Draft Questions for Anti-Infective Drug Advisory Committee Meeting
September 12, 2006

Questions:

Subject: Supplemental NDA 21-158/S-006 Factive™ (gemifloxacin), Oscient Pharmaceuticals, proposed for 5-day treatment of acute bacterial sinusitis.

1. Do the safety and effectiveness data presented support the use of Factive™ (gemifloxacin) for the treatment of acute bacterial sinusitis?

   If yes, are there any special caveats or warnings that should be included in the label?

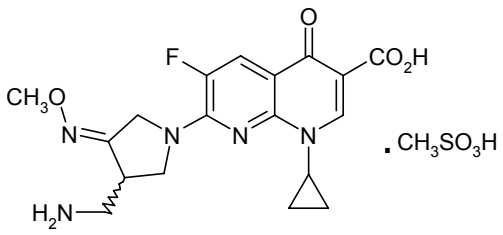
   If no, what other information would be required?

2. If you believe the data presented support safety and effectiveness for this indication, do you have any specific risk-management recommendations for Factive™ (gemifloxacin) post approval?

FDA Briefing Package

Anti-Infective Drugs Advisory Committee

September 12, 2006



Application: **NDA 21-158/S-006: Factive® (Gemifloxacin)**
Indication: **Treatment of Acute Bacterial Sinusitis**
Applicant: **Oscient Pharmaceuticals Corporation**

Prepared by the Division of Special Pathogen and Transplant Products, Office of Antimicrobial Products, CDER

August 1, 2006

Executive Summary

Factive® (gemifloxacin) is a fluoroquinolone antimicrobial originally developed by SmithKline Beecham (SKB) – later GlaxoSmithKline (GSK) – for the treatment of several bacterial infections. The New Drug Application NDA 21-158 was originally submitted in December 1999 for community acquired pneumonia (CAP), acute bacterial exacerbation of chronic bronchitis (ABECB), acute bacterial sinusitis (ABS), uncomplicated urinary tract infections (uUTI) and acute pyelonephritis. SKB also requested approval of penicillin- and macrolide-resistant *S. pneumoniae* as a pathogen in the respiratory tract infections. In these studies, gemifloxacin was dosed 320 mg PO for 3 to 14 days, depending on the indication. The FDA review staff concluded, however, that the NDA should not be approved primarily due to concerns regarding the high incidence of rash observed with gemifloxacin use when compared to the rate seen in patients receiving the control drugs. (See Tables 7 through 10, Figure 1) There were also questions regarding potential hepatic injury and QT prolongation. SKB was issued a non-approval letter on December 15, 2000, indicating there were concerns regarding the safety of gemifloxacin and requesting additional clinical studies particularly to better assess the risk of gemifloxacin-associated rash (and related symptoms such as pruritus, urticaria, dermatitis, "skin and appendages body system"), especially in women under 40 years of age, and to assess the risk from rechallenge to gemifloxacin in patients who experienced a rash on first exposure to this agent.

The original NDA contained two controlled studies of Acute Bacterial Sinusitis (ABS), both of which tested a 7-day course of gemifloxacin. In one study gemifloxacin was compared to cefuroxime axetil, in the other to trovafloxacin. In these studies, the success rates in the ITT populations were comparable between the study arms. However, the rate of rash was 8.6% in the 7-day gemifloxacin arm compared to 0.6% in the cefuroxime axetil arm; and 9.4% in the gemifloxacin arm compared to 1.0% in the trovafloxacin arm. Thus, GSK submitted two additional studies in which a 5-day regimen of gemifloxacin was used in ABS, stating the rate of rash was lower for this shorter duration. This application (NDA 21-376) was submitted in June 2001 and reviewed. The comparator in the 5-day gemifloxacin study was the 7-day gemifloxacin regimen, and while the study showed that the rate of rash in the 5-day arm (2.8%) was lower than in the 7 day (8.9%), this was still higher than rash seen with other control drugs. (See Tables 7 and 10). In the clinical review, the following specific concerns were identified:

- The higher rate of gemifloxacin-associated rash relative to all comparators in controlled studies.
- The potential for cross-sensitization after gemifloxacin use to other fluoroquinolone antibiotics.
- The possibility that the high rate of gemifloxacin-associated rash will result in patients being labeled as "quinolone allergic" resulting in the restriction of the quinolone class of antibiotics as a therapeutic option for individuals exposed to gemifloxacin.
- The absence of an unmet medical need for the treatment of ABS that warranted risk associated with gemifloxacin therapy.
- Concern that attempts to limit the duration of gemifloxacin therapy may be met with limited success.

Thus the applicant GSK was issued a non-approval letter for NDA 21-376 on April 12, 2002. The FDA stated that the applicant had not addressed the safety concerns communicated in the original December 2000 action.

Based on the review of the adverse events, it was noted that the rash was related to age and gender, with women younger than 40 years of age having the greatest incidence of rash, and older patients having a lower incidence. Therefore the company conducted a study (Study 344) in approximately 1000 women who received either 10 days of gemifloxacin or 10 days of ciprofloxacin, and evaluated the development of rash in all patients and cross-sensitization in a subset of the patients. In this study, rash was seen in 260/819 (31.7%) of gemifloxacin and 7/164 (4.3%) of ciprofloxacin treated women.

During a meeting with GSK, FDA staff expressed concerns regarding the adverse event profile of gemifloxacin for indications where mostly young patients, particularly women, would be treated, and the risk of rash was judged to outweigh the benefit. On the other hand, it was possible that for indications, such as community acquired pneumonia or acute exacerbations of chronic bronchitis the benefit may be greater than risk. During this time, ownership of the drug was transferred to LG Life Sciences Ltd.

NDA 21-158 was resubmitted October 2002 for the indications of 7-day treatment of community acquired pneumonia and 5-day treatment of acute exacerbation of chronic bronchitis. The application was presented before an open public Advisory Committee meeting on March 4, 2003 and the committee recommended approval for the 2 indications. For both indications it was determined that benefit outweighed risk and LG Life Sciences, c/o Parexel International was issued an approval letter on April 4, 2003. (See attached Factive® product labeling)

Ownership of the product was transferred to GeneSoft Pharmaceuticals in May 2003, and in 2004 Oscient was formed from the merger of GeneSoft and Genome Therapeutics. In 2005, FDA met with Oscient to review the ABS indication, including the efficacy and safety findings of the studies. In November 2005, Oscient submitted two supplemental applications for the following indications:

> <u>NDA 21-158/S-006, acute bacterial sinusitis, 5-day treatment</u>
> The FDA review staff determined that there was no new information addressing the safety concerns previously communicated to the applicant for acute bacterial sinusitis and issued a refuse-to-file letter for this indication. Although the application contained a proposal for a post-approval epidemiological study to address FDA's safety concerns, FDA's recommendation was that this study be completed prior to approval of an indication for acute bacterial sinusitis. The applicant requested nevertheless that FDA review the application and asked that it be filed over protest.
>
> <u>NDA 21-158/S-007, community acquired pneumonia, 5-day treatment</u>
> The supplement for community acquired pneumonia was accepted for review.

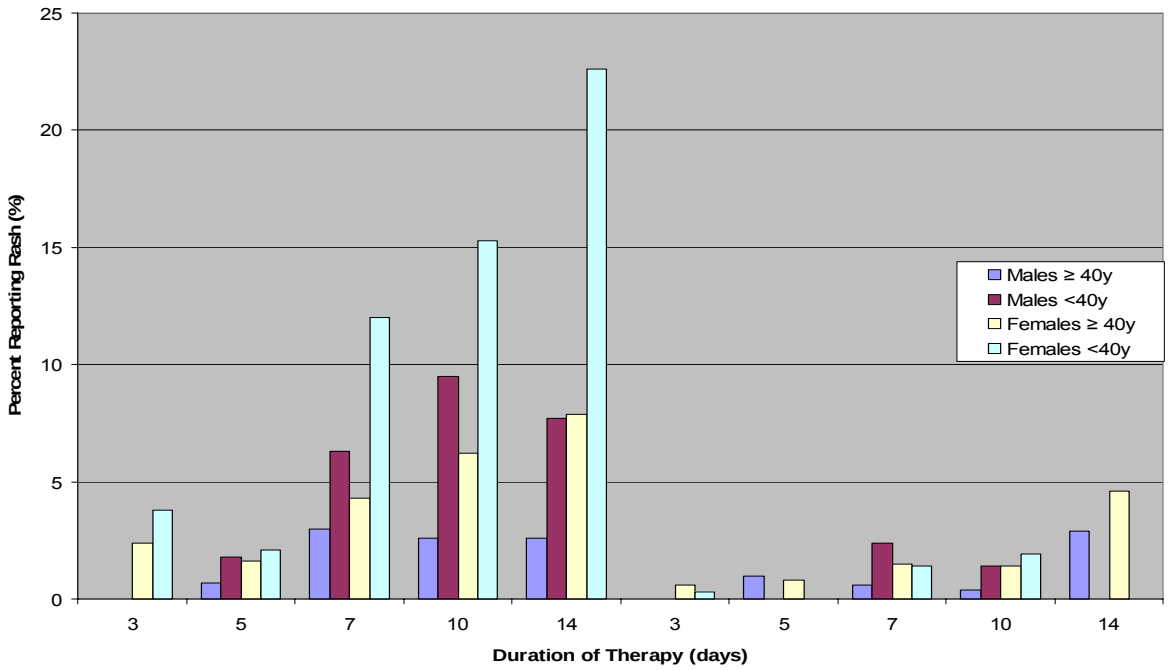
The two applications are currently under review; the application for the 5-day treatment of acute bacterial sinusitis is being brought before the Advisory Committee for discussion.

The following background document summarizes information from the above-cited submissions regarding the regulatory history, the efficacy results from the four ABS studies, the safety information from the gemifloxacin development program including ABS, the incidence and severity of rash. Attached to this document are

(a) the currently approved Factive® package insert,
(b) the Medical Officer Review of NDA 21-376 (studies of 5-day treatment in ABS)
(c) consult from the Office of Surveillance and Epidemiology (OSE), Division of Drug Risk Evaluation (DDRE) of post-marketing Adverse Events Reports for gemifloxacin since approval.
(d) acute bacterial sinusitis and non-inferiority studies

As summarized in this document and shown in Figure 1., below, the incidence of cutaneous adverse effects correlates with duration of treatment, age and gender, as reported from each clinical study of ABS and other indications, with lower rates reported for shorter duration and higher rates reported for longer courses of gemifloxacin therapy (gemifloxacin rash rates on left side; control rash rates on right side of figure). Based on the consult from OSE regarding post-marketing data it appears that the risk of rashes is greater for gemifloxacin compared to the other approved products evaluated.

Figure 1. Rash Rates by Treatment Duration, Age and Gender



All of these findings form the basis of FDA's concern and are consistent with the FDA's previous regulatory actions on the indication of acute bacterial sinusitis. However, as part of the review of Oscient's gemifloxacin application, NDA 21-158/S-006, FDA is asking the input of the Anti-Infective Drug Product Advisory Committee regarding the relative benefits and risks of this fluoroquinolone antimicrobial for the indication of acute bacterial sinusitis.

