Clinical Review Cover Sheet

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Clinical Review for NDA 21-158

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The overall risk benefit balance for gemifloxacin favors approvability based on its efficacy in the treatment of the indications ABECB and CAP and its relative safety. There are safety concerns, especially adverse cutaneous reactions, but these are not of the magnitude to prohibit the use of this medication for the indications being sought.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The Sponsor's program included a large clinical pharmacology program (slightly over 1800 enrollees received gemifloxacin) to evaluate preliminary safety and pharmacokinetics in healthy subjects and patients with renal or hepatic impairment. A large study (approximately 1100 subjects, 819 who received gemifloxacin) was performed in women under the age of 40 to better characterize the rash associated with gemifloxacin.

The clinical studies program included studies of ABECB and CAP and also for ABS, cUTI, uUTI, SSSI, and NGU. Although only data from ABECB and CAP studies were used to evaluate the drug's efficacy in this application, data from all of the studies were examined to evaluate the safety of gemifloxacin. The total number of patients enrolled in

the combined clinical studies who received gemifloxacin 320mg po qd was 6775 and the total number who received a comparator agent was 5248.

B. Efficacy

Please see by Dr. Alivisatos' Medical Officer Review of Community Acquired Pneumonia (CAP) and Dr. Navarro's Medical Officer Review of ABECB. This review concentrates on the safety of gemifloxacin.

C. Safety

Overall gemifloxacin is a well tolerated drug of the fluoroquinolone class. The adverse events of note with gemifloxacin are rash, elevation in LFTs, mild prolongation of the QTc interval, and elevation of CPK. Other quinolone class toxicities such as tendonopathy, CNS effects, phototoxicity, and hypoglycemia were not observed to occur more frequently than comparator in the combined clinical studies.

The most notable of the adverse reactions to gemifloxacin is rash. The overall incidence was 3.6% compared to 1.1% for comparator in the combined clinical population. There was also a higher incidence of serious adverse events due to rash (7 versus 1), withdrawals due to rash, and urticaria in gemifloxacin treated patients than comparator. The rash occurred with increased frequency in women, those less than age 40, and those receiving therapy for longer than 7 days. A study to examine the characteristics of the rash, Study 344, enrolled over 1000 women under the age of 40. Over 800 received gemifloxacin for 10 days (The comparator was ciprofloxacin for 10 days.). The incidence of rash in the women who received gemifloxacin was 31.7%. Seven percent of the rashes were reported as severe but no serious cutaneous events (such as SJS/TEN) occurred and the histpathology was consistent with an exanthem.

Elevations in liver function tests were seen at rates comparable to the comparator group. There was one healthy male who had an elevation in BR to 7.5mg/dl and 2 individuals in study 287 (ongoing CAP study of suspected pneumococcal pneumonia study) with combined ALT>3xULN and bilirubin>1.5mg/dl. An increase in the incidence of elevated LFTs was seen in those who received higher doses. Two women who received a single dose of 640mg in an uncomplicated UTI study had ALT elevations to >8xULN. All of these elevations resolved after therapy was discontinued.

Quinolone antimicrobials possess the ability to prolong the QT interval. In both preclinical assays and in the clinical studies the effect of gemifloxacin on cardiac repolarization appears to be in the range of the other marketed quinolones and in the mid-range of all quinolones. The mean change in QTc in the combined clinical trial population was 2.6 msec.

CPK elevations were seen twice as frequently in the gemifloxacin group in comparision to the comparator group (0.8% versus 0.4%). Since these numbers are small the clinical sigmificance of this finding is not clear.

D. Dosing

The recommended doses are 320 mg po daily for 5 days for ABECB and 7 days for CAP. For patients with a creatinine clearance of 40 ml/min or less the dose should be halved to 160 mg po for either 5 or 7 days for ABECB or CAP, respectively.

E. Special Populations

This drug has not been studied for use in individuals under the age of 18 and therefore is not approved for use in this age group. Safety has not been assessed for pregnant or nursing women but since it is a fluoroquinolone there are concerns about its safety in those conditions.

All individuals under the age of 40 especially women and women over the age of 40 on hormone replacement therapy had an increased risk of rash with this drug over those who received comparators in the clinical trials. Very little information on the outcome of the rash in people of color was obtained from the clinical trials because of the low rate of enrollment of people of color in the clinical trials and in rash study 344.

Clinical Review

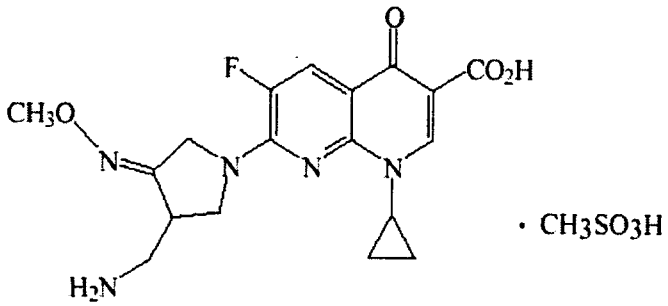
I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Name: Gemifloxacin

Drug Name: Factive.... (Gemifloxacin mesylate) Tablets

Chemical Name: (..)–7–(3–aminomethyl–4–(Z)–methoxyimino–1–pyrrolidinyl)–1–cyclopropyl–6–fluoro–1,4–dihydro - 4–oxo–1,8–naphthyridine–3– carboxylic acid methanesulfonate



Drug Class: Fluoroquinolone Antimicrobial

Sponsor's Proposed Indications: Community Acquired Pneumonia and Acute Exacerbation of Chronic Bronchitis

Dose: One 320 mg tablet orally once a day for 5 days (AECB)
One 320 mg tablet orally once a day for 7 days (CAP)

Age: 18 and older only

B. State of Armamentarium for Indication(s)

Please see Dr. Navarro's Review of Efficacy of Gemifloxacin for ABECB
Please see Dr. Alivisatos' Review of Efficacy of Gemifloxacin for CAP

C. Important Milestones in Product Development

The tablet formulation of gemifloxacin was developed under IND [redacted] The following are important milestones in the product development of gemifloxacin. IND [redacted] and [redacted]

August 6, 1997	IND submitted (No Pre-IND Meeting requested
August 11, 1998	End of Phase 2 meeting
May 27, 1999	Pre-NDA Meeting
July 16, 1999	rat micronucleus studies show clastogenicity leading to SB's temporary suspension of clinical studies
July 28, 1999	SB submits pre and postnatal repro-tox studies
December 15,1999	NDA submitted
January 21, 2000	request to submit 8-month safety update and waive 4 month update
February 8, 2000	NDA application deemed fileable (45 day filing meeting)
February 17, 2000	Bio-Pharm request for additional analyses on QT recommend that two regression analyses be performed.
March 9, 2000	consult to CDER genotoxicity committee
March 31, 2000	pediatric waiver/deferment response by SB Full waiver for [redacted] AECB, [redacted] Partial waiver for CAP children <1 year of age Deferment for CAP children >1 year of age
April 27, 2000	[redacted]
June 20, 2000	OPDRA consult regarding Factive name (see above)
August 14, 2000	8 month safety update submitted
December 15, 2000	Action Letter sent-Non-Approval-safety issues of cutaneous reactions and liver effects specifically raised. Sponsor urged to perform study to further characterize the rash events.
February 2002	FDA-Sponsor meeting to discuss rash Study 344, other post NDA submission efficacy and safety data and plan future actions
October 4, 2002	NDA 21-158 Resubmission for the indications of AECB and CAP
March 4, 2003	Anti-Infective Advisory Committee votes to approve Gemifloxacin for mild-moderate CAP and AECB

C. Other Relevant Information

Dr. John Powers of the FDA completed a medical officer review of safety of gemifloxacin for the first submission on this NDA. This review may be referred to for further detail on safety issues in the studies completed prior to that submission. That data is also included in this review which focuses on the combined clinical data of both prior and subsequent to the first submission.

Three studies were begun to evaluate an intravenous formulation of gemifloxacin. These studies were discontinued since an analysis of the data showed that the intravenous and oral doses did not coincide in achieved serum levels. Consequently, the development of the intravenous form of the drug was discontinued. The safety data from these IV studies were reviewed separately from the safety data from the oral studies. The safety results of

these partially completed IV studies were consistent with the results from the much lager oral experience. Therefore the results are not specifically enumerated in this review of the safety of gemifloxacin tablets.

E. Important Issues with Pharmacologically Related Agents

The fluorquinolones have adverse effects which are common to many members of the class. Most of these effects are more prominent in 1 or 2 members of the class. The adverse events include QT prolongation, phototoxicity, hepatotoxity, CNS effects, cartilage and tendon effects, and rash.

One potentially concerning adverse effect of the fluoroquinolones is their potential to prolong the QT interval and produce tosades de pointes. In the preclinical assays of these effects inhibition of herG channels and the lengthening of action potential duration in dog Purkinje fibers are assessed. In these assays sparfloxacin and grepafloxacin have the most prominent effect. The NDA for clinofloxacin was submitted and subsequently withdrawn because of the frequency and severity of phototoxicy it caused and because of hypoglycemia. Hypoglycemia has also recently been seen in some patients on gatifloxacin.

Mild hepatotoxicity has been seen throughout the class but there have been severe cases of hepatic failure requiring transplantation on patients receiving trovafloxacin usually for prolonged courses. This has caused a restriction in the use of trovafloxacin. Temafloxacin was associated with a multi-organ hypersensitivity syndrome characterized by hepatic and renal failure with eosinophilia and was subsequently removed from the market.

CNS effects such as dizziness, tremors, confusion, and hallucinations have been seen with some quinolones. There have been rare reports of seizures and toxic psychoses occurring while on a quinolone. Caution is recommended in using this class of drugs in patients with a history of epilepsy. Tendonopathy and tendon rupture are adverse events which have been experienced uncommonly on quinolones. Arthropathy has been seen in juvenile dogs in preclinical studies and this is the main reason for limiting the use of quinolones in the pediatric population.

Mild to moderate cutaneous adverse events occur with all quinolone agents but not with the frequency seen with gemifloxacin. Photoxicity is common to many of the drugs of this class but those members with a halogen atom at position 8 have the highest likelihood of causing phototoxic reactions.(8) There have been 12 reports of severe cutaneous events (SJS/TEN) with 4 different fluoroquinolone agents.

For a listing of sources for the above discussion please see Appendix B.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Microbiology

Gemifloxacin is a synthetic fluoroquinolone antibacterial agent. Gemifloxacin has good *in vitro* activity against a number of gram-positive organisms including the most common respiratory pathogens. It is somewhat less active against some of the Enterobacteriaceae and poor activity against *Pseudomonas aeruginosa.*

Gemifloxacin's *in vitro* MIC_{90} values against *Streptococcus pneumoniae* are 4-8 times lower than those of trovafloxacin and moxifloxacin and over 16-64 times lower than the MIC_{90} values for ciprofloxacin. At the proposed human dose, the AUC value for gemifloxacin (8.4 µg/mL) is only about one-fourth that of most of the other fluoroquinolones. Therefore the four-fold lower gemifloxacin MIC_{90} value for *Streptococcus pneumoniae* compared to trovafloxacin or moxifloxacin is largely offset by the lower AUC values achieved with gemifloxacin at the proposed dose of 320 mg orally once daily.

