on body weights or food consumption.

Single oral dose of 1000 mg/kg and 2000 mg/kg, male dogs, showed no clinically apparent MDL16,455A related effects.

Dogs-1/sex/dose-daily oral doses of 10 or 30 mg/kg/day for 10 days
daily oral doses of 100 or 300 mg/kg/day for 15 days

Conclusion: Oral MDL16,455A was well tolerated clinically up to 300 mg/kg/day for 15 days, with only single sporadic episodes of emesis in dogs given 300 mg/kg/day.

Dogs-Oral-3/sex/dose were given a total of 0, 90, 300, or 900 mg/kg/day

Conclusion: MDL16,455A was well tolerated with only a minimal reversible clinical effects at 900 mg/kg/day.

No reproductive toxicology studies have been done.

SECTION 12: Ecological Information

Not available.

SECTION 13: Disposal Considerations

Dispose of according to local, state, and/or federal regulations.

SECTION 14: Transport Information

This material is not regulated as hazardous by U.S.-DOT. A copy of this MSDS should accompany shipments of this material.

SECTION 15: Regulatory Information

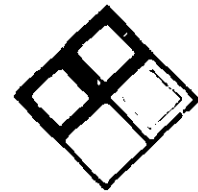
No additional information at this time.

SECTION 16: Other Information

The information provided in this Material Safety Data Sheet has been compiled from our experience and the data presented in various technical publications. It is the users responsibility to determine the suitability of this information for the adoption of safety precautions as may be necessary. We reserve the right to revise the Material Safety Data Sheet from time to time as new information becomes available. The user has the responsibility to contact the company to make sure the sheet is the latest one issued.



MATERIAL SAFETY DATA SHEET



PREPARATION DATE: 19 June, 1995

SECTION 1: Chemical Product and Company Identification

Common Name: (used on the label) (Trade Name and Synonyms)	MDL16.455A Capsules fexofenadine hydrochloride
Chemical Name:	4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]- α,α -dimethyl-, hydrochloride, ($\pm$)
Chemical Formula:	$C_{22}H_{30}NO_4 \cdot HCl$
Manufacturer's Name:	Marion Merrell Dow
Address:	10236 Marion Park Drive Kansas City, MO 64137
Emergency Telephone Numbers:	816-966-5000
Other Information Calls:	816-966-5000

SECTION 2: Composition/Information on Ingredients

Material:	MDL16.455A Capsules
Concentration:	Each capsule contains 60 mg fexofenadine hydrochloride.
Nature of Hazard:	Pharmaceutical Product.

SECTION 3: Hazards Identification

Appearance:	Capsules have a white opaque cap and a pink opaque body.

MDL16.455A is indicated for the relief of symptoms associated with seasonal allergic rhinitis.

SECTION 4: First Aid Measures

There is no clinical experience with an acute fexofenadine hydrochloride overdose.

Single doses of fexofenadine hydrochloride up to 800 mg and doses up to 690 mg bid for one month were investigated without the development of clinically significant adverse events. The maximum tolerated dose of fexofenadine hydrochloride was not reached.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

SECTION 5: Fire Fighting Measures

Extinguisher media: Carbon Dioxide, Dry Chemical Powder, Alcohol of Polymer Foam. Water may be effective for cooling.

Unusual Fire and Explosion Hazards: None.

Vapor Pressure: Not applicable.

Vapor Density: Not applicable.

Flashpoint: Not applicable.

Auto-ignition Temperature: Not applicable.

SECTION 6: Accidental Release Measures

Shovel or sweep up spill. Place in DOT approved container and seal. Dispose of in accordance with RCRA and applicable state and local regulations.

SECTION 7: Handling and Storage

Incompatibility: Not applicable.

Store capsules at controlled room temperature 20-25°C (68-77°F)

SECTION 8: Exposure Controls/Personal Protection

OSHA Permissible Exposure Limit: Not available.

SECTION 9: Physical and Chemical Properties

Appearance: See section 3 for detailed information.