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Abbreviations

ABECB	Acute Exacerbation of Chronic Bronchitis
ABS	Acute Bacterial Sinusitis
AERS	FDA Adverse Event reporting System
bid	Twice daily administration (bis in die)
CAP	Community Acquired Pneumonia
cUTI	Complicated urinary tract infection
DSPTP	Division of Special Pathogen and Transplant Products
FDA	Food and Drug Administration
ITT	Intent-to-Treat
NDA	New Drug Application
NGU	Non-gonococcal urethritis
po	Oral administration of drug (per os)
PP	Per protocol
qd	Once daily administration (quaque die)
SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
uSSSI	Uncomplicated soft tissue and skin structure infection
uUTI	Uncomplicated urinary tract infection

I. Regulatory Background

Factive® (Gemifloxacin) is a fluoroquinolone antimicrobial product currently licensed by Oscient Pharmaceuticals. It was approved by FDA in April, 2003 for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) and mild to moderate community acquired pneumonia (CAP). The currently approved package insert is included as an appendix to this document.

Gemifloxacin was originally submitted to FDA under NDA 21-158 in December 1999 by Smith-Kline Beecham for the following proposed indications, studied as 320 mg PO qd for durations as noted:

- Acute bacterial exacerbation of chronic bronchitis (ABECB) - 5-day, 7-day, 10-day regimen
- Acute bacterial sinusitis (ABS) - 7-day dosing regimen
- Community-acquired pneumonia (CAP) – 7-day, 14-day regimen
- Uncomplicated urinary tract infection – 3-day regimen
- Acute pyelonephritis – 10-day regimen

(The application also contained data from studies of 10-day regimen in complicated urinary tract infections and uncomplicated skin and skin structure infections)

The efficacy and safety results for the ABS studies are summarized in Sections II and III, below.

The initial application was issued a Not Approvable (NA) letter in December, 2000. The primary basis for this action was communicated as follows:

> In accordance with 21 CFR 314.125(b)(4), based on your NDA submission, we conclude, "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling." Of particular concern is the lack of data available in your NDA to fully assess the potential risks posed by the high incidence of hypersensitivity/rash in the clinical trials in order to balance these with the efficacy profile of gemifloxacin.
>
> Other safety concerns identified were the possibility of liver toxicity. The application, however, was assessed to have shown evidence of gemifloxacin efficacy for all proposed indications except acute pyelonephritis.
>
> The letter states that based on the review of the clinical trial data in the NDA, gemifloxacin was effective in CAP, ABECB, ABS and uUTI, and approval depended on demonstration of an acceptable safety profile for each indication.

The sponsor submitted results from studies testing 5-day treatment of acute bacterial sinusitis in June, 2001 (NDA 21-376). This application received a Not Approvable action in April

2002; the applicant was cited for specifically not addressing safety concerns expressed in the original December, 2000 letter.

In October, 2002, NDA 21-158 was resubmitted by LG Life Sciences for the two indications of CAP and ABECB. This application contained a total patient population of 6,775 individuals who received gemifloxacin. The overall incidence of rash was 3.6%, compared to a pooled rate of 1.1% in 5248 patients across all comparators. This submission also contained results of a study (Study 344) specifically designed to better understand the incidence of rash in women age 40 and under, a request by FDA originally outlined in the December, 2000 not approvable letter. This study enrolled slightly over 1000 healthy women. Of the 819 subjects randomized to gemifloxacin 320 mg orally daily for 10 days, 31.7 % (260/819) developed rash compared to 4.3% (7/164) of subjects receiving ciprofloxacin as a comparator. Seven percent of gemifloxacin-associated rashes were considered severe. There were no cases of Stevens-Johnson Syndrome (SJS) or Toxic epidermal necrolysis (TEN). [See Section III.d. for detailed information.]

The safety and efficacy information was presented to an FDA Advisory Committee in March 2003[1]. For the proposed indications of CAP and ABECB, the benefit of gemifloxacin was believed to outweigh the safety concerns that were identified, specifically the risk of rash. The recommendation to approve the indications was based on the lower incidence of rash in the older populations believed to be most at risk for these diseases and the absence of cases of SJS or TEN. Specifically, less that 1% of the patients enrolled in the ABECB studies were under the age of 40, and less than 25% of the patients who participated in the CAP studies were under the age of 40. FDA concurred with the recommendation and gemifloxacin was approved for the treatment of CAP (7 days) and ABECB (5 days) in April, 2003. Post-marketing commitments at the time included a 7,500 person study comparing gemifloxacin (5,000 subjects) with an active control to assess the incidence of rash, particularly in minority populations not studied in the original NDA application.

In January, 2005, Oscient Pharmaceuticals contacted FDA regarding resubmission of gemifloxacin for the indication of ABS. Concerns expressed by the division to the applicant at that time included those previously stated in the Not Approvable letters and further elaborated in other communications:

- Uncertainty regarding the incidence of severe skin reactions with broader use, especially in populations outside those studied in previous trials.
- The overall lower morbidity of acute bacterial sinusitis compared to CAP and ABECB, yielding a less favorable benefit/risk profile for this indication.
- The high incidence of rash overall, but especially in women under 40.
- Concern regarding sensitization after exposure to gemifloxacin therapy, both to future courses of gemifloxacin therapy or subsequent exposure to other quinolone antibiotics.
- Concern regarding the potential for cross-sensitization to gemifloxacin after earlier exposure to other quinolone products

[1] http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective (March 4, 2003)

Of these considerations, the greatest concern was that there was insufficient information available to assess the risk of severe rash in the populations most likely to be exposed to gemifloxacin for the treatment of acute bacterial sinusitis.

Following these discussions, the sponsor proposed a large epidemiological study using a managed care medical claims database to more directly assess the incidence of severe cutaneous events. The Division of Drug Risk Evaluation (DDRE), within the Office of Surveillance and Epidemiology (OSE) was consulted to review this protocol (OP-634-501), and to specifically comment whether this protocol would yield information sufficient to address FDA's concerns regarding risk in the patient population most likely to be exposed gemifloxacin for treatment of ABS. Several concerns were expressed in their consultation questioning whether this protocol could achieve its stated purpose. This is discussed further below, and complete consultation is included as an appendix to this document. Comments regarding the proposed protocol were communicated to the sponsor in September, 2005.

In November, 2005, the sponsor resubmitted Supplement S-006 to NDA 21-158 for the indications of 5-day treatment of ABS and CAP; previous CAP approval was for a 7 day dosing regimen. This submission included the following:

- Previously submitted ABS studies with an integration of the safety data "into 2 general categories based on planned regimen of dosing."
- A new study of 5-day versus 7-day treatment of CAP.
- A final study report for CAP Study 287, open-label treatment of *S. pneumoniae*.
- Additional postmarketing safety data.
- A final protocol for the prospective epidemiological study referred to above. In this submission the sponsor proposed the epidemiological study as a post-marketing commitment following approval of the 5 day regimen for ABS.

The FDA review staff determined that there was no new information addressing the safety concerns previously communicated to the applicant for acute bacterial sinusitis and issued a refuse-to-file letter for this indication. Although the application contained a proposal for a post-approval epidemiological study (OP-634-501) to address FDA's safety concerns, FDA's recommendation was that this study be completed prior to approval of an indication for acute bacterial sinusitis. Excerpts from the letter sent to Oscient are provided below:

> "We refer you to our December 15, 2000 letter to NDA 21-158 and our April 12, 2002 letter to NDA 21-376, indicating that data provided to date do not indicate a favorable risk versus benefit profile to support the approval of Factive for the proposed indication of ABS.
>
> "The pooled analyses of previously evaluated safety data from controlled and uncontrolled studies in your November 18, 2005 submission to NDA 21-158 do not constitute the substantial new evidence necessary to support a re-evaluation of the risk versus benefit profile regarding the proposed use of Factive as a 5-day regimen for the treatment of ABS.
>
> …….

> "As noted in our February 3, 2005 facsimile, clinical studies have already demonstrated that the incidence of skin reactions is greater with Factive than comparators, even with 5 day therapy. The remaining key question is what would be the occurrence of skin reactions, including serious skin reactions, when very large numbers of persons are exposed. This information could be obtained only from very large, usually post-marketing, studies. In effect, a large post-marketing study(ies) would need to disprove the findings from previous studies. Given the consistent findings regarding the incidence of skin reactions (rashes) in clinical studies and the correlation of skin reactions to dose, duration, age and gender, we believe that demonstrating that benefit outweighs risk in ABS with additional studies would be extremely difficult, if not impossible.
>
> "Additionally, attempting to design such a study to prove this hypothesis would be challenging and we have serious concerns about the feasibility of such a study. For example, your proposed post-marketing protocol, OP-634-501, submitted on March 15, 2005, was reviewed and comments were provided via FAX on August 11, 2005. We have also reviewed your proposed revisions to this protocol in your submission of November 30, 2005, and continue to have concerns about the protocol's ability to achieve its stated goal. It is our opinion that demonstrating an acceptable risk benefit profile for Factive for the indication of ABS is not feasible."

Oscient requested nevertheless that FDA review the application for the 5-day treatment of ABS and asked that it be filed over protest and is seeking the following addition to the currently approved labeling:

> **Acute Bacterial Sinusitis** due *S. pneumoniae, H. influenzae, M. catarrhalis, S .aureus (methicillin susceptible strains only), K. pneumoniae and E. coli.*
>
> The proposed dosage regimen is 320 mg qd PO for 5 days.

II. Efficacy and Safety of Gemifloxacin for Acute Bacterial Sinusitis

Four clinical studies have been conducted in which gemifloxacin was evaluated for the treatment of ABS. Three of these were double-blind (009, 010, 186), comparative studies and one was an open, non-comparative studies (206). Studies 009 and 010 evaluated 7-day treatment with gemifloxacin versus an approved comparator and were submitted with the original NDA application. Study 186, an active control study of 5-day treatment with gemifloxacin for ABS, was submitted in 2001 with NDA 21-376 (an application for the single indication of acute bacterial sinusitis). Study 206 was an open-label microbiology study of patients with ABS also submitted as part of NDA 21-376. Study 333 was an open label study submitted to support the safety of the 5-day regimen.

Table 1: Acute Bacterial Sinusitis Studies

Study	Treatment Regimen	Duration	N*	USA (n)	Geographic Region
Studies 009 and 010 were reviewed in NDA 21-158, submitted December 1999					
009 [a]	**gemifloxacin 320 mg po qd**	**7 days**	**338**	**147**	**N. America, Europe**
	cefuroxime axetil 250 mg po bid	**10 days**	**339**	**144**	
010 [b]	**gemifloxacin 320 mg po qd**	**7 days**	**202**		**Europe**
	trovafloxacin 200 mg po qd	**10 days**	**200**		
Studies 186 and 206 were reviewed in NDA 21-376, submitted June 2001					
186 [b]	**gemifloxacin 320 mg po qd**	**5 days**	**220**		**Europe, Canada**
	gemifloxacin 320 mg po qd	**7 days**	**203**		
206 [a]	**gemifloxacin 320 mg po qd**	**5 days**	**469**	**132**	**North America, Europe**
Study 333reviewed in NDA 21-158 resubmission dated October 2002, submitted in support of safety for 5 day regimen					
333	**gemifloxacin 320 mg po qd**	**5 days**	**449**		

* N= number of patients randomized to treatment
[a] In Study 009 and 206, patients underwent sinus puncture with aspiration for culture at screening
[b] In studies 010 and 186, at the request of European regulatory group, a few patients in select European centers had endoscopy done to isolate pathogen
Source: Adapted from Applicant's Table 8.G.49 from NDA 21-158, Vol. 1.8.095, p. 133. and NDA 21-376, Vol. 4/17 Table 8G1 p 12

FDA's interpretation of these studies at the time of the original application review was that the sponsor had demonstrated efficacy for this indication. However, on October 29, 2003, FDA brought up for discussion drug development in acute bacterial sinusitis before the Anti-Infective Drug Product Advisory Committee[2] and presented data from published sinusitis studies. During the meeting, the limitations of available placebo-controlled studies in acute bacterial sinusitis were discussed and it has been recognized there is some uncertainty in the interpretation of a non-inferiority study. Therefore, it was recommended that studies showing superiority would provide the most convincing evidence of drug efficacy in ABS. The recommendation to conduct superiority studies in sinusitis has been communicated to sponsors more recently seeking this indication.

a. 7-day treatment for Acute Bacterial Sinusitis

Two studies examined a 7 day regimen of oral gemifloxacin, 320 mg once daily, for treatment of acute bacterial sinusitis, compared to other antimicrobials. A third study (Study 186) actually compared the 7-day regimen to a 5-day gemifloxacin regimen and is discussed below.