Table 1. *In vitro* Activity of Gemifloxacin and Comparators Against *S. pneumoniae*

No. of Isolates	Gemifloxacin MIC_{90} (µg/mL)	Ciprofloxacin MIC_{90} (µg/mL)	Levofloxacin MIC_{90} (µg/mL)	Gatifloxacin MIC_{90} (µg/mL)	Moxifloxacin MIC_{90} (µg/mL)
6247	0.047	NT	1	NT	NT
550	0.03	2	1	0.5	0.25
1450	0.06	1	1	0.25	NT

NT = not tested

Gemifloxacin had MIC values of 0.008 ug/mL and and 0.015ug/mL against *Haemophilus influenzae* and *Moraxella catarrhalis.* Gemifloxacin also appears to have activity in experimental models against *Legionella pneumophila* similar to azithromycin and levofloxacin. It also demonstrates actvity against *Mycoplasma pneumoniae.*

Gemifloxacin was also shown to be active against penicillin-, macrolide-,and cefuroxime-resistant strains although the clinical significance of the later two resistances has yet to be determined.

Gemifloxacin targets both the *parC* (topoisomerase IV) and *gyrA*(DNA gyrase) enzymes. This dual mechanism of action is similar to that seen in moxifloxacin and gatifloxacin. Single mutations may therefore not produce important resistance to gemifloxacin. Gemifloxacin's susceptibility to double resistant strains is similar to moxifloxacin and gatifloxacin. Please refer to Microbiologist Peter Dionne's Review for further discussion of this and other bacteriogic activity of gemifloxacin.

Pharmacology/Toxicology

Preclinical findings of note incude effects in three areas: hepatic, cardiac, and clastogenic activity. At high doses cholangitis and pericholangitis with crystalline deposits of drug in bile canaliculi. This was associated with hepatocellular degeneration and single cell necrosis and elevations in ALT and Alkaline Phosphatase. Assays to look at the potential for cardiac repolarization effects found that gemifloxacin inhibited herG–IKr channels and prolonged action potentials in dog Purkinje fiber assays in the mid range of quinolones tested. Preclinical evaluation has extensively looked at the clastogeneticity of gemifloxacin and its effect in a mouse lymphoma cell line. Please see Dr. Stephen Huntley's Review for further discussion of pharmacology/toxicology issues.

Chemistry

There were no safety concerns of special note from the chemistry evaluation of gemifloxacin. Please see Dr. Ramesh Sood's Review for further details about the chemistry of gemifloxacin.

Statistics

Statistical issues in the evaluation of the safety of gemifloxacin are discussed in the section on critical safety findings. Statistical analyses were performed on the results of Study 344 to determine the risk factors associated with rash and the confidence intervals on the incidence of rash in the various arms of that study. Please also see Dr. Cheryl Dixon's Statistical Review.

III. Human Pharmacokinetics and Pharmacodynamics

The bioavailability of gemifloxacin from the tablet formulation is about 61% of that from an IV formulation. The peak plasma concentrations of gemifloxacin after oral administration of tablet formulation are observed at about 1 hour after dosing. Binding to plasma proteins is about 60 - 70%, and whole blood concentrations and plasma concentrations are similar. The gemifloxacin elimination half-life averages 7 hours. Metabolism does not contribute significantly to gemifloxacin elimination, and there is very little involvement of cytochrome P450 enzymes. Over 60% of the dose is excreted unchanged following either oral or intravenous dosing. Metabolites contribute minimally to gemifloxacin pharmacologic activity. Gemifloxacin elimination occurs by both renal (60% of an IV dose) and hepatic (40% of an IV dose) routes.

Gemifloxacin renal clearance (11.0 L/h) exceeded glomerular filtration rate (7 L/h), suggesting that active tubular secretion contributes significantly to gemifloxacin excretion by the kidney. Gemifloxacin clearance is significantly lower only in severe renal impairment and therefore dosage adjustment should occur if creatinine clearance is below 40mL/min. In such patients, including those on hemodialysis or peritoneal dialysis, the dose should be halved to 160 mg po qd.

Dosage adjustment is not necessary in patients with any degree of hepatic impairment. In a pharmocokinetic study in patients with severe hepatic impairment AUC and Cmax were increased by 40-45% but ther T1/2 (elimination half-life) was unchanged.

There were no significant metabolism-based (i.e., CYP450 enzymes) pharmacokinetic interactions with gemifloxacin. In both *in vitro* and *in vivo* studies, no pharmacokinetic interactions were observed between gemifloxacin and theophylline, omeprazole, and oral

contraceptives. No pharmacodynamic interaction was demonstrated when gemifloxacin was administered concomitantly with warfarin or digoxin.

Gemifloxacin can be administered with antacids/di- and trivalent cations (e.g., aluminum hydroxide, magnesium hydroxide, and ferrous sulfate) if these products are given 3 hours before or 2 hours after gemifloxacin administration. Sucralfate could be given only at 2 hours after gemifloxacin. Co-administration with calcium (1,000 mg) resulted in ~20% or oral bioavailability of gemifloxacin.

There was no relationship seen among exposure to the N-acetyl metabolite to gemifloxacin. There was a dose response relationship noted with mean QTc. For further discussion of this and other pharmocokinetic issues please see Dr. Jang-Ik Lee's Review.

IV. Description of Clinical Data and Sources.

A.Overall Data

Safety data derived from the gemifloxacin clinical studies where participants received 320 mg po qd will be presented to describe the safety profile of gemifloxacin. In addition to data from these clinical studies, data from studies where subjects received higher doses, data from a study to evaluate rash in healthy women (Study 344) and data from relevant clinical pharmacology studies will be presented where these data add additional information to the data from the 320 mg clinical studies data. The safety experience in the clinical studies is derived from data from 12,023 patients: 6775 of whom received gemifloxacin 320 mg po qd and 5248 received comparators (this population is referred to as the Combined Clinical Population). The duration of exposure to gemifloxacin for the patients in the clinical studies are summarized in Table 2.

Table 2. Duration of Exposure to Study Medication in Clinical Studies (Combined Population)

Duration of Exposure	Gemifloxacin 320mg qd N = 6775		All Comparators N = 5248	
	n	(%)	n	(%)
0 days*	1	(0.0)	0	
1 day	55	(0.8)	41	(0.8)
2 to 3 days	553	(8.2)	456	(8.7)
4 to 5 days	3009	(44.4)	464	(8.8)
6 to 7 days	1911	(28.2)	1903	(36.3)
8 to 10 days	812	(12.0)	1766	(33.7)
11 to 14 days	356	(5.3)	526	(10.0)
15+ days	22	(0.3)	33	(0.6)
Unknown	56	(0.8)	59	(1.1)

Data Source: Applicant's Table 3.5 from p. 99 NDA 21-158 18 month safety update
*In the NDA population, 1 patient (011.038.05278) was reported as having 0 days of therapy. This patient received 1 dose of study medication (placebo) and was withdrawn prior to receiving active study medication (gemifloxacin)

The average age for patients that received gemifloxacin in the combined population was approximately 53 years of age. The populations were relatively evenly divided between males and females. In the gemifloxacin treatment group, 87% of the patients were white,

4.4% were black, 3.4% were oriental, and 5.6 % were categorized as other (Table 3). The patients that comprise the Combined Population were derived from clinical studies in a variety of indications as listed in Table 3.

Table 3. Demographic Characteristics in Clinical Studies (Gemifloxacin 320 mg versus All Comparators) (Combined Population)

	Treatment Group			
Demographic Characteristics	**Gemifloxacin 320mg qd N=6775**		**All Comparators N=5248**	
Age (years) n (%)				
≥16 - <18	22	(0.3)	8	(0.2)
≥18 - <40	1689	(24.9)	1029	(19.6)
≥40 - <65	3000	(44.3)	2398	(45.7)
≥65 - <75	1285	(19.0)	1126	(21.5)
≥75	779	(11.5)	687	(13.1)
Mean (SD)	52.8 (17.98)		55.1 (17.19)	
Median	54		57	
Range	16-97		16-99	
Gender n (%)				
Male	3278	(48.4)	2511	(47.8)
Female	3497	(51.6)	2737	(52.2)
Race n (%)				
White	5871	(86.7)	4825	(91.9)
Black	298	(4.4)	192	(3.7)
Oriental	227	(3.4)	43	(0.8)
Other	379	(5.6)	188	(3.6)
Region				
North American Countries	2693	(39.7)	2402	(45.8)
European countries	3611	(53.3)	2745	(52.3)
Other countries	471	(7.0)	101	(1.9)
Indication				
AECB	2847	(42.0)	2591	(49.4)
CAP	1160	(17.1)	926	(17.6)

Data Source: Applicant's Table 4.3 from p. 107 NDA 21-158 18 month safety update

AECB = Acute exacerbation of chronic bronchitis; CAP = Community-acquired pneumonia;

B. Tables Listing the Clinical Trials

1. Clinical Pharmacology Studies (1797 healthy subjects, 81 with renal or hepatic impairment)

1. NDA-Non patient volunteers (666, 519 received gemifloxacin in Studies 004,005,018,020,026,030,031,032,034,037,040,045,047,055,057,062,066,072,076,084,006,019,021,022,023,038,042,046,073,
2. NDA-Patient Volunteers Studies 031 (renal) and 032 (hepatic)
3. IV studies 029, 030, 048, 082
4. Post NDA -8 completed studies

   6 single dose:

   1 SD 160 mg oral dose (pediatric suspension) and 250 mg IV (Study 114)

   5 SD 320 mg oral-2 drug interaction studies Studies 024 and 077)

   -1 bioequivalence study (Study 033)

   -1 tissue penetration study (Study 036)

   -1 hepatic impairment study (Study 059)

   2 repeat dose:

   1 rash study-344(1011 subjects, 819 received gemifloxacin)

   -1`study in renal impairment 9Study 056)

2. Clinical Studies-6775 patients received 320mg of gemifloxacin

Table 4. Clinical Studies Included in the Safety Evaluation of Gemifloxacin

Population Name	Description
NDA Population (15 studies*)	The original NDA gemifloxacin double-blind studies in the following indications: CAP: 011, 012, 049, AECB: 001, 008, 068, 069, 070, [redacted] Data are presented only for those patients receiving at least one dose of gemifloxacin 320mg or a comparator.
Post-NDA Population (8 studies)	Gemifloxacin 320mg/comparator data from Post-NDA studies in the following indications: CAP: Study 185, AECB: Studies 105, 112, 207, 212, [redacted]
Combined Population (24 studies)	Studies 001+, 002+, 003+, 008, 009, 010, 011, 012, 013, 014, 049, 053*, 061, 068, 069, 070, 105, 112, 126, 185, 186, 206, 207, 212.
All Exposed Population (25 studies)	All patients who received at least 1 dose of gemifloxacin, regardless of dosage: Studies 001, 002, 003, 008, 009, 010, 011, 012, 013, 014, 049, 053, 061, 067, 068, 069, 070, 105, 112, 126, 185, 186, 206, 207, 212.

* Study 061 was detailed in the NDA but was reported separately because it was an open-label study.
+ Gemifloxacin 320mg only.
Indications: CAP = community-acquired pneumonia; AECB = acute exacerbation of chronic bronchitis; [redacted]

C. Post Marketing Experience

Gemifloxacin has been approved in two other countries-New Zealand and Korea. It has not been marketed in any country and therefore there is no post marketing experience to evaluate at this time.

D. Literature Review.

The relevant medical literature was reviewed in three major areas. These included safety issues with the fluorquinolone class, cutaneous reactions to drugs, and resistance to fluoroquinolone agents. The safety concerns of other quinolones was discussed above in section **I.E.**Important Issues with Pharmacologically Related Agents.

An extensive review of cutaneous reactions to drugs, especially other quinolones, was performed because of the frequency of rash seen in clinical trials with gemifloxacin. This review revealed the relative rates of rash to various drugs and the histologic patterns associated with various rashes. A review of severe cutaneous reactions to drugs and a specific search for such severe reactions associated with other quinolones revealed that a small number of cases of SJS/TEN have occurred in individuals on quinolone agents.