SECTION 10: Stability and Reactivity

Material is stable under normal conditions.

Hazardous polymerization: Will not occur.

SECTION 11: Toxicological Information

An oral LD₅₀ in rodents was not determined for fexofenadine hydrochloride as no deaths occurred, even at doses up to 5000 mg/kg. Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg.

Fexofenadine is an active metabolite of terfenadine and is an end product of terfenadine metabolism. The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were exposed to fexofenadine plasma AUC values four times human therapeutic value (based on 60 mg fexofenadine hydrochloride bid dose) for 18 months and 24 months, respectively. In rat reproduction and fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at fexofenadine plasma AUC values greater than or equal to three times human therapeutic value. These effects occurred at maternally toxic doses.

In vitro and in vivo fexofenadine hydrochloride mutagenicity tests showed no evidence of mutagenicity.

Teratogenic potential of fexofenadine hydrochloride was assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma AUC values). There was no evidence of teratogenicity in rats or rabbits at fexofenadine plasma AUC values four times and 37 times human therapeutic value, respectively.

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

SECTION 12: Ecological Information

Shovel or sweep up spill. Place in DOT approved container and seal. Dispose of in accordance with RCRA and applicable state and local regulations.

SECTION 13: Disposal Considerations

This material should be disposed of in accordance with local, state, and/or federal regulations.

SECTION 14: Transport Information

This material is not regulated as hazardous by U.S.-DOT. A copy of this MSDS should accompany shipments of this material.

SECTION 15: Regulatory Information

No additional information.

SECTION 16: Other Information

The information provided in this Material Safety Data Sheet has been compiled from our experience and the data presented in various technical publications. It is the users responsibility to determine the suitability of this information for the adoption of safety precautions as may be necessary. We reserve the right to revise the Material Safety Data Sheets from time to time as new information becomes available. The user has the responsibility to contact the company to make sure the sheet is the latest one issued.

Marion Merrell Dow Inc.
Kansas City, Missouri 64133

REDACTIONS MADE
BY APPLICANT

NDA 20-625

S3-V1.12-P285

levonorgestrel hydrochloride capsule

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment **FOI COPY**

Attachment 5. MDL 16,455A Data Summary Chart

NDA 20-635

S3-V1.12-P286

levotifenadine hydrochloride capsule

3 Chemistry, Manufacturing and Controls
1 Environmental Assessment - FOI COPY

MDL 16,4 '5A Data Summary Chart

Test	Results
Water solubility (mg/mL at 25 °C)	2.44
Hydrolysis Rate Constant (estimated)	<10E-5/second
Dissociation Constant (pK _a at 25 °C)	pK ₁ = 4.25 pK ₂ = 9.53
Octanol/Water Partition Coefficient (log K _{ow} at pH 7)	0.30
Vapor Pressure (mmHg)	<5 x 10 ⁻¹⁰
Melting Temperature (°C)	>190
Ultraviolet-Visible Spectrum (absorption maxima, nm)	259 and 254
Aerobic Biodegradation in Water	
Mineralization (% CO ₂)	0
Biotransformation (% degradation products)	3.3
Log K _{oc} *	1.54
Microbial Inhibition (MIC, mg/L) <i>Pseudomonas fluorescens</i> , <i>Bacillus megaterium</i> , <i>Azotobacter chroococcum</i> , <i>Aspergillus clavatus</i> , <i>Penicillium canescens</i> , <i>Chaetomium globosum</i> <i>Anabaena flos-aquae</i>	400
<i>Daphnia magna</i> EC ₅₀ (mg/L)	780
<i>Daphnia magna</i> NOEC (mg/L)	330
<i>Lepomis macrochirus</i> LC ₅₀ (mg/L)	>940
<i>Lepomis macrochirus</i> NOEC (mg/L)	570
* Absorption Coefficient calculated from the equation Log K _{oc} = 0.554 Log K _{ow} + 1.377, where K _{ow} = n-Octanol/Water partition coefficient.	