Study 009 compared gemifloxacin for 7 days versus cefuroxime axetil 250 mg twice daily for 10 days and Study 010 compared gemifloxacin for 7 days to trovafloxacin 200 mg once daily for 10 days.

The clinical and microbiological results for both studies are summarized in the following table. Note that since the 95% confidence intervals for the difference between gemifloxacin and control for clinical response exclude the protocol's pre-specified value for non-inferiority, both studies demonstrated non-inferiority of gemifloxacin to the study comparator at the test-of-cure visit (day 17 to 24).

Study 009 also included a microbiological component, and patients underwent maxillary sinus puncture to document a bacterial etiology. The results demonstrated similar rates of protocol-defined bacterial response to gemifloxacin and cefuroxime axetil.

Study 010 evaluated only clinical outcome in the majority of patients, although a few sites performed endoscopy to isolate bacteria (this procedure was not accepted as a diagnostic standard for documentation of bacterial etiology).

[2] http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective (October 29, 2003)

Table 2: Clinical and Microbiological Results for Studies 009 and 010

Clinical and Bacteriological Per Protocol Response at Follow-Up (Day 17-24): Acute Bacterial Sinusitis Studies 009 and 010 (NDA 21-158)				
	Study 009		**Study 010**	
	Gemifloxacin	**Cefuroxime**	**Gemifloxacin**	**Trovafloxacin**
	320 mg po qd x 7 days	**250 mg po qd x 10 days**	**320 mg po qd X 7 days**	**200 mg po qd X 10 days**
Clinical PP Follow-Up	284	296	158	162
Success, n (%)	249 (87.7)	263 (88.9)	143 (90.5)	148 (91.4)
Failure, n (%)	35 (12.3)	33 (11.1)	15 (9.5)	14 (8.6)
Treatment difference, %*	-1.2		-0.9	
95% CI	-6.4, 4.1		-7.1, 5.4	
Intent to Treat Follow-up	338	337	202	199
Success, n (%)	278 (82.2)	290 (86.1)	169 (83.7)	165 (82.9)
Failure, n (%)	60 (17.8)	47 (13.9)	33 (16.3)	34 (17.1z)
Treatment difference, %*	-3.9		0.8	
95% CI	-9.4, 1.6		-6.5, 8.1	
Bacteriological Response PP Follow-Up (Per Patient)**	138	141	13	15
Success, n (%)	129 (93.5)	132 (93.6)	11 (84.6)	13 (86.7)
Failure, n (%)	9 (6.5)	9 (6.4)	2 (15.4)	2 (13.3)
Treatment difference, %*	-0.1		-2.1	
95% CI	-5.9, 5.6		-28.1, 24.0	

* Gemifloxacin minus comparator.

** In Study 010, only patients at study centers in France underwent sinus endoscopic culturing at screening. This was done at the request of the French Regulatory Authorities. Bacteriology in Study 009 was determined by maxillary sinus puncture.

Source: Adapted from Original submission of NDA 21-158 and presented in MO Review of NDA 21-376.

More detailed information regarding bacteriologic response in Study 009 is summarized below:

Table 3: Detailed Microbiological Results for Study 009

Pre-Therapy Pathogens Eradicated or Presumed Eradicated at Follow-Up: ABS Study 009								
	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin		Cefuroxime		Gemifloxacin		Cefuroxime	
Follow-Up	**N=138 n/N* %**		**N=141 n/N* %**		**N=165 n/N* %**		**N=156 n/N* %**	
All Pathogens	142/153	(92.8)	144/155	(92.9)	157/185	(84.9)	152/173	(87.9)
S. pneumoniae	54/55	(98.2)	54/58	(93.1)	58/66	(87.9)	57/64	(89.1)
H. influenzae	27/29	(93.1)	31/31	(100.0)	29/37	(78.4)	33/36	(91.7)
K. pneumoniae[a]	13/15a	(86.7)	17/18	(94.4)	15/18	(83.3)	18/19	(94.7)
S. aureus[b]	14/15b	(93.3)	8/9	(88.9)	14/17	(82.4)	8/11	(72.7)
M catarrhalis	7/7	(100.0)	6/6	(100.0)	9/9	(100.0)	6/6	(100.0)

Note: failures at end of therapy are carried forward into the follow-up analysis by applying the following algorithms:
(1) failures and 'unable to determines' at end of therapy are added to the denominator at follow-up
(2) successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.
* n/N = number of pathogens eradicated or presumed eradicated / number of pathogens.
** Bacteriology PP population at follow-up.
[a] All but one of the *K. pneumoniae* isolates were derived from a single center where 85% of the patients had *K. pneumoniae* isolated – contamination is a likely explanation for this unique finding.
[b] Only 10 of the S. aureus isolates were in pure culture at a quantity of 104 cfu/mL, only 4 of these 10 patients had WBCs at a quantity of moderate or greater on gram stain. 3/10 patients had symptoms of <7 days duration.

Source: Adapted from Applicant's Table 8.G.60 from NDA 21-158, Vol. 1.8.095, p.155

In study 009, a total of 126 patients (37.3%) in the gemifloxacin group and 111 patients (32.9%) in the cefuroxime axetil group had at least one adverse event during the interval on-therapy plus 30 days post-therapy. The most common adverse event in the gemifloxacin group was rash. The incidence of rash was significantly higher in the gemifloxacin group (8.6%) than in the cefuroxime axetil group (0.6%) ($p<0.0001$). In the cefuroxime axetil group, the most common adverse events were diarrhea (4.5%) and headache (4.2%).

Drug related (suspected or probable) adverse events occurred in 71 patients (21.0%) in the gemifloxacin group and 45 patients (13.4%) in the cefuroxime axetil group. In the gemifloxacin group, the most frequently reported drug related adverse events were rash (6.8%), nausea (3.0%), and diarrhea (2.7%). In the cefuroxime axetil group, the most frequently reported drug related adverse events were diarrhea (3.0%), nausea (1.8%), and taste perversion (1.5%). As with adverse events overall, rash related to study drug was statistically significantly higher in the gemifloxacin group than in the cefuroxime axetil

group ($p<0.0001$).

Most of the adverse events were mild to moderate in severity. Symptoms were classified as severe in 4.7% of gemifloxacin treated patients and 4.2% of cefuroxime axetil treated patients. There were 5 (1.5%) gemifloxacin patients and 2 (0.6%) cefuroxime axetil patients with serious adverse events and no deaths in the study. Five patients in the gemifloxacin group and one patient in the cefuroxime axetil group had a serious adverse event that was reported to be related to study treatment.

Nineteen patients (5.6%) in the gemifloxacin group and 10 patients (3.0%) in the cefuroxime axetil group discontinued study drug due to adverse events. Rash, urticaria, nausea, and diarrhea were the most commonly reported (at least 0.5%) reasons for discontinuation. Discontinuation due to rash occurred more often in the gemifloxacin group. Discontinuation due to urticaria was unique to gemifloxacin treated patients. Discontinuation due to diarrhea was unique to cefuroxime axetil treated patients. All adverse events leading to withdrawal were reported as suspected/probably related to study drug. [Source: stats review]

Ten gemifloxacin-treated patients were withdrawn from Study 009 for protocol violation "concomitant medication", all 10 received corticosteroids (4 received PO, 4 IM, and 4 IV corticosteroids). The indications for the administering of corticosteroids were rash (6), urticaria (3) and continued sinus pain (1). There were 0 patients withdrawn for this violation in the cefuroxime axetil arm. [Source: MO review]

In study 010, a total of 81 patients (40.1%) in the gemifloxacin group and 82 patients (32.9%) in the trovafloxacin group had at least one adverse event during the interval on-therapy plus 30 days post-therapy. The most common adverse event in the gemifloxacin group was rash. The incidence of rash (erythematous rash and rash) was significantly higher in the gemifloxacin group (9.4%) than in the trovafloxacin group (1.0%) ($p=0.0002$). In the trovafloxacin group, the most common adverse events were vertigo (11.1%), nausea (5.0%), and dizziness (4.5%). The incidence of vertigo and dizziness was significantly higher in the trovafloxacin group than in the gemifloxacin group ($p<0.0001$ and $p=0.01$, respectively).

Drug related (suspected or probable) adverse events occurred in 50 patients (24.8%) in the gemifloxacin group and 59 patients (29.6%) in the trovafloxacin group. In the gemifloxacin group, the most frequently reported drug related adverse events were rash (8.9%) (erythematous rash (5.4%) and rash (3.5%)) and diarrhea (3.5%). In the trovafloxacin group, the most frequently reported drug related adverse events were vertigo (9.0%), nausea (5.0%), dizziness (4.0%), and asthenia (4.0%). As with adverse events overall, rash related to study drug was statistically significantly higher in the gemifloxacin group than in the trovafloxacin group ($p=0.0003$).

Most of the adverse events were mild to moderate in severity. Symptoms were classified as severe in 6.9% of gemifloxacin treated patients and 5.0% of trovafloxacin treated patients. There were no patients with serious adverse events and there were no

deaths in the study.

Fifteen patients (7.4%) in the gemifloxacin group and 13 patients (6.5%) in the trovafloxacin group discontinued study drug due to adverse events. Rash, nausea, diarrhea, vertigo, asthenia, and vomiting were the most commonly reported (at least 1.0%) reasons for discontinuation. Discontinuation due to rash occurred more often in the gemifloxacin group. Discontinuation due to vertigo, asthenia, and vomiting were unique to trovafloxacin treated patients. All adverse events leading to withdrawal were reported as suspected/probably related to study drug with the exception of fever and sinusitis in the trovafloxacin group. [Source: stats review]

(In June 1999, trovafloxacin indications were severely restricted due to safety concerns, specifically hepatotoxicity. There were no restrictions because of any efficacy concerns. Before the restrictions, trovafloxacin was approved for the indication of acute bacterial sinusitis.)

b. 5-day treatment for Acute Bacterial Sinusitis

Two studies were submitted in NDA 21-376 in support of 5-day treatment of ABS with gemifloxacin. Study 186 was a randomized, double-blind controlled trial comparing 5 days of gemifloxacin to 7 days of gemifloxacin therapy for ABS. Study 206 was an open label, single arm study of gemifloxacin 320 mg for 5 days designed primarily to examine bacteriologic response and patients underwent maxillary sinus puncture to obtain a specimen for culture.

More detailed discussion of the design and outcomes for studies 186 and 206 are included in the Medical Officer Review of NDA 21-376, included as an appendix to this document. A brief summary of these studies is provided below.