For a listing of the sources for the literature review please see Appendix B.

V. Clinical Review Methods

A. How the Review was Conducted
B. Overview of the Materials Consulted in the Review.
C. Overview of Methods to Evaluate Data Quality and Integrity

The review was conducted by examining items submitted by the Sponsor including the Resubmission of October 4, 2002, the briefing documents for the meetings between the Sponsor and the FDA in February, 2002, and January 2003, any adddtional submissions of additional data since the resubmission, and the Sponsor's Briefing Package for the Anti-Infective Advisory Committee on March 4, 2003. The original submission of NDA 21-158 from December 15, 2002 was also examined when necessary and The Medical Officer Review of Safety by Dr. John Powers of that submission was used as a resource.

The items which were most particularly examined included the Sponsor's 18 month Safety Update of the Resubmission, the Report of Study 344, Dr. Paul Watkin's Review of the hepatic safety of gemifloxacin, and Patient Narratives for all Deaths and Serious Adverse Events. All safety update data was examined for consistency and clarity and if further understanding of the data was required the original study report and the study's CRFs would be examined. If there were further questions about the data the Sponsor would be asked to provide additional analyses.

Study 344 was reviewed in great detail. CRFs were provided for all patients with rash. A random sample of 100 CRFs were examined. A random selection of 4 study sites was done and all the CRFs from those sites were reviewed. In addition all the CRFs of patients with severe rash, mucus menmbrane involvement with rash, fever and accompanying rash, and steroid therapy were examined.

Our statisticians Drs. Higgins and Dixon were consulted for any relevant questions. Many multi-disciplinary meetings were held to discuss the application and information from chemists, microbiologists, pharmacologists, and our dermatology division were obtained on a regular basis.

Whenever necessary experience was sought from the literature especially regarding severe cutaneous adverse events, drug induced hepatotoxicity, and cardiac repolarization effects of quinolones.

D. Were Trials in Accordance with Accepted Ethical Standards

All protocols were deemed to have been performed with appropriate IRB approval and with appropriate informed consent.

All clinical pharmacology trials were performed with appropriate safeguards. Information from prior trials, prior clinical experience, or preclinical data predicted that the risks undertaken in these trials were acceptable.

The comparative clinical trials were performed with comparators approved for the indications which were being studied. In all the studies infomed consent included criteria to prevent unintended pregnancy during the study period.

E. Evaluation of Financial Disclosure

There were 4861 investigators (physicians, nurses, and pharmacists) who were involved in the clinical pharmacology and clinical trial program evaluating the safety and efficacy of gemifloxacin. Patients were not enrolled at every site. Of the 4861 investigators, 4695 completed financial disclosure forms and reported no financial conflicts, 160 (11 of these were GSK employees) did not complete the form, and six disclosed potential financial conflicts. Four of these conflicts were described as pension plans with potential holdings of conflict.One form sited being a GSK employee as the financial disclosure. There was a grant of just over $30,000 made to a research center in the name of one of the investigators. This site did not enroll any patients.

VI. Integrated Review of Efficacy

Please see Medical Officer Reviews by Drs. Alivisatos (CAP) and Navarro (AECB) This review is limited to safety.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The overall safety profile of gemifloxacin reveals that in general it is a well tolerated antimicrobial in comparison to comparators. There are 4 adverse event areas of special interest. They are cutaneous adverse events, hepatic effects, QT prolongation and CPK elevation.

In the overall combined clinical population there was a rash rate of 3.6% in the gemifloxacin group. However when certain subgroups are analyzed it is noted that rash rates are higher in anyone under 40, especially women and those who receive drug for

longer than 7 days. Study 344 was designed to further elucidate the nature of the rash to gemifloxacin. There was an incidence of rash of 31.7% in the 819 enrollees who received gemifloxacin (all subjects were women under the age of 40 who received drug for 10 days). There were no cases of SJS/TEN and the histopathology was notable for a lack of concerning findings. However over 25% of the rashes seen covered over 60% BSA. There were 12 cases of mild mouth mucus membrane involvement and approximately 5% of all the rashes were treated with systemic steroids. In summary the risk of an individual experiencing a rash to gemifloxacin is at least twice that of comparators for all ages and sexes. Those under 40, women, and those receiving treatment for longer than 7 days with gemifloxacin may experience rash rates up to 15% or greater. The rash appears to be a self limited exanthem but can cover a large percentage of body surface area and in a small number of cases may require treatment with systemic steroids.

Hepatic effects of gemifloxacin were not common and were seen particularly in patient with more comorbidity, those with baseline liver disease and in those who received higher doses of 480 and 640 mg in early studies. The only 2 cases of ALT elevations of >8xULN in those whose LFTs were in range at screening occurred in 2 young women who received a single dose of 640 mg. Only 2 cases of combined ALT >3xULN plus Bilirubin >1.5 mg/dl were seen in Study 287-a CAP study enrolling those with a suspicion of pneumococcal pneumonia. One case of markedly high bilirubin elevation was reported in a healthy male in his thirties in a clinical pharmacology trial.

In preclinical assays gemifloxacin does demonstrate some capacity to inhibit herG channels and falls in the mid range of drugs in the fluoroquinolone class. The mean change in QTc in the combined clinical population was 2.6 msec-considered in the range of the other quinolones on the market. There were a small number of individuals who had treatment emergent changes in QTc of > 60msec or actual QTc of >500msec.

There is a slightly increased incidence of CPK elevations noted in the gemifloxacin arm especially in patients with baseline liver disease and ABECB. The significance of this finding is not clear at the present time.

B.Description of Patient Exposure

Please see above in IV-A Overall Data for a description of Patient Exposure

C.Methods and Specific Findings of Safety Review

The findings of the safety review of gemifloxacin will be presented in the following manner. First adverse experience information will be provided by discusssing overall adverse events, serious adverse events and deaths, and withdrawals due to adverse events. Then special attention will be made to the discussion of the cutaneous adverse events, the hepatic effects of gemifloxacin, and the cardiac effects of gemifloxacin.This will be followed by an examination of the effect on other laboratory tests of gemifloxacin

including CPK. Lastly discussion of the safety of gemifloxacin by indication will be presented.

Adverse Experiences (AEs)

In the clinical studies combined population, 44.7% of patients treated with gemifloxacin reported having at least one AE in comparison to 47.5% for comparator. Diarrhea, headache and nausea were the three most common AEs reported for both groups, all with a slightly higher incidence in the comparator arm. Rash was the fourth most common AE in gemifloxacin treated patients at 3.6% in contrast to 1.1% in comparator.
Table **5**).

Table 5. Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences in Either Treatment Group (Combined Population)

	Treatment Group Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	3029	(44.7)	2492	(47.5)
Diarrhea	343	(5.1)	325	(6.2)
Headache	304	(4.5)	273	(5.2)
Nausea	265	(3.9)	237	(4.5)
Rash*	241	(3.6)	59	(1.1)
Abdominal Pain	157	(2.3)	116	(2.2)
Vomiting	123	(1.8)	106	(2.0)
Dizziness	117	(1.7)	134	(2.6)
Rhinitis	105	(1.5)	74	(1.4)
Insomnia	100	(1.5)	92	(1.8)
Hyperglycemia	98	(1.4)	70	(1.3)
Injury	96	(1.4)	60	(1.1)
Back Pain	93	(1.4)	75	(1.4)
Creatinine Phosphokinase Increased	90	(1.3)	64	(1.2)
Sinusitis	84	(1.2)	69	(1.3)
Constipation	73	(1.1)	62	(1.2)
Flatulence	69	(1.0)	40	(0.8)
Myalgia	67	(1.0)	45	(0.9)
SGPT Increased	67	(1.0)	49	(0.9)
Dyspepsia	66	(1.0)	74	(1.4)
Fatigue	66	(1.0)	57	(1.1)
Bronchitis	64	(0.9)	75	(1.4)
Upper Respiratory Tract Infection	58	(0.9)	67	(1.3)
Pharyngitis	57	(0.8)	73	(1.4)
Moniliasis Genital	48	(0.7)	57	(1.1)
Mouth Dry	33	(0.5)	51	(1.0)
Taste Perversion	21	(0.3)	108	(2.1)

Data Source: Applicant's Table 4.3 from p. 125 NDA 21-158, 18 month safety update
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular and rash pustular.

The most common AE's in the gemifloxacin treated patients with a suspected or probable relationship (based upon the investigator's assessment) to gemifloxacin were diarrhea, nausea, rash, headache, and vomiting (

Table 6). The rate of rash with a suspected or probable relationship to study drug was 2.8% for gemifloxacin and 0.6% for comparators.

Table 6. Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences of Suspected or Probable Relationship to Study Medication in Either Treatment Group (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE of suspected or probable relationship to study medication	1179	(17.4)	1047	(20.0)
Diarrhea	244	(3.6)	242	(4.6)
Rash*	192	(2.8)	34	(0.6)
Nausea	182	(2.7)	168	(3.2)
Headache	81	(1.2)	80	(1.5)
Abdominal Pain	60	(0.9)	58	(1.1)
Vomiting	58	(0.9)	57	(1.1)
Dizziness	55	(0.8)	80	(1.5)
Taste Perversion	18	(0.3)	101	(1.9)

Data Source :Applicant's Table 5.7 from NDA 21-158 18 month Safety Update

Deaths

There were no deaths in the clinical pharmacology studies in subjects treated with gemifloxacin. There was one death in a 34 yo woman treated with ciprofloxacin who suffered a dissection of her left coronary artery. This event was not felt to be secondary to study medication. In the combined population of clinical studies there were 33 deaths in the gemifloxacin treated population and 30 deaths in the all comparators group during the on therapy plus 30 day post therapy period. Most of the deaths in both groups were secondary to cardiorespiratory or respiratory causes and all were deemed by the investigators to be unrelated or unlikely to be related to the study drugs. The adverse events associated with death are summarized in Table 7. .All deaths were associated with at least one adverse event. The 3 cases of sudden death in the gemifloxacin arm are discussed at length in the section on ECG effects entitled "Conditions associated with Cardiac Arrythmias."