1. Study 186

Study 186 was a multicenter, randomized, double-blind, parallel group, comparative phase 3 study of adult patients with ABS in Europe and Canada. The study was designed to demonstrate the non-inferiority of gemifloxacin 320 mg once daily for 5 days versus gemifloxacin 320 mg once daily for 7 days. Although this study was primarily a clinical study of ABS, patients recruited from specific sites in Germany and Lithuania underwent endoscopic sinus aspiration to assess microbiological response. The primary efficacy endpoint of the study was Clinical Response (Success or Failure) at the follow-up visit on Day 16-35.

The study was designed to achieve a 90% power to detect that the lower bound of the two-sided 95% confidence interval for the difference in the rates (gemifloxacin 5 days minus gemifloxacin 7 days) is no less than -15%. The ITT population consisted of 212 patients in the 5-day arm and 198 patients in the 7-day arm. The two groups had comparable baseline

demographics and clinical characteristics. Withdrawal rates were similar in both groups overall compliance with study drug was over 97% in both arms of the study.

The clinical results at end of therapy and at follow-up for study 186 are summarized in the following tables. Note that since the 95% confidence intervals for the difference between gemifloxacin and control for clinical response exclude the protocol's pre-specified value for non-inferiority, study 186 demonstrated non-inferiority of gemifloxacin to the study comparator at the test-of-cure visit (day 16 to 35). End-of-therapy comparisons showed lower success rates in the gemifloxacin arm compared to comparator, significantly so for the ITT population. Bacteriological responses were insufficiently powered for further analysis in this study (39 total).

Table 4: Study 186 - Clinical and Radiological Response in ABS at Follow-Up (Day 16 to 35)

	Gemifloxacin 320 mg qd for 5days	Gemifloxacin 320 mg qd for 7days
Clinical PP Follow-Up Population	N=178	N=171
Success, n (%)	155 (87.1)	148 (86.5)
Failure, n (%)	23 (12.9)	23 (13.5)
Treatment difference % (gemi 5d – gemi 7d)	0.53	
95% CI	-6.57, 7.63	
ITT Population	N=212	N=198
Success, n (%)	176 (83.0)	166 (83.8)
Failure, n (%)	36 (17.0)	32 (16.2)
Treatment difference % (gemi 5d – gemi 7d)	-0.82	
95% CI	-8.02, 6.38	

Source: Statistical Review and Evaluation of NDA21-376 dated 3/27/2002

Table 5: Study 186 - Clinical Response in ABS at End of Therapy

	Gemifloxacin 320 mg qd for 5 days	**Gemifloxacin** 320 mg qd for 7 days
Clinical PP End of Therapy Population	N=186	N=180
Success, n (%)	173 (93.0)	173 (96.1)
Failure, n (%)	13 (7.0)	7 (3.9)
Treatment difference % (gemi 5d – gemi 7d)	-3.10	
95% CI	-7.73, 1.53	
ITT Population	N=212	N=198
Success, n (%)	188 (88.7)	189 (95.5)
Failure*, n (%)	24 (11.3)	9 (4.5)
Treatment difference % (gemi 5d – gemi 7d)	-6.78	
95% CI	-11.93, -1.62	
*Includes five patients in the gemifloxacin 5-day treatment group and two patients in the gemifloxacin 7-day treatment group with an outcome of unable to determine.		

Source: Statistical Review and Evaluation of NDA21-376 dated 3/27/2002

The safety information for study 186 is presented under Section III b.

2. Study 206

Study 206 was an open-label non-comparative study evaluating the efficacy and safety of gemifloxacin 320 mg po qd for 5 days in patients with a bacterial pathogen documented by maxillary sinus puncture. The study was conducted in the US, Hungary, Poland, and Costa Rica. For analyses, four 4 study populations were designated: the clinical ITT, bacteriological ITT, clinical PP, and bacteriological PP; the primary efficacy populations were the bacteriology ITT and bacteriology PP populations. The primary efficacy parameter defined in the protocol was the bacteriological response at the follow-up visit. As noted in Table 6 below, overall per patient success rates were 86% (203/236) and 90.3% (195/216) in the bacteriology ITT and bacteriology PP populations, respectively. The success in the clinical ITT population was 87%. The overall per pathogen response at in the Bacteriology ITT was 85.6% (236/275). For individual pathogens, the response rate was 87.1% (88/101) for *S. pneumonia*e, 88.0% (44/50) for *H. influenza*e, 100.0% (15/15) for *M. catarrhali*s, 75.0% (9/12) for *S. aureus,* and 91.7% (11/12) for *E. col*i. Results of the secondary efficacy parameters were similar to the results observed for the primary efficacy parameter.

Table 6: Study 206 - Summary of Efficacy Results

	5-day gemifloxacin 320 mg qd	95% CI
Enrolled	469	
Received Medication **(ITT)**	469	
Clinical ITT		
Success at FU	410/469 (87.4%)	
Withdrawn	17 (3.6%)	
Bacteriology ITT	236	
Success at F/U	203 (86.0%)	(81.59, 90.44)
Bacteriology PP at F/U	216	
Success at F/U	195 (90.3%)	(86.33, 94.23)
Pathogen Eradication Bacteriology ITT at F/U		
All pathogens	236/275 (85.8%)	
S. pneumoniae	88/101 (87.1%)	
H. influenzae	44/50 (88.0%)	
M. catarrhalis	15/15 (100%)	
**S. aureus*	9/12 (75%)	
* The Applicant's data included 9 acceptable cases (>10^4 cfu/ml & pure culture) for further review; 4/9 isolates were suggestive of contamination.		

Source: MO Review of NDA 21-376.

The safety information for study 206 is presented under Section III c.

III. Safety of Gemifloxacin in NDA 21-158 (2002)

The integrated summary of safety in NDA 21-158 that was resubmitted in 2002 provided cumulative data on 6775 patients exposed to gemifloxacin in clinical trials for CAP, ABECB, ABS, uncomplicated urinary tract infection, complicated urinary tract infection and pyelonephritis, uncomplicated skin and soft tissue structure infection, and NGU. The three areas of particular interest during the review of this application were skin related adverse events, hepatic toxicity, and effects of gemifloxacin on the QTc interval.

a. Cutaneous Adverse Events Evaluated Across All Indications Studied

In the original NDA, various reviewers looking at the indications noted a consistent finding that skin rashes were seen more commonly in the gemifloxacin arm compared to the control antimicrobials (including beta-lactams and fluoroquinolones). Therefore, SKB was asked to provide a tabulation to show if the rash was related to specific demographic characteristics. As seen in Figure 1 (and Table 2 of Factive® product labeling) the rates are most frequent in young patients less than 40 years of age, especially females, and there is a clear pattern related

to duration of exposure. In addition, rashes were more frequent in certain indications (for example 7-day treatment of ABS), although this may reflect the age and gender of the population studied, given that more than half the ABS patients were less than 40 years of age (in contrast to age in the ABECB and CAP studies submitted to NDA 21-158, where the majority of patients were over 40 years of age). Thus, because gemifloxacin demonstrated higher rates of skin related adverse events compared to comparator drug in all studies, the review of cutaneous adverse events was a specific focus in the safety review of NDA 21-158.

Cutaneous Adverse Events. The table below summarizes the incidence of skin adverse events in gemifloxacin exposed subjects across all indications studied:

Table 7. Cutaneous Adverse Events (Combined Population)

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 320 mg qd		All Comparators	
	N = 6775		**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)
*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).				

Source: Tables 012b & Table 219a; NDA 21-158, 18 month safety update, pp. 4090-4102 and 6210

Separate analyses were performed to better characterize the rash associated with gemifloxacin administration. These included time to rash onset, severity of rash, and association of rash with age, gender, and indication.

Time to rash onset: Analysis of the time of rash onset by treatment group showed that two-thirds of comparator treated patients had onset of the rash in the first 7 days while two-thirds of the gemifloxacin treated patients had rash onset after 7 days. The most likely time of rash onset for gemifloxacin-treated subjects were days 8, 9, and 10, with 35% having rash onset on those days. Subjects were followed after drug discontinuation: the table below includes subjects who may have developed rash up to 72 hours after drug discontinuation. Therefore, a subject who discontinued drug at day 5 but developed rash on day 7 would be represented in the table below at day 7.

Table 8: Time to Onset of Rash (Combined Populations)

	Gemifloxacin 320 mg qd		All Comparators	
Patients with Rash*	**N = 241** (overall N = 6775)		**N = 59** (overall N = 5248)	
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)
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.				

Source: Applicant's Table 14.14 from NDA 21-158 18 month Safety Update.

Severity of rash is summarized in Table 9:

Table 9: Severity of Rash by 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)
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.				

Source: Adapted from Applicant's Table 14.16 from NDA 21-158 18 month Safety Update.

Thirteen percent of subjects with rash (or 0.4% of the total population exposed to gemifloxacin) experienced a serious rash and 27 patients required systemic steroids to treat their rash. Of patients with rash, 11% of subjects treated with gemifloxacin required systemic steroid therapy versus 5% of comparator treated patients.

Rash by Indication. Table 10 summarizes rash by therapeutic indication. While the rates differ for individual indications, the rate in the gemifloxacin arm is consistently higher than in the comparator arm:

Table 10: Rash by Therapeutic Indication (Combined Population)

	Treatment Group			
	Gemifloxacin 320 mg qd		All Comparators	
	N = 6775		N = 5248	
Indication	**n**	**(%)**	**n**	**(%)**
ABECB	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 21-158 18 month Safety Update

Rash by Gender and Age is summarized in Table 11:

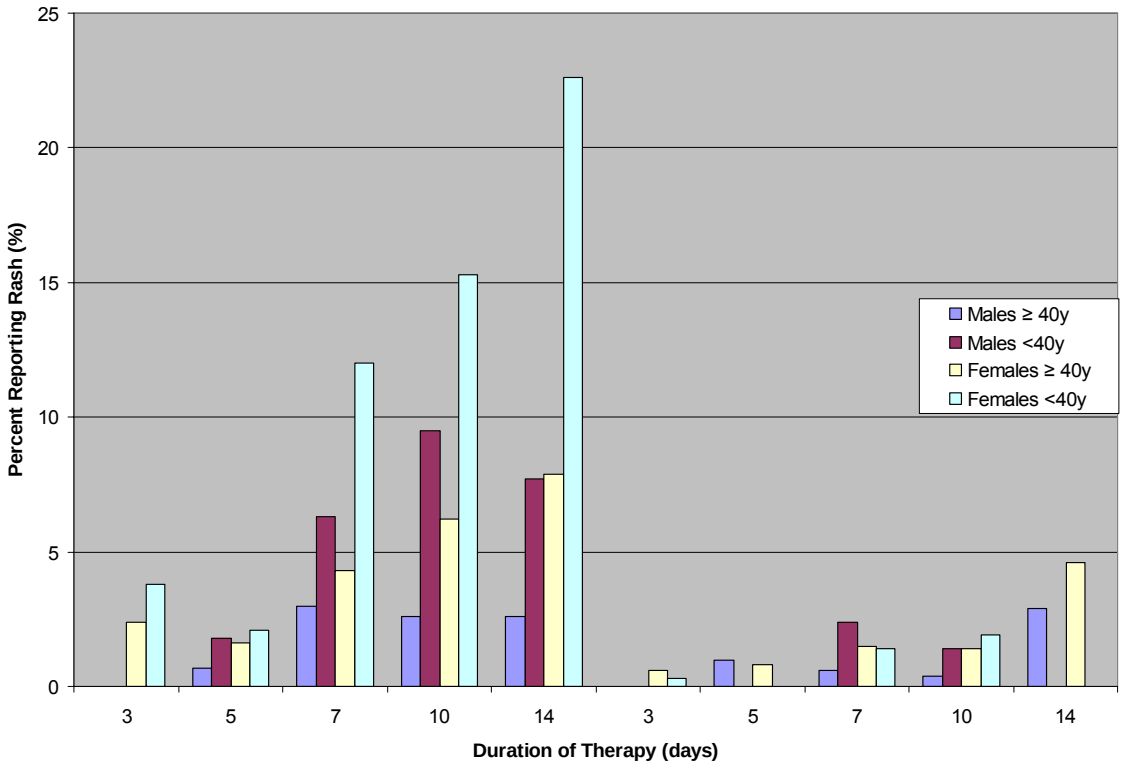
Table 11: Rash by Gender and Age (Combined Population)

	Gemifloxacin 320mg qd		All Comparators	
	N=6775		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)

Table 11 suggests an association of rash with both age and gender. Both men and women under 40 experienced a higher incidence of rash than those over 40, with women of all ages experiencing rash more frequently than men of similar ages.