Table 7. Most Commonly Reported (≥ 2 Patients in Either Treatment Group) Adverse Experiences Associated With Death During the On-Therapy Plus 30 Days Post-Therapy Interval (Combined Population)

	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
	N	(%)	N	(%)
Patients with Adverse Events Associated with Death	33	0.1	30	0.6
Cardiac Arrest	5	0.1	4	0.1
Respiratory Insufficiency	5	<0.1	5	0.1
Cardiac Failure	3	<0.1	5	0.1
Sudden Death	3	<0.1	0	<0.1
COPD	2	<0.1	1	<0.1
MI	2	<0.1	5	0.1
Pneumonia	2	<0.1	0	0.0
Lung Cancer	2	<0.1	2	0.1
Pulmonary Edema	2	<0.1	1	0.1
Acute Renal Failure	2	<0.1	0	0.0
Dyspnea	1	<0.1	2	<0.1
Suicide Attempt	0	0.0	2	<0.1

Data Source: Applicant's Table 6.2 from NDA 21-158 18 month Safety Update

Table 8. Deaths Reported Anytime after First Dose of Study Medication Up Until 30 Days after the Last Dose

Patient	Cause of Death	SAEs Associated with Death	Days from Drug Start	Days from Drug Stop	Relation
	Cardio-respiratory arrest	Cardiac Arrest/Coronary Artery Disorder/COPD /Peripheral Ischemia/Death due to coronary artery disease-CR arrest-peripheral vascular disease-COPD	38	24?	Unrelated (Gemifloxacin)
112-056-35853	Tension pneumo-thorax	Adenocarcinoma of the lung	29	22	Unrelated (Gemifloxacin)
112-512-35226	Malignant Arrythmia	Arrythmia	5	0	Unrelated (Gemiflox)
112-560-35531	Respiratory Insufficency/Pneumonia	Pneumonia	2	1	Unrelated (Gemifloxacin)
185-208-29391	Tumor Bronchi	Neoplasm	14	1	Unrelated (Gemifloxacin)
185-314-29872	Critical Aortic Stenosis	Aortic Stenosis	27	19	Unrelated (Gemifloxacin)
185-441-29778	Nosocomial Pneumonia	Pneumonia (worsening)	19	17	Unrelated (Gemifloxacin)
207-098-30630	Circulatory Failure	Circulatory Failure	18	14	Unlikely (Gemifloxacin)
207-114-30425	Cardiac Arrest	Cardiac Arrest	7	3	Unrelated (Gemifloxacin)
112-009-38208	Probable MI	Myocardial Infarction	14	9	Unrelated
112-122-38697	Emphysema, respiratory failure	Respiratory Insufficiency/ Respiratory Distress	2	1	Unlikely
112-134-38365	Respiratory Distress due to COPD exacerbation	COPD/Respiratory Distress due to exacerbation of COPD leading to death	25	19	Unrelated (Gemifloxacin)
185-305-29899	Acute	Arrythmia	21	13	Unlikely

	cardiac arrythmia				
185-363-29746	Unknown	Dyspnea /Respiratroy Distress	2	0	Unrelated
185-601-29472	Cardiac Arrest	Cardiac Arrest/Sudden Death	22	11	Unrelated
207-111-30599	Acute Resp. Failure	Respiratory Insufficiency	27	24	Unrelated
212-101-54373	Sudden Death	Myocardial Infarction/Sudden Death	15	9	Unrelated
112-720-400039		Cardiac Failure	26	20	Unlikely
185-022-30053	Sudden Heart Death	Cardiac Failure	26	15	Unlikely
185-252-29626	MI/IschemicHeart Disease	Myocaridal Infarction,COPD,DM	16	6	Unrelated

Abridged and Adapted from NDA 21-158 18 month Safety Update Table 6.1

Serious Adverse Experiences (SAEs)

In the clinical pharmacology population the only SAE's believed to have a relationship to study medication by the investigators were instances of colitis or enteritis. The following table depicts the SAE's which occurred in the clinical pharmacology trials.

Table 9. Serious Adverse Experiences in Clinical Pharmacology Studies

Regimen	Serious Adverse Event	Relationship to Treatment
Gemifloxacin SD	Gastrointestinal Hemorrhage	Not related
"	Transjugular intrahepatic porto-Systemic shunt	Not related
"	Lower abdominal pain	Unlikely
"	Stroke	Not related
GemifloxacinRD	Pregnancy (Spontaneous Abortion)	Unlikely
"	Ectopic Pregnancy	Unrelated
"	Pregnancy (Spontaneous Abortion)	Unlikely
"	Dysplastic Naevus	Unrelated
"	Uterine Fibroid	Unrelated
"	Rotator Cuff Infection	Unrelated
"	Pseudomembranous Colitis	Suspected
"	Enteritis	Suspected
"	Carcinoma in situ of Cervix	Unrelated
"	Gastritis	Unlikely
Ciprofloxacin RD	Dissection of Coronary Artery leading to death	Unrelated
"	Clostridium difficile colitis	Suspected

Data Source Adapted from Applicant's Table 7.1 from the 18 month Safety Update

The percentage of patients in the Combined Population who experienced serious SAE's during the interval on therapy to 30 days post therapy was 3.6% (247/6775) in the gemifloxacin 320 mg qd group and was 4.3% (228/5248) in the all comparator group. There was no single SAE which occurred in greater than 1% of the patients in either group.

Rash, increase in hepatic enzymes, pyelonephritis, sudden death, and injury are noteworthy SAE's which occurred more frequently in the gemifloxacin population than in the all comparators group. Whereas in the comparator group, the SAEs of myocardial infarction, diarrhea, and abscess were reported more frequently. Please refer to Table 10.

Table 10. Number (%) of Patients (≥3 Patients in Either Treatment Group) With Serious Adverse Experiences by Preferred Term (Combined Population)

	Gemifloxacin 320mg N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one SAE	247	(3.6)	228	(4.3)
Pneumonia	21	(0.3)	25	(0.5)
Chronic Obstructive Airways Disease	14	(0.2)	17	(0.3)
Bronchitis	13	(0.2)	16	(0.3)
Dyspnea	13	(0.2)	10	(0.2)
Pulmonary Carcinoma	13	(0.2)	8	(0.2)
Respiratory Insufficiency	12	(0.2)	10	(0.2)
Injury	10	(0.1)	3	(0.1)
Therapeutic Response Increased	10	(0.1)	5	(0.1)
Respiratory Disorder	8	(0.1)	8	(0.2)
Cardiac Arrest	6	(0.1)	5	(0.1)
Cardiac Failure	6	(0.1)	8	(0.2)
Chest Pain	6	(0.1)	2	(0.1)
Pleural Effusions	5	(0.1)	1	(0.1)
Pyelonephritis	5	(0.1)	2	(<0.1)
Rash*	6	(0.1)	1	(<0.1)
Fever	4	(0.1)	2	(<0.1)
GI Hemmorrhage	4	(0.1)	2	(<0.1)
Myocardial Infarction	4	(0.1)	10	(0.2)
Neoplasm NOS	4	(0.1)	1	(<0.1)
Pleurisy	4	(0.1)	1	(<0.1)
Renal Failure Acute	4	(0.1)	2	(<0.1)
Angina Pectoris	3	(<0.1)	2	(<0.1)
Cerebrovascular Disorder	3	(<0.1)	3	(0.1)
Coughing	3	(<0.1)	0	(0.0)
Dehydration	3	(<0.1)	3	(0.1)
Atrial Fibrillation	3	(<0.1)	2	(<0.1)
Hepatic Enzymes Increased	3	(<0.1)	0	(0.0)
Sudden Death	3	(<0.1)	0	(0.0)
Suicide Attempt	3	(<0.1)	3	(0.1)
Vomiting	3	(<0.1)	1	(<0.1)
Asthma	2	(<0.1)	4	(0.1)
Abdominal Pain	1	(<0.1)	5	(0.1)
Abscess	1	(<0.1)	6	(0.1)
Angina Pectoris Aggravated	1	(<0.1)	3	(0.1)
Embolism Pulmonary	1	(<0.1)	3	(0.1)
Hemoptysis	1	(<0.1)	3	(0.1)
Infection TBC	1	(<0.1)	5	(0.1)
Myelomatosis Multiple	1	(<0.1)	3	(0.1)
Sepsis	1	(<0.1)	4	(0.1)
Diarrhea	0	(0.0)	4	(0.1)

Data Source: Adapted from NDA 21-158, 18 month Safety Update, Table 025c, p.004646.

Serious Adverse Events With a Suspected or Probable Relationship to Study Medication

In the combined population the percentage of patients with at least one SAE with suspected or probable relationship to study medication (based upon the investigator's assessment) during the on therapy plus 30 day post therapy period was 0.4% (29/6775) in the gemifloxacin 320 mg group and in the all comparator group was also 0.4% (19/5248.) (Table 11.) The most frequent SAE's with a suspected or probable relationship to study medication in the gemifloxacin treated group included rash, increased hepatic enzymes or altered hepatic function, pneumonia, and increased therapeutic response. The SAE of diarrhea was reported in only comparator treated patients. Further discussion of the adverse events of rash, and hepatic and cardiac safety will be provided in sections within this review to follow that specifically address these issues.

Table 11. Number (%) of Patients (≥3 in Either Treatment Group) Reporting a Serious Adverse Experience With a Suspected or Probable Relationship to Study Medication (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least 1 SAE of suspected or probable relationship to study medication	29	(0.4)	19	(0.4%)
Rash*	7+	(0.1)	1	(<0.1)
Hepatic Enzymes Increased	3	(<0.1)	0	
Pneumonia	3	(<0.1)	2	(<0.1)
Therapeutic Response Increased	3	(<0.1)	3	(<0.1)
Diarrhea	0		3	(<0.1)

Data Source: Table 7.5, NDA 21-158, 18 month Safety Update, Table 7.5, p. 155
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, rash pustular.
+Includes PID 206.003.28549, which had a preferred term serum sickness-like reaction SAE associated with a maculo-papular rash

Table 13 . Serious Adverse Events by Indication for the Interval On-Therapy Plus 30 Days Post Therapy

Indication	Gemifloxacin 320 mg od		All Comparators	
	n /N	%	n /N	%
CAP	89/1161	7.7	96/927	10.4%
AECB	105/2879	3.6	96/2620	3.7

Abridged and Adapted from the Applicants Table 7.6 from NDA 21-158 in the 18 month Safety Update

The above table divides the incidence of Serious adverse events by indication. The incidence of serious adverse events for the 2 indications being applied for in this resubmission are 7.7% for CAP in the gemifloxacin arm versus 10.4% in the all comparator group and 3.6% for ABECB in the gemifloxacin group versus 3.7% for all comparators.

Withdrawals Due to Adverse Experiences•

In the clinical pharmacology studies 106 of 1874 patients were withdrawn because of an adverse event. Of these 106 subjects 72 were withdrawn after receiving gemifloxacin alone (4.9% of those receiving gemifloxacin alone), 15 after receiving gemifloxacin plus other (6.8% of those receving gemifloxacin and another medication), 12 receiving other alone (1% of those receiving only another drug), 8 in the placebo group (0.7%) and 4 patients were withdrawn before receiving any study drug. Only rash as an AE caused withdrawal of more than 1% of participants in either group. Rash caused 2.2% of the gemifloxacin alone participants to withdraw, 5% of the gemifloxacin plus other drug group and 0.2% of those receiving only other drug. Nausea, vomiting, and abdominal pain did not cause more than 0.4% of subjects to be withdrawn in any arm of the study and were evenly distributed across the treatment but not placebo groups.

In the clinical studies the most common adverse experiences leading to withdrawal in patients treated with gemifloxacin were rash, nausea, and diarrhea. Urticaria was also reported as an adverse event leading to withdrawal in 0.2% of gemifloxacin treated patients and 0.1% of comparator treated patients. The AE's most often associated with withdrawal for patients treated with comparator were diarrhea, nausea, vomiting, abdominal pain and rash. The major AE's leading to withdrawal in the gemifloxacin group were related to skin or allergic complications whereas gastrointestinal side effects were more prominent in patients treated with comparator agents.

Table 14. Number (%) of Patients (≥5 in Either Treatment Group) Withdrawn Due to Adverse Experiences (Gemifloxacin 320mg qd vs All Comparators) – On Therapy Plus 30 Days Post Therapy (Combined Population)

	Treatment group			
	Gemifloxacin 320mg qd N = 6775		All comparators N = 5248	
Preferred term*	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE leading to withdrawal	264	(3.9)	226	(4.3)
Rash+	64	(0.9)	15	(0.3)
Nausea	23	(0.3)	20	(0.4)
Diarrhea	22	(0.3)	25	(0.5)
Urticaria	15	(0.2)	4	(0.1)
Vomiting	15	(0.2)	16	(0.3)
Pneumonia	12	(0.2)	12	(0.2)
Dyspnea	8	(0.1)	7	(0.1)
Headache	6	(0.1)	4	(0.1)
Respiratory insufficiency	6	(0.1)	6	(0.1)
Abdominal pain	5	(0.1)	15	(0.3)
Cardiac arrest	5	(0.1)	5	(0.1)
SGPT increased	5	(0.1)	2	(<0.1)
Chronic obstructive airways disease	4	(0.1)	8	(0.2)
Dizziness	4	(0.1)	8	(0.2)
Bronchitis	3	(<0.1)	6	(0.1)
Cardiac failure	2	(<0.1)	5	(0.1)
Respiratory disorder	2	(<0.1)	10	(0.2)
Sinusitis	2	(<0.1)	5	(0.1)
Vertigo	1	(<0.1)	9	(0.2)
Creatinine clearance decreased	0	(0.0)	5	(0.1)

Data Source: NDA 21-158, 18 month Safety Update, Table 8.6, p. 171
* Adverse events are sorted by decreasing frequency in the gemifloxacin 320mg qd group.
+ The term rash includes AEs recorded with the preferred terms rash, rash erythematous, rash maculopapular, and rash pustular.