This relationship is further depicted in the figure below. These associations become more pronounced with longer durations of therapy. Percentages for gemifloxacin-treated are in the left-hand side of the figure and comparator agents on the right side of the figure.

Figure 1: Incidence of Rash by Age, Gender, and Duration of Treatment



b. Study 186: 5-day gemifloxacin versus 7-day gemifloxacin 7 for Treatment of ABS

The design of study 186 was described earlier. The cutaneous adverse events occurring in this study were reported for the interval on-therapy plus 30 days post-therapy. As shown in Table 12, there were 6/218 (2.8%) cutaneous adverse events in the five day gemifloxacin treatment group. There were 3/218 (1.4%) rash events and 3 additional other skin adverse events (dermatitis and urticaria) reported. Of the six patients in the 5-day treatment group that experienced a cutaneous adverse event, 2/6 were classified as mild, 3/6 as moderate and 1/6 as severe. Four of the six events were considered by investigators as a suspected relationship to study medication and 2/6 were considered as probably related to study medication. One subject with a maculo-papular rash was withdrawn from treatment.

There were 18/203 (8.9%) cutaneous adverse events in the seven day treatment group, 12 of which were rash. Of the 18 adverse events, 5/18 were classified as mild, 10/18 as moderate and 3/18 as severe. In terms of relationship to study medication, 2/18 were considered unrelated, 7/18 were considered as suspected relationship and 9/18 were considered as probably related to study medication. No subject was withdrawn from therapy in this group.

There were 18/203 (8.9%) cutaneous adverse events in the seven day treatment group. Of the 18 adverse events, 5/18 were classified as mild, 10/18 as moderate and 3/18 as severe. In terms of relationship to study medication, 2/18 were considered unrelated, 7/18 were considered as suspected relationship and 9/18 were considered as probably related to study medication. No subject was withdrawn from therapy in this group.

Table 12: Study 186 - Incidence of Rash

	Gemifloxacin 320 mg qd for 5 days	**Gemifloxacin** 320 mg qd for 7 days
	N = 218	N=203
Rash	1 (0.5%)	1(0.5%)
Rash Maculo-papular	2(0.9%)	4(2.0%)
Rash erythematous	0	7(3.4%)
Urticaria	1(0.5%)	5(2.5%)
Dermatitis	2(0.9%)	1(0.5%)
Total # of Patients with a Cutaneous AE	6 (2.8%)	18(8.9%)
Withdrawn due to rash	1	0

Adapted from data in original submission NDA 21-376.

c. Study 206: 5-day open-label bacteriological study of gemifloxacin for ABS

The design of study 206 was described earlier. Table 13 shows the overall rate of cutaneous adverse events in this study was 2.6%:

Table 13: Study 206 - Cutaneous Adverse Events

	N= 469	%
Number of Patients with Any Cutaneous Adverse Event*	**12**	**2.6**
Rash Maculo-papular	8	1.7
Urticaria	3	0.6
Pruritus	3	0.6
Rash Pustular	1	0.2
Rash	1	0.2
* Five subjects experienced more than cutaneous event.		

Source: Adapted from Study Report 206, NDA 21-376

In the combined subset of patients in studies 186 and 206 with rash and urticaria only, the incidence in the 5-day treatment arm was 17/687 (2.5%) compared to 17/203 (8.3%) in the 7-day treatment arm. No rash in subjects receiving the 5-day regimen was characterized as severe although 2 subjects (1%) had severe rash in 7-day groups. It is important to note that although the reported rate of rash/urticaria in the 5-day treatment arm is less than the 7-day treatment arm, it is still approximately 2.5-fold higher than the 0.9% incidence rate for comparator agents observed for NDA 21-158.

d. Study 344: 10-day treatment safety study of gemifloxacin compared to ciprofloxacin

1. Part A

In earlier discussions with FDA regarding clinical development of gemifloxacin, it was recommended that a study specifically designed to better understand the nature and severity of the rash associated with gemifloxacin be performed, especially targeting use in younger women. This study which was included in the 2002 resubmission of NDA 21-158, was entitled Study 344. It was performed at multiple sites in the US, Europe, and Asia in approximately 1000 healthy women ages 40 or younger. Subjects were enrolled in a 4:1 ratio of gemifloxacin to ciprofloxacin. Subjects received blinded treatment with gemifloxacin 320 mg po qd or ciprofloxacin 500 mg po bid for 10 days in part A. Part B of this study was designed to determine if sensitization or cross sensitization from gemifloxacin exposure would occur: study patients who developed a rash to gemifloxacin in Part A were randomized to receive ciprofloxacin or placebo, and patients who did not develop a rash to the first course of gemifloxacin were randomized to either gemifloxacin or placebo. All patients in both parts of the study were observed closely for the development of rash by blinded observes. All rashes were biopsied for histopathological examination. These results are summarized below:

Figure 2: Study Design for Protocol 344 (10 day Exposure)

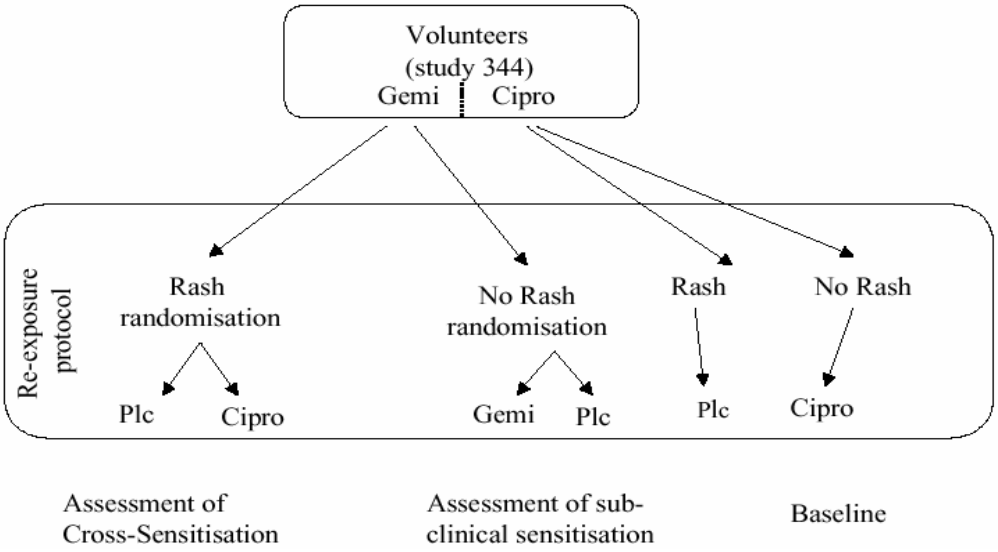


Table 14: Study 344 - Incidence of Rash in Part A

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

Table 15: Study 344 - Day of Onset of Rash in Part A

Day of Onset	Gemifloxacin (n = 260)	Ciprofloxacin (n = 7)
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

The following tables provide descriptive information regarding rashes observed in Study 344. Rashes were overwhelmingly macular papular with 7% classified as severe. Slightly over 25% of rashes affected 60% or more of the body surface area. Sixteen percent of subjects with rashes had some involvement of either eyes, genitalia, or mucus membranes. There were no cases of severe blistering, EM, TEN, or SJS.

Table 16: Study 344 - Rash Description by Regimen and Severity In Part A

Regimen	Severity			
Description	**Mild (%)**	**Moderate (%)**	**Severe (%)**	**Total (%)**
Gemifloxacin (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)
Ciprofloxacin (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 Report of Study 344 Appendix C

Table 17: Study 344 - Summary of Surface Area Covered in Part A by Regimen and Severity of Rash

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

Table 18: Study 344 - Summary of Mucous Membrane Involvement by Regimen and Severity of Rash in Part A

Regimen	Mucous Membrane Involvement	Severity of Rash: Mild	Moderate	Severe	Total
Gemifloxacin (n=260)	None	152 (58.5%)	72 (27.7%)	17 (6.5%)	241 (92.7%)
	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 (n=7)	None	6 (85.7%)	1 (14.3%)	0 (0.0%)	7 (100.0%)
	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

All rashes were biopsied in order to better elucidate the nature of the rash associated with gemifloxacin usage. Histopathology specimens were obtained from 288 of the 299 total rash episodes in Parts A and B of Study 344 following exposure to gemifloxacin, ciprofloxacin or placebo. 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:

- The most common finding was mild superficial perivascular infiltrate.
- 10 biopsies with moderate superficial or deep perivascular infiltrate were identified.
- 10 biopsies with eosinophils in the infiltrate (1 in unaffected skin) were identified.
- T cell type infiltrates were seen with both CD-4 and CD-8 cell types but with no common pattern noted.
- No evidence of vasculitis
- For activation of endothelial cells and staining for ICAM and HLA-DR, HLA-DR staining was noted in a significant number of cases.
- Immunoflourescence revealed faint deposits of IgM and/or C3 in dermal vessels "lumina" in some cases involving unaffected and affected skin.
- One case of linear IgM along basement membrane (the linear IgM deposition was seen along skin that was affected by rash and skin that was unaffected by rash).
- No bulla formation, epidermal, or eccrine necrosis was seen.

In summary, the results were most consistent with a mild to moderate drug exanthem. No specific finding of particular concern was observed in the pathology specimens.

2. Part B

Part B of Study 344 was designed to assess if cross sensitization to gemifloxacin could be demonstrated, i.e., to observe if patients who had developed a rash to gemifloxacin would have a higher incidence of rash when exposed to ciprofloxacin than patients who had received gemifloxacin but had not developed a rash. Ten percent of patients who had developed a rash on gemifloxacin also developed a rash on ciprofloxacin while 4% of those who had not developed a rash on gemifloxacin experienced a rash when exposed to ciprofloxacin. These results suggest that while there may be some cross sensitization occurring, the incidence would not be high. This is supported by the relatively low incidence of rash after re-exposure to gemifloxacin in subjects who had previously received gemifloxacin without developing rash.