6. Pregnancies

A total of 18 pregnancies were reported in the clinical pharmacology studies and clinical studies. Five pregnancies occurred during participation in the clinical pharmacology studies and 13 in the clinical studies.

Clinical Pharmacology

All of the 5 pregnancies in the clinical pharmacology program occurred in the post NDA period, all in study 344. These occurred despite protocol defined criteria requiring double barrier contraceptive mechanisms throughout. Two of these pregnancies resulted in spontaneous

abortions, one required a medical termination because of an ectopic pregnancy, one was terminated electively and one healthy baby was born. Further details of these pregnancies are listed below.

Subject number 344.004.00181 is a 39 yo woman with 2 prior full term pregnancies who probably conceived within 1- 2 days of beginning medication and received the full 10 days of gemifloxacin.=- A spontaneous abortion occurred at 9 weeks.

Subject number 344.009.00507 is a 28 yo female whose LMP occurred on 6/29/01 and who received gemifloxacin from 5/30/01 until 6/9/01. The outcome was a healthy baby.

Subject number 344.017.00774 is a 20 yo female whose LMP was 4/29/01. She received study drug from 5/14/01 until 5/23/01. She was also taking ethinylestradiol/norethisterone (Ovcon 35). This pregnancy was electively terminated.

Subject number 344.029.01394 is a 24 yo female whose LMP was 5/22/01 and who received gemifloxacin from 6/19/01 until 6/28/01. She was on no other medication and had a history of 2 previous Caesarian sections. At approximately 9 weeks of gestation she experienced a spontaneous abortion.

Subject number 344.034.01207 is a 24 yo female who had an ectopic pregnancy. Her LMP was 6/26/01 and she received drug from 6/26/01 until 7/5/01. The tubal pregnancy was terminated by therapeutic abortion.

Clinical Studies

There were a total of 13 pregnancies, 7 in subjects treated with gemifloxacin and 6 in the all comparator group.

In the comparator group, 4 of 6 pregnancies resulted in normal healthy babies. One was lost to followup. One had an elective abortion. Efforts are being made to determine the outcome of the lost to followup pregnancy.

Of those treated with gemifloxacin 5 occurred in patients receiving 320 mg dosing and 2 in patients who received single dose 640 mg.

Three of the pregnancies in the 320 mg dose group produced normal healthy babies. The outcome of 1 of the pregnancies is unknown since the patient was lost to followup. The fifth pregnancy in this group resulted in a spontaneous abortion as described below.

Patient number 206.601.28875 is a 25 yo female whose LMP is not known. She received gemifloxacin from 2/4/00 until 2/8/00. On March 23 she was found to be approximately 7-8 weeks pregnant. On May 12 she was diagnosed with a miscarriage by ultrasound and underwent a dilatation and curettage the next day. She had also been taking multiple other allergy and cold medicines for her sinusitis.

In the 620 mg group one of the pregnancies was lost to followup and the other pregnancy was terminated by elective abortion.

Table 15. Summary of Pregnancies in Clinical Pharmacology and Clinical Studies
Clinical Pharmacology=5 all on gemifloxacin
1 healthy baby
2 spontaneous abortions
1 elective abortion
1 therapeutic abortion secondary to ectopic pregnancy

Clinical Studies=13
Comparator=6
4 healthy babies
1 elective abortion
1 lost to follow-up

APPEARS THIS WAY
ON ORIGINAL

Gemifloxacin=7
640 mg 1 elective abortion
1 lost to follow-up

320mg 3 healthy babies
1 lost to follow-up
1 spontaneous abortion

Totals-Gemifloxacin 12
4 healthy babies
2 elective abortions
1 therapeutic abortion
2 lost to follow-up 3 spontaneous abortions

Comparator 6
4 healthy babies
1 elective abortion
1 lost to follow-up

Cutaneous Adverse Events: Rash

During the review of the original submission of the Factive (gemifloxacin mesylate) NDA, a high rate of rash was noted in the gemifloxacin clinical studies, particularly among women. This section of the review will summarize the data from the clinical studies Combined Population regarding the adverse event of rash. Following the discussion of the data from the clinical studies population, data from Study 344 will be discussed. Study 344 was a special study conducted to specifically characterize gemifloxacin associated rash including histopathology, potential for cross-sensitization, and subclinical sensitization to gemifloxacin.

Clinical Studies

The incidence of all AE's of the skin and appendage body system was 5.8% in gemifloxacin treated patients and 2.6% in comparator treated patients. Within the skin and body system category, rash was the most frequently reported adverse event with 3.6% of gemifloxacin treated and 1.1% of comparator treated patients reporting rash. Urticarial reactions were seen in 36 (0.5%) of gemifloxacin treated patients compared to 11 (0.2%) of comparator patients. Six cases of facial edema were reported but upon review none appeared to represent angioedema.

Table 16. Number (%) of Patients in the Combined Population (≥ 3 Patients in Either Treatment Group) Reporting Adverse Experiences by Preferred Term in the Skin and Appendages Body System (On-Therapy plus 30 Days Post-Therapy Interval)

Preferred Term	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
	n	(%)	n	(%)
Patients With At Least One AE in the Skin and Appendages Body System	396	(5.8)	137	(2.6)
Rash* - (Composite term)	241	(3.6)	59	(1.1)
Rash	159	(2.3)	43	(0.8)
Rash Erythematous	57	(0.8)	12	(0.2)
Rash Maculo-Papular	28	(0.4)	4	(0.1)
Rash Pustular	3	(<0.1)	0	(0.0)
Pruritus	47	(0.7)	23	(0.4)
Urticaria	36	(0.5)	11	(0.2)
Dermatitis	25	(0.4)	3	(0.1)
Eczema	13	(0.2)	9	(0.2)
Pruritus, Genital	18	(0.3)	6	(0.1)
Dermatitis, Fungal	7	(0.1)	3	(0.1)
Acne	4	(0.1)	6	(0.1)
Skin Hypertrophy	3	(<0.1)	0	(0.0)
Skin Discoloration	3	(<0.1)	0	(0.0)
Skin Dry	6	(0.1)	6	(0.1)
Skin Ulceration	3	(<0.1)	5	(0.1)
Photosensitivity Reaction	3	(<0.1)	1	(0.0)
Bullous Eruption	1	(<0.1)	3	(0.1)
Skin Disorder	1	(<0.1)	3	(0.1)

Data Source: Tables 012b & Table 219a; NDA #21-158, 18 month Safety Update, pp.4090-4102 and 6210.
*Rash as a composite term includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.
Note: One patient (049.080.11311) in the gemifloxacin treatment group had an AE of erythema multiforme (NDA population).

Time and Rash

The timing of the onset of rash by treatment group was examined. The results show that two-thirds of comparator treated patients have onset of the rash in the first 7 days while two-thirds of the gemifloxacin treated patients have rash onset after 7 days with 35% having onset on days 8, 9, or 10.

Table 17. Time to Onset of Rash (Combined Populations)

	Treatment Group			
	Gemifloxacin 320mg qd		All Comparators	
Patients with Rash*	N=241		N=59	
Time to Rash Onset (days)	n	(%)	n	(%)
1	9	(3.7)	6	(10.7)
2	19	(7.9)	9	(15.3)
3	14	(5.8)	10	(16.9)
4	10	(4.1)	6	(10.2)
5	12	(5.0)	3	(5.1)
6	7	(2.9)	2	(3.4)
7	6	(2.5)	2	(3.4)
8	36	(14.9)	1	(1.7)
9	46	(19.1)	4	(6.8)
10	38	(15.8)	3	(5.1)
11	19	(7.9)	1	(1.7)
12-14	11	(4.6)	2	(3.4)
15-19	7	(2.9)	5	(8.5)
20-24	2	(0.8)	2	(3.4)
25-29	2	(0.8)	2	(3.4)
≥30	3	(1.2)	1	(1.7)

Data Source: Applicant's Table 14.14 from NDA 21-158 18 month Safety Update.
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

The duration of rash by treatment group was also evaluated. In general there appears to be a trend toward longer duration of rash in gemifloxacin treated patients than in comparator treated patients reporting rash.

Table 18. Duration of Rash (Combined Populations)

	Treatment Group			
	Gemifloxacin 320 mg qd		All Comparators	
Patients with Rash*	N=241		N=59	
Duration of Rash (days)	**n**	**(%)**	**n**	**(%)**
1	4	(1.7)	4	(6.8)
2	19	(7.9)	11	(18.6)
3	30	(12.4)	5	(8.5)
4	39	(16.2)	7	(11.9)
5	22	(9.1)	3	(5.1)
6	17	(7.1)	3	(5.1)
7	11	(4.6)	4	(6.8)
8	13	(5.4)	1	(1.7)
9	9	(3.7)	2	(3.4)
10-14	30	(12.4)	3	(5.1)
15-19	10	(4.1)	4	(6.8)
20-24	7	(2.9)	1	(1.7)
25-29	4	(1.7)	0	(0.0)
≥30	5	(2.1)	1	(1.7)
Unknown/Ongoing	21	(8.7)	10	(16.9)

Data Source: Applicant's Table 14.13 from NDA 21-158 18 month Safety Update.
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

The frequency of rash by severity across treatment arms is summarized in Table 19. The frequency of rash of all severities was greater among gemifloxacin treated patients. Among the patients with rash, there is a slightly greater rate of more severe rash among gemifloxacin treated patients. Twenty-seven of the rashes which occurred in the gemifloxacin groups were treated with systemic steroids versus 3 in the all comparators group.

Table 19. Frequency of Rash by Severity in Either Treatment Group (Combined Populations)

	Treatment Group			
	Gemifloxacin 320mg qd		All Comparators	
	N=6775		N=5248	
	n	**(%)**	**n**	**(%)**
Patients with AE of Rash*	**241**	**(3.6)**	**59**	**(1.1)**
Mild	123	(1.8)	34	(0.6)
Moderate	90	(1.3)	22	(0.4)
Severe	33	(0.4)	4	(0.1)
Treatment with Systemic Steroids	27	(0.3)	3	(0.1)

Data Source: Adapted from Applicant's Table 14.16 from NDA 21-158 18 month Safety Update.
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

Risk Factors for Rash Development

In order to investigate factors that may be related to the adverse event of rash, the data from the clinical studies database (Combined Population) were examined stratifying by a number of factors. The rates of rash vary across indications, reflecting in part the differences in the patient populations enrolled in the studies (age and gender) and the duration of therapy. The rates of rash by indication consistently reveal higher rates of rash in the gemifloxacin treated patients compared to comparator treated patients.

Table 20. Number (%) of Patients With Rash by Therapeutic Indication (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Indication	**n**	**(%)**	**n**	**(%)**
AECB	44/2847	(1.5)	21/2591	(0.8)
CAP	55/1160	(4.7)	19/926	(2.1)
ABS	73/1397	(5.2)	5/521	(1.0)
cUTI	48/758	(6.3)	11/729	(1.5)
uUTI	14/430	(3.3)	2/444	(0.5)
uSSSI	5/39	(12.8)	1/37	(2.7)
NGU	2/144	(1.4)	0/0	(0.0)

Data Source: Tables 105a, 105b, 105c, 105d, 105e, 105f, 105g.
Source: Applicant's Table 14.20 from NDA 21058 18 month Safety Update

Rash was noted more frequently in female than male patients in both treatment groups. Age less than 40 years was associated with higher rates of gemifloxacin associated rash. In general, longer duration therapy was associated with increasing rates of rash. For both treatment arms rash rates were higher in the North American and US sites than the Non North American sites.

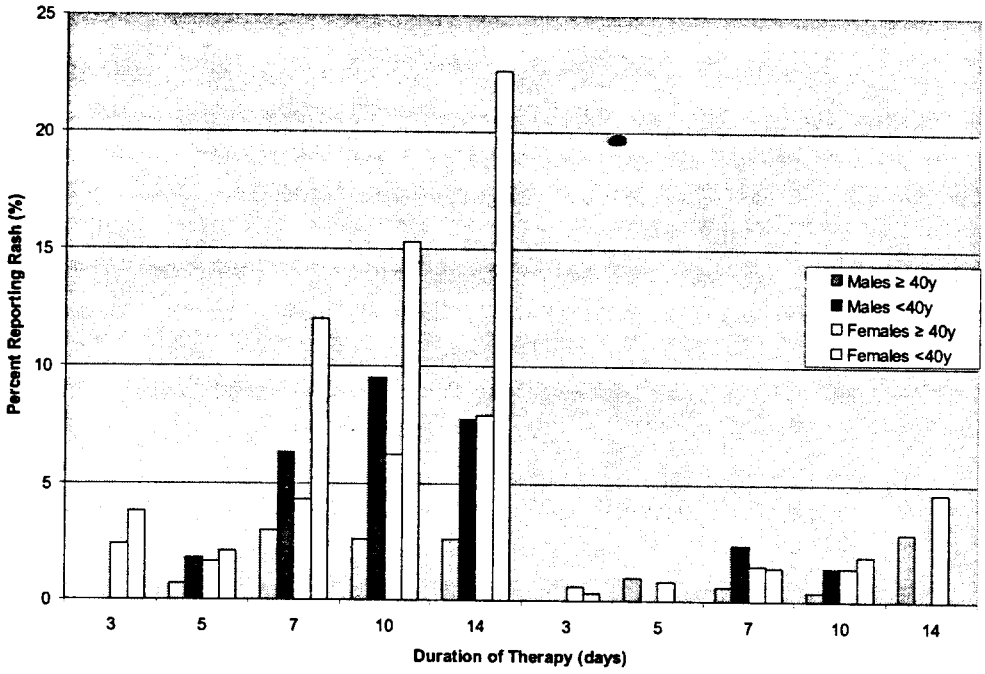
Table 21. Number (%) of Patients With Rash by Gender, Age, Duration of Treatment, and Country (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
	n/N	(%)	n/N	(%)
Gender				
Male	78/3278	(2.4)	20/2511	(0.8)
Female	163/3497	(4.7)	39/2737	(1.4)
Age, yrs				
<40	115/1711	(6.7)	13/1037	(1.3)
≥40	126/5064	(2.5)	46/4211	(1.1)
Duration of Treatment, n (%)				
3	14/501	(2.8)	2/444	(0.5)
5	37/2991	(1.2)	3/334	(0.9)
7	112/2113	(5.3)	22/1985	(1.1)
10	55/858	(6.4)	25/2240	(1.1)
14	23/312	(7.4)	7/245	(2.9)
Country				
North America*	125/2693	(4.6)	42/2402	(1.7)
United States	99/2283	(4.3)	34/2086	(1.6)
Non North America+	116/4082	(2.8)	17/2846	(0.6)

Source: Applicants' Tables 14.21-14.24 from NDA 21-158 18 month Safety Update

Logistic regression was used to analyze the effects of several explanatory variables (indication, gender, grouped country, age, and planned treatment duration) on the development of rash in gemifloxacin treated patients. The results of the analysis examining the individual explanatory variables found an association of rash with female gender, indication, age less than 40, enrollment in a North American site, and duration of treatment. Figure 1 below graphically depicts the relationship of age, gender and duration of therapy in the combined clinical population whereas Tables 22 and 23 more specifically present that data for CAP and ABECB.

Figure 1
Rash by Gender, Age and Duration of Therapy-Combined Population



Source: Combined from Data in NDA 21-158 18 Month Safety Updates and Supplements

Table 22. Rash in ABECB by Gender, Age, and Duration of Therapy

	5 days	7 days	10 days	Total
Females <40	0/4	2/2	0/2	2/8 (25%)
Females >40	16/1046	7/218	1/23	24/1287 (1.9%)
Males <40	0/5	1/2	0/0	1/7 (14.3%)
Males >40	8/1190	8/319	1/36	17/1545 (1.1%)

Source: Data from NDA 21-158 18 Month Safety Update and Supplements

Table 23. Rash in CAP by Age, Gender, and Duration of Therapy

	7 days	14 days	Total
Females <40	8/98	7/31	15/129 (11.6%)
Females >40	9/284	10/126	19/410 (4.6%)
Males <40	6/138	3/39	9/177 (5.1%)
Males >40	9/328	3/116	12/444 (2.7%)

Source: Data from NDA 21-158 18 Month Safety Update and Supplements.

The above graphs and tables elucidate the relationship with duration and the incidence of rash. Although this relationship is strongest in women under 40 is is also seen in men under 40 and women over 40. Only men over 40 have a relativley flat incidence across treatment duration. It is also apparent that the lower overall incidence of rash in ABECB compared to CAP is in part due to the very few enrollees under the age of 40 in the ABECB trials.

The following table was deriverd from the 18 month Safety Update by Dr. Cheryl Dixon, Statistician, to further examine the incidence of rash by decade. These date show that although younger women have the highest risk, younger men are also at an increased risk. The risk starts to decline in the forties to a plateau level in the fifties and sixties.

Table 24. Rash Incidence by Decade

	Total population	Females only
≤ 19	7/147 (4.8)	4/92 (4.3)
20-29	54/787 (6.9)	40/455 (8.8)
30-39	54/776 (7.0)	37/445 (8.3)
40-49	40/1124 (3.6)	24/658 (3.6)
50-59	30/1211 (2.5)	22/638 (3.4)
60-69	31/1294 (2.4)	22/591 (3.7)
70-79	18/1110 (1.6)	10/461 (2.2)
80-89	6/292 (2.1)	3/133 (2.3)
≥ 90	1/32 (3.1)	1/22 (4.5)

Additional analyses were performed to determine if oral contraceptive use and/or hormone replacement therapy were associated with the development of gemifloxacin associated rash. In the population of female patients less than 40 years of age, oral contraceptive (OC) use was not associated; 8.6% of oral contraceptive users developed a rash and 7.9% of women under 40 who did not use OCs experienced a rash. In the population of female patients 40 years of age and older, hormone replacement therapy (HRT) did appear to have a correlation with gemifloxacin

associated rash; for gemifloxacin treated patients, 5.6% of HRT users developed a rash in comparison to 2.8% of nonusers with an odds ratio of 1.9 which was sattistically significant.

The Applicant examined the safety database to evaluate the rates of rash in gemifloxacin-treated patients with prior gemifloxacin exposure, prior other quinolone exposure, and quinolone exposure subsequent to gemifloxacin exposure. While these data probably represent selected populations and the number of patients available for analyses was limited in some categories, the analyses did not reveal any striking findings.

Table 25. Effect of Prior or Subsequent Quinolone Usage on the Development of Rash

Exposure Category	% Incidence of Rash
Prior Gemifloxacin Exposure (41/4659-0.5%)	0
Prior Other Quiolone Exposure (181/7659-2.45)	3/181 (1.7%)
Subsequent Quinolone Exposure N=13	0

Source: From text and tables 14.28 and 14.28 from NDA 21-158 18 month Safety Update

The data from the clinical studies were also reviewed to investigate rates of rash in patients with other adverse events that might suggest a systemic syndrome. Rates of rash in patients who had increased liver function tests, fever, arthralgia, or arthralgia and lymphadenopathy are summarized in Table . There does not seem to be any suggestion in these data of a multi-organ hypersensitivity syndrome as a casue of the rash.

Table 26. Rates of Rash in Gemifloxacin Treated Patients with Signs of Potential Systemic Syndromes

	Number of Patients Exhibiting Sign n/N (%)		Number of Patients with Sign Reporting an AE of Rash n/N (%)	
Increased Liver Function Tests or Eosinophilia	38/6775	(0.6)	2/38	(5.3)
Fever	52/6775	(0.8)	3/52	(5.8)
Arthralgia	45/6775	(0.7)	3/45	(6.7)
Arthralgia and Lymphadenopathy	4/6775	(0.06)	1/4	(25.0)

Adapted from the text and tables, NDA 21-158, 18 month safety update, pp. 383-387.

One patient did experience a serum sickness like reaction. This patient's course is summarized in the following section.

Patient number 206.003.28549 was a 42 y.o. Caucasian female resident of the United States. She had a history of allergic rhinitis and asthma. She was entered into study 202 for the treatment of Acute Bacterial Sinusitus and received gemifloxacin 320 mg po qd for 5 days. Thirteen days after

completing therapy she developed a generalized maculopapular rash, fever, chills, joint pains and cough. Her liver function test and hematologic parameters stayed within normal limits. She was treated with Vicodin and decadron. The rash cleared in approximately 26 days and the other symptoms were resolved by 2 months There is also a possibility there may have been a coincident Mycoplasma infection.

STUDY 344

Design

The factors associated with the increased likelihood of rash in the clinical studies database for gemifloxacin were female gender, age less than 40, and gemifloxacin use longer than 7 days. Study 344 was designed to further characterize gemifloxacin-associated rash in a population predisposed to the development of rash (women under 40 years of age receiving gemifloxacin for 10 days). Study 344 was a clinical pharmacology study enrolling healthy female volunteers under the age of 40 who were randomized in Part A using a 5:1 ratio to receive either gemifloxacin 320 mg po qd for 10 days or ciprofloxacin 500 mg po bid for 10 days, respectively (Figure). After a washout period of 4-6 weeks, subjects entered Part B of the study as shown in the study schema. Subjects who developed gemifloxacin rash were randomized to either ciprofloxacin or placebo in a 3:1 ratio; subjects who did not develop a rash to gemifloxacin treatment were randomized to receive a second course of gemifloxacin or placebo. The subjects who received ciprofloxacin in Part A received placebo in Part B if they developed a rash to ciprofloxacin in Part A, or a second course of ciprofloxacin if the subject did not develop a rash to ciprofloxacin in Part B. The objectives of the study were to characterize the following:

- Clinical and histological characteristics of gemifloxacin associated rash
- Potential for cross sensitization to ciprofloxacin in subjects who experienced gemifloxacin-associated rash
- Potential for subclinical sensitization to repeat exposure to gemifloxacin in subjects not developing a rash on first exposure to gemifloxacin
- Relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash

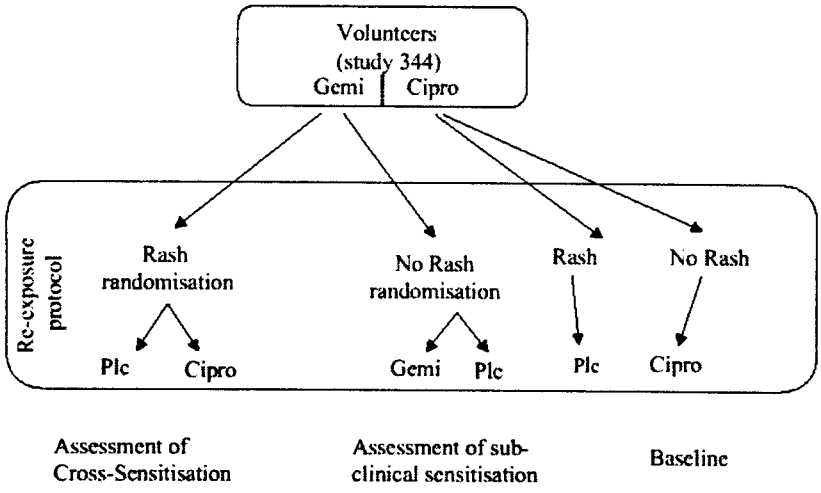


Figure 2. Schema for Study 344

The age range of the 1011 female volunteeers in this study was 18 to 40 with a mean age of 28. The racial demographics were white 929, black 2, oriental 20, hispanic 49, and other 11. The skin type breakdown was Type I –76, Type II-218, Type III 478, and Type IV- 239.