Table 19: Study 344 - Incidence of Rash in Study in Part B

Regimen	**No. of Subjects**	**Subjects With Rash**	Point **Estimate (%)**	**95% C.I. Normal Approximation**	**Exact Method**
Gemifloxacin ⇒ rash ⇒ ciprofloxacin	144	15	10.4	(5.1, 15.8)	(5.9, 16.6)
Gemifloxacin ⇒ rash ⇒ placebo	51	2	3.9	(0.0, 10.2)	(0.5, 13.5)
Gemifloxacin ⇒ no rash ⇒ gemifloxacin	250	8	3.2	(0.8, 5.6)	(1.4, 6.2)
Gemifloxacin ⇒ no rash ⇒ placebo	258	7	2.7	(0.5, 4.9)	(1.1, 5.5)
Ciprofloxacin ⇒ rash ⇒ placebo	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
Ciprofloxacin ⇒ no rash ⇒ Ciprofloxacin	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

e. Incidence of rash pooled across all 5-day and 7-day gemifloxacin studies

The sponsor has pooled data on the incidence of rash by duration of therapy from all ABS studies performed. This information is reproduced in the table below:

Table 20: Pooled incidence of rash across all 5 and 7-day gemifloxacin studies

Preferred Term	Gemifloxacin 5-day treatment* N = 1122	Gemifloxacin 7-day treatment** N = 724	All Comparators N = 521
Pts with at least 1 Rash AE	29 (2.6%)	62 (8.6%)	5 (1.0%)
Rash	7 (0.6%)	38 (5.2%)	3 (0.6%)
Rash Maculo-papular	21 (1.9%)	6 (0.8%)	0
Rash erythema	2 (0.2%)	18 (2.5%)	2 (0.4%)
Rash pustular	1 (0.1%)	0	0

* Gemi 5-day group includes both controlled and uncontrolled data.
** Gemi 7-day group and all comparator groups contain only controlled data.

Adapted from submission of NDA 21-158/S-006

As noted earlier, the overall rate of 2.6% rash in the gemifloxacin 5-day arm is 2.5-times greater than that observed in the all comparators arm; the gemifloxacin rate may also be biased downward by inclusion of uncontrolled data in the 5-day gemifloxacin group.

IV. Postmarketing Safety Data

At the request of the Division of Special Pathogen and Transplant Products, the Division of Drug Risk Evaluation (DDRE), Office of Surveillance and Epidemiology has reviewed post marketing experiencing with Factive®; as noted earlier, gemifloxacin was approved for the 5-day treatment of ABECB and 7-day treatment of community acquired pneumonia (CAP). The complete document is included as an appendix to this document. The executive summary from their review is reproduced below:

> **EXECUTIVE SUMMARY**
> Factive® (gemifloxacin) was approved on April 4, 2003 as a 5-day regimen for the treatment of acute bacterial exacerbation of chronic bronchitis and as a 7-day regimen for the treatment of community-acquired pneumonia of mild to moderate severity. In clinical trials it was noted that the incidence of rash was higher in patients receiving gemifloxacin, and rash was commonly observed in patients < 40 years of ages, especially in females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment durations (>7days). On both December 5, 2000 (NDA 21-158) and April 12, 2002 (NDA 21-376) the Agency issued a not approvable letter for a 7-day acute bacterial sinusitis (ABS) regimen and a 5-day ABS regimen, respectively, because data provided do not

indicate a favorable risk versus benefit profile to support the approval of gemifloxacin for ABS.

The sponsor submitted a new efficacy supplement to NDA 21-158 (S-006) on November 18, 2005 for a proposed 5-day ABS regimen. The Division of Special Pathogens and Transplant Products (DSPTP) refused to file (RTF) this efficacy supplement because data submitted to date do not constitute substantial new evidence necessary to support a reevaluation of the risk benefit profile regarding the proposed 5-day regimen for the treatment of ABS. The sponsor appealed the RTF decision and the supplement is currently under review by DSPTP. DSPTP will discuss the 5-day ABS regimen at a September 12, 2006 Advisory Committee meeting and requested an overview of postmarketing cutaneous adverse event reports associated with the use of gemifloxacin in FDA's Adverse Event Reporting System (AERS) as background material for this meeting.

As of May 31, 2006 (approximately 3 years post-approval) there were 799 reports in AERS for gemifloxacin; 83% (or 667) of all reports for gemifloxacin listed a cutaneous adverse event. Six (6) percent or 41 of these cutaneous adverse event reports had a serious outcome and where stated, approximately 73% (430/592) of the cutaneous adverse events were reported in women. Drug use data estimate that 363,000 prescriptions for gemifloxacin were dispensed by retail pharmacies between January 1, 2004 and May 31, 2006. The majority were dispensed to women (211,000 or 58%).

Where both age and gender are stated (n=247 for women), the postmarketing reports listed 42% (104/247) of women ≤40 year of age reporting a cutaneous adverse event associated with the use of gemifloxacin. Of all prescriptions dispensed to females during this time period (January 1, 2004 through May 31, 2006), approximately 21% were age 40 years or less. In a subset of reports (categorized as a severe cutaneous event, photosensitivity reaction, allergic reaction, or rash) approximately 41% (range, 33-49%) of women ≤ 40 years of age experienced one of these cutaneous adverse events (see Table 1). For men, adverse event report counts for the ≤ 40 years of age group were 45% (42/93). Of all prescriptions dispensed to males during this time period (January 1, 2004 through May 31, 2006), approximately 23% were age 40 years or less. In addition to age and gender, we analyzed time to onset of rash with gemifloxacin therapy. In a subset review of 291 postmarketing reports coded with the MedDRA preferred term Rash (see Table 4) the median time to event onset was 4 days (range, 3-5 days); 77 of 291 reports reviewed had a time to onset of rash of ≤ 5 days. Further, upon review of 10 reports of specific severe skin events of interest (Stevens Johnson Syndrome (SJS), Erythema Multiforme EM), Skin Exfoliation (SE) and Dermatitis Exfoliative (DE), see Table 2) the time to event onset in 4 of these cases was ≤ 5 days as well as a review of 37 cases with a serious outcome, the time to event onset in 8 of these cases was ≤ 5 days.

Thirty-seven patients (derived from individual review of the cases and removal of duplicate reports) experienced a **serious** adverse event (per regulatory definition). Out of these 37 patients, 3 died, 19 were hospitalized, 2 required intervention, 1 was considered life-threatening and 12 were determined to be medically important by the reporter. The three fatalities were not attributable to gemifloxacin use as death was associated with cardiomegaly, hemophagocytic syndrome and dental surgery. Of the 19 cases that required hospitalization, the majority experienced gemifloxacin-associated adverse events and required treatment such as steroids, antihistamines, oxygen, and intravenous fluids. Many of these serious cases under the "required intervention" and "other medically important" categories described a hypersensitivity component to the adverse reaction including urticaria, swelling of face, anaphylaxis, allergic vasculitis, etc. that required intervention with epinephrine, steroids, and

antihistamines. Interestingly, of these 37 serious outcome cases, 9 (25%) reported previous fluoroquinolone use and 13 (35%) reported a history of drug allergy. Of the 10 **severe** skin reports (EM, SJS, SE and DE), the available information in the reports was either lacking or incomplete to adjudicate the three EM and four SJS reports as definitive cases of EM and/or SJS. The remaining three cases described the adverse events as skin peeling or exfoliating.

We also calculated crude reporting rates for categorically serious skin reactions (as per regulatory definition) reported in association with gemifloxacin and selected comparators. (Categorically serious refers to reports that indicate an outcome of death, life-threatening, hospitalization, intervention required, resulted in disability or considered medically significant by reporter.) Reporting rate calculations are typically based on case counts divided by dispensed prescriptions. Standard reporting rate comparisons require 1) similar drug products [e.g., time on market, route of delivery, spectrum of indication(s)] and 2) assumption that reporting practices are similar for similar drug products over the observed reporting period. Furthermore, standard reporting rate comparisons require an accurate estimate of drug exposure or utilization within the population. Due to the voluntary, spontaneous nature of MedWatch reports submitted to AERS, reporting rates cannot be interpreted as true incidence rates within the population.

Crude (not adjudicated) counts for categorically serious reports were used in this analysis because the large number of reports precluded analysis of individual reports at this time. Categorically serious reports of cutaneous adverse events have been reported more frequently in association with gemifloxacin than with either cefditoren or telithromycin. The reporting rate for gemifloxacin (105 per million prescriptions) was 7.5 times that of cefditoren (14 per million prescriptions) and 5 times that of telithromycin (20 per million prescriptions). This difference was notable and concerning. An individual review of serious skin reports with these three drugs (gemifloxacin, cefditoren, and telithromycin) is planned to assess if the differences observed in analysis of crude counts will be maintained after adjudication of cases.

Clinical trial data found a higher incidence of rash in patients receiving gemifloxacin than in those receiving comparator antibiotics, and a 2003 Advisory Committee presentation on gemifloxacin identified female gender, age <40, planned duration of treatment >7 days, and hormone replacement therapy in women >40 years of age as risk factors for rash development. Postmarketing data from AERS showed the propensity of gemifloxacin to be associated with cutaneous adverse events predominately in females. AERS data for gemifloxacin also indicated that the proportions of cutaneous adverse event reports were greater in the ≤ 40 of age group for both females and males in comparison to the amount of drug use in that same age bracket. Clinical trial data of cutaneous safety4 showed that 2/3 of rash in gemifloxacin patients began after day 7 of therapy. However, in our postmarketing analyses, time-to-event was shorter with AERS reports of cutaneous events coded as rash having a median time-to-event onset at 4 days. One-quarter and 1/3 of the serious skin adverse event reports listed previous fluoroquinolone use or history of drug allergy, respectively. Further, many of the serious outcome cases reported an allergic/hypersensitivity component to the cutaneous events with numerous cases reporting significant morbidity. Although information included in the three cases of EM and the four cases of SJS was insufficient to assign such diagnoses, the lack of a definitive EM or SJS case does not imply that severe skin adverse reactions have not or cannot occur in association with gemifloxacin use. Spontaneous adverse event reporting databases such as AERS have multiple limitations. Under reporting, as well as incomplete reporting, coupled with the low postmarketing drug utilization for gemifloxacin may underlie the current lack of definitive EM or SJS cases reported to the AERS database. Comparisons of gemifloxacin with other recently approved oral antibiotics used to treat minor infections

showed that for serious skin reactions, the safety of gemifloxacin is of concern. In addition, the crude reporting rate of serious skin reactions was notably higher for gemifloxacin than the comparator drugs. Individual case review of all serious skin reactions associated with gemifloxacin and comparator drugs (cefditoren and telithromycin) is planned to calculate case-adjudicated reporting rates.

Given the concerning nature of these post-marketing data analyses which add to the already known definitive clinical trials data delineating drug-related cutaneous adverse reactions, we recommend that the magnitude of the drug benefit for the indication under review by DSPTP (acute bacterial sinusitis) be clearly defined so that the magnitude of the drug risk can be appropriately examined and weighed in context.

V. Proposed Factive Epidemiologic Study to Determine Incidence of Severe Cutaneous Events

As discussed earlier, the sponsor's current application includes an epidemiologic study to assess the incidence of severe adverse post-approval of the ABS indication. The objectives of protocol OP-634-501 are:

1. To estimate incidence of skin reactions in patients using Factive®.
2. To estimate incidence of skin reactions in patients using other antibiotics, including fluoroquinolones.
3. To determine whether there is cross-sensitization between Factive® and other antibiotics; that is, whether the risk of skin reactions increases when other antibiotics are used prior to Factive®.
4. To determine whether there is sub-clinical sensitization with Factive®; that is, whether the risk of rash in patients treated with Factive® is greater for patients previously exposed to Factive® than those who were not.