In Part A of the study, there were 819 evaluable subjects that received gemifloxacin and 164 that received ciprofloxacin (Figure 3). In the gemifloxacin group 31.7% (260/819) of women developed rash and 4.3% (7/164) developed rash to ciprofloxacin (Table).

Part A

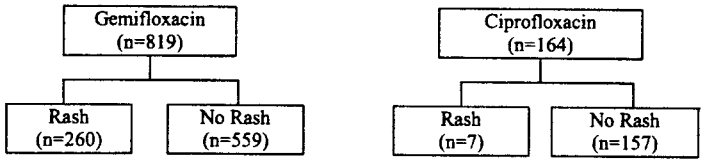


Figure 3. Summary of subject disposition in Part A

Table 27. Point Estimates and 95% Confidence Intervals for Incidence of Rash in Part A

Regimen	No. of Subjects	Subjects With Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemifloxacin	819	260	31.7	(28.5, 35.0)	(28.6, 35.1)
Ciprofloxacin	164	7	4.3	(0.9, 7.7)	(1.7, 8.6)

Source: Applicant's Table 14.1 from NDA 21-158 18 month Safety Update

In Part B of the study, subjects were randomized or assigned to further gemifloxacin, placebo, or ciprofloxacin therapy depending on their outcome in Part A and according to the study schema in Figure 4. Subject disposition in the Part B portion of the study is shown in Figure . The results for rates of rash in each of the groups in Part B of the study are summarized in

Table 28. For subjects that developed rash to gemifloxacin in Part A, 10.4% of these subjects randomized to ciprofloxacin in part B developed a rash compared to 4.9% of the subjects who recieved placebo. For the subjects who received gemifloxacin in Part A and did not develop a rash, 3.2% of subjects randomized to a second course of gemifloxacin in Part B developed rash compared to 2.7% of their placebo counterparts in Part B.

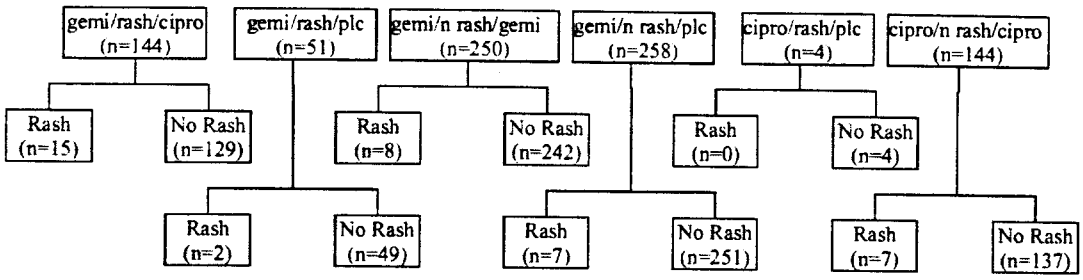


Figure 4. Summary of Subject Disposition in Part B

Table 28. Point Estimates and 95% Confidence Intervals for Incidence of Rash in Part B

Regimen	No. of Subjects	Subjects With Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
gemi/rash/cipro	144	15	10.4	(5.1, 15.8)	(5.9, 16.6)
gemi/rash/plc	51	2	3.9	(0.0, 10.2)	(0.5, 13.5)
gemi/N rash/gemi	250	8	3.2	(0.8, 5.6)	(1.4, 6.2)
gemi/N rash/plc	258	7	2.7	(0.5, 4.9)	(1.1, 5.5)
cipro/rash/plc	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
cipro/N rash/cipro	144	7	4.9	(1.0, 8.7)	(2.0, 9.8)

Source: Applicant's Table 14.2 from NDA 21-158 18-month safety update

The point estimates and their 95% confidence intervals for differences in incidence rates for rash in several groups of interest are provided in Table .

Table 29. Point Estimates and 95% Confidence Intervals for Differences in Incidence of Rash

Regimen	Point Estimate(%)	95% C.I.*
(gemi/rash/cipro/rash) – (cipro/N rash/cipro/rash)*	5.6	(-1.2, 12.4)
(gemi/rash/cipro/rash) – (gemi/rash/plc/rash)**	6.5	(-2.1, 15.1)
(gemi/rash/cipro/rash) – (cipro/rash)***	6.1	(-0.4, 12.7)

* Difference in incidence of rash for dosing with ciprofloxacin Part B following gemifloxacin associated rash in Part A relative to dosing with ciprofloxacin in Part B following ciprofloxacin without rash in Part A.

** Difference in incidence of rash for dosing with ciprofloxacin Part B following gemifloxacin associated rash in Part A relative to dosing with placebo in Part B following gemifloxacin associated rash in Part A.

*** Difference in incidence of rash for dosing with ciprofloxacin Part B following gemifloxacin associated rash in Part A relative to dosing with ciprofloxacin in Part A.

Source: Adapted from Applicant's Table 14.3 from NDA 21-158 18 month safety update

In Part B, one of the study centers had remarkably high incidence of rash in Part B (>66%) with all 3 subjects receiving placebo reported as having a rash. Therefore additional analyses were performed examining rates of rash in Part B excluding results from this one center (Table). The rash rate for the group gemi/rash/cipro was 5.9% and the rash rate in the gemi/rash/placebo group was 2.0% when data from this one center was excluded.

Table 30. Point Estimates and 95% Confidence Interval for Incidence of Rash in Part B – Excluding Center 027

Regimen	No. of Subjects	Subjects with Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemi/rash/cipro	136	8	5.9	(1.6, 10.2)	(2.6, 11.3)
Gemi/rash/plc	50	1	2.0	(0.0, 6.9)	(0.1, 10.6)
Gemi/N rash/gemi	248	6	2.4	(0.3, 4.5)	(0.9, 5.2)
Gemi/N rash/plc	256	5	2.0	(0.1, 3.8)	(0.6, 4.5)
Cipro/rash/plc	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
Cipro/N rash/cipro	141	5	3.5	(0.1, 7.0)	(1.2, 8.1)

Data Source: Applicant's Table 21 NDA 21-158, Study Report Study 344, p. 00093.

The preceding tables demonstrate the high incidence of rash in Part A of 31.7% in the gemifloxacin treated subjects in comparison to the rate of 4.3% in the ciprofloxacin treated subjects. In part B subjects who had rash to gemifloxacin in Part A had either 10.2 or 5.9% (if Center 027 is excluded) incidence of rash possibly suggesting some cross sensitization.

Rash Characteristics – Part A

The rashes observed in Parts A and B were characterized by examining the description, surface area involved, day of onset, and duration of rash. Since there were only 7 rashes in the ciprofloxacin arm in Part A it is difficult to make significant comparisons between the groups. However, the information gathered provided important detail on the nature of the rash and can also be compared to what was seen in the clinical trials group and what would be expected overall.

The following tables and graphics depict the characteristics of the rash in Parts A and B. The rash in Part A of Study 344 appears to have a later onset and longer duration similar to what was observed in the combined clinical trials population. Eighty percent of subjects who developed a rash to gemifloxacin did so on days 8, 9, or 10. The average duration for gemifloxacin rash was 7 days in comparison to 4 days for rashes secondary to ciprofloxacin treatment.

Table 31. Day of Onset of Rash in Part A

Day of Onset	Gemifloxacin	Ciprofloxacin
1	10 (3.8%)	0 (0.0%)
2	6 (2.3%)	2 (28.6%)
3	2 (0.8%)	1 (14.3%)
4	2 (0.8%)	1 (14.3%)
5	2 (0.8%)	0 (0.0%)
6	3 (1.2%)	0 (0.0%)
7	5 (1.9%)	0 (0.0%)
8	54 (20.8%)	1 (14.3%)
9	109 (41.9%)	0 (0.0%)
10	50 (19.2%)	1 (14.3%)
11	10 (3.8%)	0 (0.0%)
12	3 (1.2%)	0 (0.0%)
13	0 (0.0%)	0 (0.0%)
14	1 (0.4%)	0 (0.0%)
15	1 (0.4%)	0 (0.0%)
16	1 (0.4%)	0 (0.0%)
17	1 (0.4%)	1 (14.3%)
Total	260 (100.0%)	7 (100.0%)

Source: Applicant's Table 12.3 from NDA 21-158 18 month safety update

Table 32. Summary Statistics for Duration of Rash in Part A

Regimen	n	Mean	S.D.	Median	Min	Max
Gemifloxacin	258	7	5.3	6	1	52
Ciprofloxacin	7	4	1.1	3	2	5

Source : Applicant's Table 12.6 from NDA 21-158 Report of Study 344

The amount of surface area involved and the intensity of the rash secondary to gemifloxacin in Part A are both greater than what was seen in the ciprofloxacin arm in Study 344. Over 25% had a rash covering >60% of body surface area and 7.3% were classified as having a severe rash while none of the ciprofloxacin subjects had a severe rash. In addition 11.5% who developed rash to gemifloxacin had an urticarial component to that rash while none of the ciprofloxacin rashes did so.

Table 33. Summary of Description of Rash in Part A by Regimen and Severity.

Regimen Description	Severity Mild (%)	Moderate (%)	Severe (%)	Total (%)
Gemi (n=260)	161/260 (62)	80/260 (31)	19/260 (7)	260/260 (100)
Macules	125 (48.1)	70 (26.9)	14 (5.4)	209 (80.4)
Papules	122 (46.9)	71 (27.3)	17 (6.5)	210 (80.8)
Plaques	15 (5.8)	11 (4.2)	3 (1.2)	29 (11.2)
Pruritus	99 (38.1)	65 (25)	16 (6.2)	180 (69.2)
Skin Tenderness	12 (4.6)	6 (2.3)	4 (1.5)	22 (8.5)
Urticaria	18 (6.9)	6 (2.3)	6 (2.3)	30 (11.5)
Cipro(n=7)	6/7 (85.7)	1/7 (14.3)	0 (0)	7/7 (100)
Macules	3 (42.9)	0 (0)	0 (0)	3 (42.9)
Papules	5 (71.4)	1 (14.3)	0 (0)	6 (85.7)
Pruritus	3 (42.9)	1 (14.3)	0 (0)	4 (57.1)

Source: Applicant's Table 14.5 fromNDA21-158 Rpoert of Study 344 Appendix C

Table 34. Summary of Surface Area Covered with Rash by Regimen and Severity of Rash in Part A

Regimen	Surface Area Covered	Severity Mild	Moderate	Severe	Total
Gemifloxacin	Unknown	5 (1.9%)	0 (0.0%)	0 (0.0%)	5 (1.9%)
	0 - 5%	37 (14.2%)	3 (1.2%)	0 (0.0%)	40 (15.4%)
	6 - 10%	21 (8.1%)	4 (1.5%)	2 (0.8%)	27 (10.4%)
	11 - 20%	32 (12.3%)	7 (2.7%)	0 (0.0%)	39 (15.0%)
	21 - 40%	21 (8.1%)	12 (4.6%)	2 (0.8%)	35 (13.5%)
	41 - 60%	28 (10.8%)	17 (6.5%)	2 (0.8%)	47 (18.1%)
	>60%	17 (6.5%)	37 (14.2%)	13 (5.0%)	67 (25.8%)
	Total	**161 (61.9%)**	**80 (30.8%)**	**19 (7.3%)**	**260 (100.0%)**
Ciprofloxacin	Unknown	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	0 - 5%	4 (57.1%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	6 - 10%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	11 - 20%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	21 - 40%	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	41 - 60%	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
	>60%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	**6 (85.7%)**	**1 (14.3%)**	**0 (0.0%)**	**7 (100.0%)**

Source: Applicant's Table 14.6 from NDA 21-158 Report of Study 344 Appendix C

Characteristics of Rash-Part B

There were much smaller numbers of subjects to compare in the arms in Part B. However, the tendency for rashes secondary to gemifloxacin to occur later and last longer were still present but less pronounced. There were 8 Gemi/Nrash/gemi subjects with a mean onset of rash of 6 days and mean duration of 7 days while there were 15 Gemi/rash/cipro subjects with rash with a mean onset of 4 days and mean duration of 5 days. Overall, the rashes in Part B were milder and involved less surface area than the rashes in Part A.

Table 35. Summary Statistics for Day of Rash Onset in Part B

Regimen	n	Mean	S.D.	Median	Min	Max
gemi/rash/cipro	15	4	2.9	2	1	10
gemi/rash/plc	2	6	4.9	6	2	9
gemi/N rash/gemi	8	6	5.7	5	1	18
gemi/N rash/plc	7	6	7.9	2	1	23
cipro/rash/plc	0					
cipro/N rash/cipro	7	6	2.6	6	3	10

Source: Applicant's Table 12.19 from NDA 21-158 Report of Study 344

Table 36. Summary Statistics for Duration of Rash in Part B

Regimen	n	Mean	S.D.	Median	Min	Max
gemi/rash/cipro	15	5	6.0	3	2	26
gemi/rash/plc	2	3	0.7	3	2	3
gemi/N rash/gemi	8	7	5.6	6	2	19
gemi/N rash/plc	7	4	1.8	5	1	6
cipro/rash/plc	0					
cipro/N rash/cipro	7	5	3.6	4	2	12

Source: Applicant's Table 12119 from NDA 21-158 Report of Study 344

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Table 37. Summary of Surface Area Covered with Rash by Regimen and Severity of Rash in Part B

	Surface Area	Severity			
Regimen	Covered	Mild	Moderate	Severe	Total
gemi/rash/cipro	0 - 5%	13 (86.7%)	2 (13.3%)	0 (0%)	15 (100%)
gemi/rash/plc	0 - 5%	2 (100%)	0 (0%)	0 (0%)	2 (100%)
gemi/N rash/gemi	0 - 5%	4 (50%)	0 (0%)	0 (0%)	4 (50%)
	6 - 10%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	11 - 20%	1 (12.5%)	1 (12.5%)	0 (0%)	2 (25%)
	21 - 40%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	41 - 60%	1 (12.5%)	0 (0%)	0 (0%)	1 (12.5%)
gemi/N rash/plc	0 - 5%	6 (85.7%)	0 (0%)	0 (0%)	6 (87.5)
	6 - 10%	1 (14.3%)	0 (0%)	0 (0%)	1 (14.3%)
cipro/N rash/cipro	0 - 5%	5 (71.4%)	0 (0%)	0 (0%)	5 (71.4%)
	6 - 10%	2 (28.6%)	0 (0%)	0 (0%)	2 (28.6%)

Source: Applicant's Table 12.26 from NDA 21-158 Report of Study 344

Fever, Eosinophilia, Mucus Membrane Involvement and Systemic Steroid Therapy

There were 7 subjects with fever and rash in Part A. There were 3 subjects with eosinophilia in Part A. However, there was only one woman with rash, fever, and eosinophilia. There was one reported case of wheezing but this was self limited and required no therapy.

As noted in Table 24 there were 16 cases of mucus membrane involvement among the 260 subjects who developed gemifloxacin rash (6.2%) and none in the 7 subjects who developed a rash secondary to ciprofloxacin. The three cases of reported eye involvement consisted primarily of dry eyes without discrete ocular lesions and the one case of involvement of the genitalia was in a subject with "total body rash" with no specific lesions other than extension of a macular papular rash.

Eleven of the twelve case reports of subjects with mucus membrane involvement of the mouth were reviewed (one was unavailable.) Five of these reports describe one to a few ulcerations, erosions, papules, or vesicles inside the mouth or on the lips. For 2 of these subjects no therapy was prescribed, 2 were prescribed topical steroids, and 1 was treated with topical steroids and oral antihistamines. Two subjects were described as having erythema on the lips and/or inside the mouth-one of these subjects required treatment with systemic steroids. Two subjects' CRFs are unreadable for the description of the mouth involvement but one of these also required treatment with systemic steroids. Two subjects were reported to have petechiae on lips: neither required any therapy.

An additional 8 patients who received gemifloxacin and developed a rash in Part A were also treated with systemic steroids. Of the 12 subjects with rash in sudy 344 who received systemic steroids the investigators graded the rash as severe in 2, mild in 1 and moderate in the rest.

Table 38. Summary of Mucous Membrane Involvement by Regimen and Severity of Rash in Part A

Regimen	Mucous Membrane Involved	Severity of Rash			
		Mild	Moderate	Severe	Total
Gemifloxacin	None	152 (58.5%)	72 (27.7%)	17 (6.5%)	241 (92.7%)
(n=260)	Eyes	3 (1.2%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
	Genitalia	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
	Mouth	3 (1.2%)	7 (2.7%)	2 (0.8%)	12 (4.6%)
Ciprofloxacin	None	6 (85.7%)	1 (14.3%)	0 (0.0%)	7 (100.0%)
(n=7)	Eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Genitalia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mouth	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Applicant's Table 12.11 from NDA 21-158 Report of Study 344

Histopathology Results

Histopathology specimens were obtained from 288 of the 299 total rash episodes in Parts A and B of Study 344 secondary to gemifloxacin, ciprofloxacin or occuring in the placebo arm. Punch biopsies were obtained from both affected and unaffected skin. Specimens were evaluated by routine histologic examination, immunophenotypic evaluation, and stained for immunoflourescence for IgG, IgM, IgA, and C3.
The following findings were obtained:

- Most common finding-mild superficial perivascular infiltrate.
- 10 cases of moderate superficial or deep perivascular infiltrate.
- 10 cases of eosinophils in the infiltrate (1 in unaffected skin.)
- T cell type infiltrate, both CD-4 and CD-8 with no common pattern noted.
- No evidence of vasculitis
- Activation of endothelial cells –staining for ICAM and HLA-DR.
- HLA-DR staining was noted in a siginificant number of cases.
- Immunoflourescence revealed faint deposits of IgM and/or C3 in dermal vessels "lumina" in some cases inlvolving unaffected and affected skin.
- One case of linear IgM along basement membrane (affected and unaffected.)
- No bulla formation, no epidermal or eccrine necrosis.

The above results were most consistent with a mild to moderate drug exanthem. No particular concerning findings patholgic finding were noted.

Other Safety Results of Study 344

Deaths, Serious Adverse Events and Withdrawals

There was one death in Study 344 in one subject who received ciprofloxacin who developed a dissection of her left anterior descending coronary artery. This event was not believed to be study related.

There were 10 serious adverse events in the gemifloxacin group and 2 in the ciprofloxacin group. These events are depicted in Table 9 in the Serious Adverse Events-Clinical Pharmacology section of this review under the categories Gemifloxacin RD and ciprofloxacin RD. Only 2 cases of colitis in the gemifloxacin grouop and 1 case of Clostridium difficile in the Ciprofloxacin group that were considered to be drug related.

There were 113 total withdrawals in Study 344, 63 of these were secondary to an adverse event and 26 of these were removals by the investigator for rash (7 occurring in the first 24 hours). Five of 164 subjects who received ciprofloxacin were withdrawn because on an adverse event in Part A.

Adverse Events

The following 2 tables list the most common adverse events and the most common evere adverse events of probable relationship to study drug in study 344. The results are similar to the clinical studies with the exception of higher incidences of rash and headache.

Table 39 AE's with a >10% Incidence Study 344 Part A

Adverse Event	Number of Treatment Emergent Adverse Events Reported	
	Gemifloxacin	Ciprofloxacin
Rash*	258 (30.7%)	9 (5.3%)
Headache	239 (28.4%)	54 (31.8%)
Nausea	146 (17.4%)	28 (16.5%)
Diarrhoea	109 (13.0%)	15 (8.8%)
Pruritus	96 (11.4%)	11 (6.5%)
Number of subjects with TEAEs	685 (81.5%)	117 (68.8%)
Number of subjects exposed	841	170

Denominator: Number of subjects exposed with study medication in each regimen
* Does not include preferred terms of 'rash erythematous' or 'rash maculopapular'
Source:Applicant's Table 43 from NDA 21-158 Report of Study 344

Table 40. Severe AEs with a suspected or probable relationship to Gemifloxacin Study 344 Part A

AE	Relationship	Number of Subjects
Rash	Probable	19
Headache	Suspected	10

Diarrhoea	Suspected	5
Diarrhea	Probable	1
Nausea	Suspected	2
Colitis Pseudomembranous	Suspected	1
Dyspepsia	Suspected	1
Enteritis	Suspected	1
Migraine	Suspected	1
Pruritus	Probable	1
Somnolence	Suspected	1
Sweating Increased	Probable	1
Tremor	Suspected	1
Vomiting	Suspected	1
Vomiting	Probable	1

Source Applicant's Table 46 from NDA 21-158 Report of Study 344

Pregnancies

Please section on Pregnancies above for a description of the 5 pregnancies which occurred during this study.

Vital Signs and ECG Changes

See separate section on this topic to follow. All enrollees had baseline and on therapy vital sign measurement and ECG testing.

Laboratory Tests

Review of hematology lab data from parts A and B in patients with and without rash revealed no relevant differences in incidence of clinically important lab abnormalities in the 2 groups. No hematology lab abnormalty occurred more than 0.8% of the time. The incidence of eosinophilia is addressed above.

In Part A of those who did not develop a rash, there were 3 subjects with an AST>2xULN, 1 with a BR >2xULN and 2with >GGT >2xULN. These were similar to the rates seen in Part B for gemi/rash/gemi and gemi/rash/placebo. There were minimally higher than those seen in the ciprofloxacin arms.

Of those who did develop a rash there was one elevation >2xULN for AST and one for BR but no elevations greater than 3xULN in any arm in either Part A or Part B.

Hepatic Safety Assessments

Pre-Clinical Studies

Pre-clinical studies in dogs with gemifloxacin using repeat oral doses of 28 days, 3 months and 6 months duration noted cholangitis/pericholangitis accompanied by hepatocellular degeneration and single cell necrosis. The lowest effect dose was 23mg/kg/day (mean Cmax 1.1µg/mL, AUC