The following is a brief synopsis of the study methods for this protocol:

a. Data sources:
Data from two managed care medical claims databases: Ingenix (UnitedHealth Group) and Healthcore (a variety of Wellpoint and BlueCross/BlueShield health plans) will be used as the sources of information. The primary analysis will be performed by each respective managed care provider, while the sponsor will report summary statistics of the combined results.

b. Study Design:
The study is designed as a longitudinal cohort study using claims data. The study start date is January 1, 2003. The study end date is currently unknown but the sponsor proposes to end the study when the study population is large enough and the numbers of person-years of observation in each of the study groups are sufficient to make statistically sound conclusions. The sponsor estimates that approximately 60,000 person years of observation in each study group will be needed.

c. Eligibility Criteria
The first date in which Factive® or other antibiotics are used after the onset of the study is considered as the “index date” for each antibiotic exposure for each patient. A minimum 6 month eligibility period in the medical plan prior to the index date is required. In addition, patients are required to be

continuously eligible for medical and prescription claims for at least 3 months after their index date to ensure that all prescriptions or medical claims are captured in the database and that there is no gap in medical coverage.

d. Study Population

The study population includes all patients with prescription claims for Factive® and/or other antibiotics. These claims are identified using the National Drug Classification (NDC) codes. The sponsor indicates that prescription claims for Factive® are not expected in year 2003 since Factive® was introduced to the market in September 2004. Other antibiotics to be used as comparators include other fluoroquinolones, sulfonamides, macrolides, cephalosporins, aminopenicillins, and tetracyclines.

e. Study Variables

The main study exposure variable is days of medication supply as recorded in the prescription claims with days of supply serving as a proxy for drug exposure. The ending date of a prescription is calculated for each prescription by adding the number of days supplied to the claim date. To examine the effect of time since exposure and the incidence of skin reaction, patient exposure days to Factive® or other antibiotics will be categorized into currently exposed (currently on prescription), exposed within past 7 days, exposed within past 14 days, and exposed within past 30 days. A pre-determined comprehensive list of ICD-9 codes for skin reactions, including ICD-9 code 695.1 for Toxic Epidermal Necrosis (TEN) and Stevens-Johnson Syndrome (SJS), will be identified from the medical claims with confirmation of the diagnosis through medical chart review. This list is not provided in the sponsor's submission.

f. Analysis Plan

Descriptive statistics will be used to compare baseline characteristics between Factive® users and users of other antibiotics. Frequency calculations of skin reactions for each treatment group by time elapsed since exposure will be performed. Multivariate analyses will be conducted. Analyses will be also conducted to address cross-sensitization and sub-clinical sensitization. Serious skin reactions and all skin reactions will be analyzed as separate endpoints.

The Division of Drug Risk Evaluation (DDRE) also reviewed this protocol in consultation with DSPTP. Their comments and request for further information were as follows:

1. Study period
   - There is concern with the proposed study period (January, 2003 onward): using data prior to the market introduction of Factive® (1/2003-9/2004) may introduce a secular trend bias that may influence the incidence of serious skin reactions. The list of comparator antibiotics includes many that are widely used, so attaining large populations of users of those drugs is not likely to be difficult in a time period more contemporaneous with Factive® use.

2. Sample size
   - The formula and the assumption details that were used for the sample size calculation of 60,000 person-years was not included with the protocol.
   - There is concern that the proposed 60,000 person-years will require a very long time to accrue. Evidence should be provided prior to study onset that adequate prescribing of Factive® will occur in the health plans under study to allow for completion of the study within a reasonable timeframe.

- There should be clarification whether the 60,000 person-years in the comparator group refers to all other antibiotics, to each individual class, or to each individual antibiotic.
- The rationale for the appropriateness of pooling databases containing data from a variety of different health plans with different coverage criteria was not stated in the protocol.

3. Study Population
   - Details of the demographic characteristics of the participants in the two proposed databases are not discussed. There is the potential that patients under the age of 40, who would be at greater risk of a cutaneous reaction from using Factive®, would not be well represented in these databases Consequently it would take longer to enroll a number of patients in the demographic similar to that seen in ABS.

4. Enrollment /Eligibility issues
   - There is concern regarding the requirement for eligibility after the index date. Given the high mortality rate of TEN and SJS, excluding patients who may become ineligible during the follow-up period risks the ability to detect fatalities as a result of a serious skin reaction, or misses subjects who are lost to follow-up or change their health insurance as a result of their disability. Alternatively, a survival analysis approach could be used. This approach allows all patients, eligible or ineligible, to stay in the cohort and follow them until the occurrence of a severe skin reaction, their enrollment is terminated or the end of the study period, whichever comes first.

5. Exposure issues
   - Evidence that Factive® is in the formulary of the proposed health plan organizations should be obtained to assure that the study is feasible.
   - The implications of not examining risk beyond 30 days after drug exposure should be addressed, and if it is believed that such events are not likely, the evidence to support such a view should be provided.
   - How patients taking more than one antibiotic will be treated in the analysis must be addressed, as incidence will be differentiated from prevalence of prescription therapy. The issues of drug switches, consecutive prescriptions used, and the time lag between prescriptions can greatly influence risk estimates and interpretation.
   - The operational definitions of cross-sensitization and sub-clinical sensitization must be clearly stated in the protocol.

6. Outcome ascertainment
   - The protocol for retrieval and abstraction of medical charts must be defined prior to initiation of the study, and it should be confirmed that that there is the ability to obtain and abstract complete inpatient medical charts, which is required for validation of the SJS and TEN diagnoses

Overall conclusions regarding the proposed epidemiological study:

"Overall, the sponsor's suggestion to conduct a study within a large population to further investigate the adverse events associated with Factive® in a real-life use setting is valid, especially since serious skin reactions associated with the product are rare and thus would not likely to be identified in clinical trials. In this study design, the sponsor suggests obtaining information on some of the variables specified in the recommendations of the Medical

> Officer's Review of NDA 21-376 from April 11, 2002, including duration of exposure to Factive® therapy, and patient demographics. However, we have multiple concerns about the validity and usefulness of the proposed study; our most important concerns relate to the feasibility of this study in light of the large sample size needed to detect such rare events. In light of the relatively infrequent use of Factive®, the short duration of therapy, the homogeneity of the study population and the inclusion of only two large databases, attaining the needed sample size in a reasonable period of time appears infeasible based upon this proposal. Additionally we have other concerns relating to the ability of the proposed study to reliably ascertain appropriate outcomes and to accurately measure antibiotic exposure. Therefore, we recommend not proceeding with the proposed study unless these issues can be resolved."

VI. Summary

FDA recommendations regarding the proposed indication of Factive® for acute bacterial sinusitis have been consistent across several submissions for this indication. Although it is recognized that the incidence of cutaneous adverse effects are reduced relative to longer courses of gemifloxacin therapy, there is still the concern that the incidence of skin reactions is greater than comparator therapy based both on controlled clinical trial data and post-marketing data available from the Adverse Event Reporting System.

The efficacy of gemifloxacin in ABS was based on clinical studies designed and completed by 2001; these studies were designed to show non-inferiority between gemifloxacin and other antimicrobials. The use of non-inferiority trials for the indication of ABS has been called into question in recent years, and was the subject of an Anti-Infective Drug Product Advisory Committee meeting in October 2003.

For the specific indication of acute bacterial sinusitis, FDA has previously concluded that the sponsor has not demonstrated that benefit of gemifloxacin in ABS outweighs the disproportionately higher risk of rash with gemifloxacin and the concern regarding severe cutaneous reactions that may occur in these patients.

VII. Appendices

A. Current Factive® Package Insert.

B. Medical Officer Review for NDA 21-376, Factive® (gemifloxacin mesylate) 320 mg tablet in Acute Bacterial Sinusitis, 5-Day regimen (2002).

C. FDA Division of Drug Risk Evaluation (DDRE), Office of Drug Safety Consultation Review of Post-marketing of cutaneous reactions associated with the use of gemifloxacin.

D. Acute bacterial sinusitis and non-inferiority studies

E. References:

1. Bigby, M. Rates of Cutaneous Reactions to Drugs. Archives of Dermatology, 2001; 137:765-770.

2. Roujeau, JC. et. al. Medication Use and the Risk of Steven-Johnson Syndrome or Toxic Epidermal Necrolysis. New England Journal of Medicine, 1995; 333:1600-1608.

3. Roujeau JC. Stern RS. Severe Adverse Cutaneous Reactions to Drugs. N Eng Jour Med.1994; 331:1272-1285.

Appendix A:

Factive® (Gemifloxacin) Package Insert

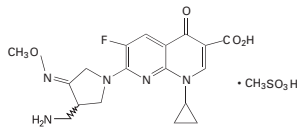
FACTIVE®
(gemifloxacin mesylate) Tablets

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 μg/mL at 37°C, pH 7.0). Its empirical formula is $C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$ and its chemical structure is:



Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40 mg to 640 mg. There was minimal accumulation of gemifloxacin following multiple oral doses up to 640 mg a day for 7 days (mean accumulation <20%). Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (Cmax) and systemic drug exposure (AUC(0-24)) were 1.61 ± 0.51 μg/mL (range 0.70-2.62 μg/mL) and 9.93 ± 3.07 μg•hr/mL (range 4.71-20.1 μg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC(0-24), 8.36 μg•hr/mL; range 3.2 – 47.7 μg•hr/mL.

The pharmacokinetics of gemifloxacin were not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore FACTIVE tablets may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60 to 70% and is concentration independent. After repeated doses, the *in vivo* plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66 – 12.12 L/kg).

Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in Table 1:

Table 1. Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean ± SD)
Plasma	1.40 (0.442) μg/mL	—
Bronchoalveolar Macrophages	107 (77) μg/g	90.5 (106.3)
Epithelial Lining Fluid	2.69 (1.96) μg/mL	1.99 (1.32)
Bronchial Mucosa	9.52 (5.15) μg/g	7.21 (4.03)

Metabolism

Gemifloxacin is metabolized to a limited extent by the liver. The unchanged compound is the predominant drug-related component detected in plasma (approximately 65%) up to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral dose); the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes is not significantly inhibited by gemifloxacin.

Excretion

Gemifloxacin and its metabolites are excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61 ± 9.5% of the dose was excreted in the feces and 36 ± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 L/hr (range 4.6-17.6 L/hr), which indicates active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady state following 320 mg to healthy subjects was approximately 7 ± 2 hours (range 4-12 hours).

Special Populations

Pediatric: The pharmacokinetics of gemifloxacin in pediatric subjects have not been studied.

Geriatric: In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age.

Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 μg·hr/mL (range, 3.21 – 42.71 μg·hr/mL) and 8.80 μg·hr/mL (range, 3.33 – 47.73 μg·hr/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

Hepatic Insufficiency: The pharmacokinetics following a single 320 mg dose of gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) liver disease. There was a mean increase in AUC (0-inf) of 34% and a mean increase in Cmax of 25% in these patients with hepatic impairment compared to healthy volunteers.

The pharmacokinetics of a single 320 mg dose of gemifloxacin were also studied in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean increase in AUC (0-inf) of 45% and a mean increase in Cmax of 41% in these subjects with hepatic impairment compared to healthy volunteers.

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. (See **DOSAGE AND ADMINISTRATION**.)

Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin Cmax was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. (See **DOSAGE AND ADMINISTRATION.**)

Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential: In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg b.i.d., or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg b.i.d. and the photosensitivity potentials for both drugs were statistically greater than that of placebo. Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin (0.039%). (See **ADVERSE REACTIONS.**)

Drug-Drug Interactions

Antacids/Di- and Trivalent Cations: The systemic availability of gemifloxacin is significantly reduced when an aluminum- and magnesium- containing antacid is concomitantly administered (AUC decreased 85%; Cmax decreased 87%). Administration of an aluminum- and magnesium- containing antacid or ferrous sulfate (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking FACTIVE tablets.

Calcium carbonate (1000 mg) given either 2 hr before or 2 hr after gemifloxacin administration showed no notable reduction in gemifloxacin systemic availability. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, not clinically significant, decrease in gemifloxacin exposure [AUC (0-inf) decreased 21% and Cmax decreased].

Sucralfate: When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69% decrease in Cmax). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected; therefore FACTIVE should be taken at least 2 hours before sucralfate. (See **PRECAUTIONS.**)

In Vitro Metabolism: Results of *in vitro* inhibition studies indicate that hepatic cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin metabolism. Therefore gemifloxacin should not cause significant *in vivo* pharmacokinetic interactions with other drugs that are metabolized by CYP450 enzymes.

Theophylline: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of theophylline (300 to 400 mg b.i.d. to healthy male subjects).

Digoxin: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

Oral Contraceptives: The effect of an oral estrogen/progesterone contraceptive product (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for 6 days) in healthy female subjects indicates that concomitant administration caused an average reduction in gemifloxacin AUC and Cmax of 19% and 12%. These changes are not considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 μg/150 μg once daily for 21 days to healthy female subjects).

Cimetidine: Co-administration of a single dose of 320 mg gemifloxacin with cimetidine 400 mg four times daily for 7 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 6%, respectively. These increases are not considered clinically significant.

Omeprazole: Co-administration of a single dose of 320 mg gemifloxacin with omeprazole 40 mg once daily for 4 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 11%, respectively. These increases are not considered clinically significant.

Warfarin: Administration of repeated doses of gemifloxacin (320 mg once daily for 7 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-induced anticoagulant activity (i.e., International Normalized Ratios for Prothrombin Time). (See **PRECAUTIONS: Drug Interactions**.)

Probenecid: Administration of a single dose of 320 mg gemifloxacin to healthy subjects who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in gemifloxacin AUC(0-inf) and a prolongation of mean half-life by 1.6 hours. Mean gemifloxacin Cmax increased 8%.

Microbiology

Gemifloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for some of these double mutants.

The mechanism of action of quinolones, including gemifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin and other quinolones. There is no known cross-resistance between gemifloxacin and the above mentioned classes of antimicrobials.

The main mechanism of fluoroquinolone resistance is due to mutations in DNA gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep mutations and efflux in a manner similar to other fluoroquinolones. The frequency of spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin.

Gemifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP])*,*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae (many strains are only moderately susceptible)
Moraxella catarrhalis

Other microorganisms

Chlamydia pneumoniae
Mycoplasma pneumoniae

The following data are available, **but their clinical significance is unknown**.

Gemifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.25 μg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Acinetobacter lwoffii
Klebsiella oxytoca
Legionella pneumophila
Proteus vulgaris

Susceptibility Tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

MIC (μg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5	Intermediate (I)
≥1.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [a]:

MIC (μg/mL)	Interpretation
≤0.12	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae* [b]:

MIC (μg/mL)	Interpretation
≤0.12	Susceptible (S)
0.25	Intermediate (I)
≥0.5	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation–adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gemifloxacin powder should provide the following MIC values:

Microorganism		MIC Range (µg/mL)
Enterococcus faecalis	ATCC 29212	0.016-0.12
Escherichia coli	ATCC 25922	0.004-0.016
Haemophilus influenzae	ATCC 49247[c]	0.002-0.008
Streptococcus pneumoniae	ATCC 49619[d]	0.008-0.03

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5µg gemifloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
16-19	Intermediate (I)
≤15	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[e]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)

[e] This interpretive standard is applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[f]:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

[f] These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gemifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5µg gemifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-36
Haemophilus influenzae	ATCC 49247[g]	30-37
Streptococcus pneumoniae	ATCC 49619[h]	28-34

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2].

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

FACTIVE is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES.**)

Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis.*

Community-acquired pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae* (including multidrug resistant strains [MDRSP])*, *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Klebsiella pneumoniae***.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g. cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

**In the clinical trials, there were 13 subjects with *Klebsiella pneumoniae*, primarily from non-comparative studies. Ten subjects had mild disease, two had moderate disease, and one had severe disease. There were two clinical failures in subjects with mild disease (one subject with bacteriologic recurrence).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Gemifloxacin is contraindicated in patients with a history of hypersensitivity to gemifloxacin, fluoroquinolone antibiotic agents, or any of the product components.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF FACTIVE IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy and Nursing Mothers subsections.)

QT Effects: Fluoroquinolones may prolong the QT interval in some patients. Gemifloxacin should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected eletrolyte disorders (hypokalemia or hypomagnesemia), and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.

Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gemifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gemifloxacin treatment in over 6775 patients, including 653 patients concurrently receiving drugs known to prolong the QTc interval and 5 patients with hypokalemia.

The likelihood of QTc prolongation may increase with increasing dose of the drug; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours following oral administration of gemifloxacin.

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

Gemifloxacin should be discontinued immediately at the appearance of any sign of an immediate type I hypersensitivity skin rash or any other manifestation of a hypersensitivity reaction; the need for continued fluoroquinolone therapy should be evaluated. As with other drugs, serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and occasionally fatal events, some due to hypersensitivity and/or some of uncertain etiology, have been reported in patients receiving fluoroquinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations usually include new onset fever and one or more of the following: rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones.

Tendon Effects: Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones.

CNS Effects: In clinical studies with gemifloxacin, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, gemifloxacin should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in gemifloxacin clinical trials, convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving other fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving gemifloxacin, the drug should be discontinued and appropriate measures instituted.

Antibiotic Associated Colitis: Pseudomembranous colitis has been reported with nearly all antibacterial agents, including gemifloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. (See **ADVERSE REACTIONS.**)

PRECAUTIONS

General: Prescribing FACTIVE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Rash: In clinical studies, the overall rate of drug-related rash was 2.8%. The most common form of rash associated with gemifloxacin was described as maculopapular and mild to moderate in severity; 0.3% was described as urticarial in appearance. Rash usually appeared 8 to 10 days after start of therapy; 60% of the rashes resolved within 7 days, and 80% resolved within 14 days. Approximately 10% of those patients developing rash had a rash described as of severe intensity. Histology was evaluated in a clinical pharmacology study and was consistent with an uncomplicated exanthematous skin reaction and showed no evidence of phototoxicity, vasculitis, or necrosis. There were no documented cases in the clinical trials of more serious skin reactions known to be associated with significant morbidity or mortality.

Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). Prolonging duration of therapy beyond 7 days causes the incidence of rash to increase significantly in all subgroups except men over the age of 40 (see Table 2). Gemifloxacin therapy should be discontinued in patients developing a rash while on treatment. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES.**)

Table 2. Rash Incidence in FACTIVE Treated Patients from the Clinical Studies Population* by Gender, Age, and Duration of Therapy

Gender & Age (yr) Category	Duration of Gemifloxacin Therapy 5 days	7 days	10 days**	14 days**
Female < 40	5/242 (2.1%)	39/324 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥ 40	19/1210 (1.6%)	30/695 (4.3%)	19/308 (6.2%)	10/126 (7.9%)
Male < 40	4/218 (1.8%)	20/318 (6.3%)	7/74 (9.5%)	3/39 (7.7%)
Male ≥ 40	9/1321 (0.7%)	23/776 (3.0%)	9/345 (2.6%)	3/116 (2.6%)
Totals	37/2991 (1.2%)	112/2113 (5.3%)	55/858 (6.4%)	23/312 (7.4%)

*includes patients from studies of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and other indications

exceeds the recommended duration of therapy (see **DOSAGE AND ADMINISTRATION)

Photosensitivity reactions have been reported very rarely in clinical trials with FACTIVE. (See **CLINICAL PHARMACOLOGY.**) However, as with all drugs of this class, it is recommended that patients avoid unnecessary exposure to strong sunlight or artificial UV rays (e.g., sunlamps, solariums), and should be advised of the appropriate use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued if a photosensitivity reaction is suspected.

Hepatic Effects: Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving gemifloxacin 320 mg daily relative to comparator antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil, amoxicillin/ clavulanate potassium, and ofloxacin). In patients who received gemifloxacin at doses of 480 mg per day or greater there was an increased incidence of elevations in liver enzymes. (See **ADVERSE REACTIONS**.)

There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy. The recommended dose of gemifloxacin 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded. (See **DOSAGE AND ADMINISTRATION**.)

Alteration of the dosage regimen is necessary for patients with impairment of renal function (creatinine clearance ≤40 mL/min). (See **DOSAGE AND ADMINISTRATION.**)

Adequate hydration of patients receiving gemifloxacin should be maintained to prevent the formation of a highly concentrated urine.

Information for Patients

Patients should be counseled:

- that antibacterial drugs including FACTIVE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When FACTIVE is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by FACTIVE or other antibacterial drugs in the future;
- that FACTIVE has been associated with rash. Patients should discontinue drug and call their healthcare provider if they develop a rash;
- that FACTIVE may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose; patients should immediately discontinue the drug at the sign of a rash or other allergic reaction and seek medical care;
- that FACTIVE may cause changes in the electrocardiogram (QTc interval prolongation);
- that FACTIVE should be avoided in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;
- that FACTIVE should be used with caution in patients receiving drugs that affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia;
- to inform their physician of any other medications when taken concurrently with FACTIVE, including over-the-counter medications and dietary supplements;
- to contact their physician if they experience palpitations or fainting spells while taking FACTIVE;
- that FACTIVE may be taken with or without meals;
- to drink fluids liberally;
- not to take antacids containing magnesium and/or aluminum or products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution within 3 hours before or 2 hours after taking FACTIVE tablets;
- that FACTIVE should be taken at least 2 hours before sucralfate;
- that phototoxicity has been reported with certain quinolones. The potential for FACTIVE to cause phototoxicity was low (3/7659) at the recommended dose in clinical studies. In keeping with good clinical practice, avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds). If a sunburn-like reaction or skin eruption occurs, contact your physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);
- that FACTIVE may cause dizziness; if this occurs, patients should not operate an automobile or machinery or engage in activities requiring mental alertness or coordination;
- that they should discontinue FACTIVE therapy and inform their physician if they feel pain, tenderness or rupture of a tendon. Patients should rest and avoid exercise until the diagnosis of tendonitis or tendon rupture has been excluded;
- that convulsions have been reported in patients receiving quinolones; and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: Administration of repeat doses of FACTIVE had no effect on the repeat dose pharmacokinetics of theophylline, digoxin or an ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. (See **CLINICAL PHARMACOLOGY: Drug-Drug Interactions.**)

Concomitant administration of FACTIVE and calcium carbonate, cimetidine, omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in the pharmacokinetics of gemifloxacin, which were considered to be without clinical significance. (See **CLINICAL PHARMACOLOGY.**)

Concomitant administration of FACTIVE with probenecid resulted in a 45% increase in systemic exposure to gemifloxacin. (See **CLINICAL PHARMACOLOGY**.)

FACTIVE had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy. However, because some quinolones have been reported to enhance the anticoagulant effects of warfarin or its derivatives in patients, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of an antacid containing aluminum and magnesium. Magnesium- and/or aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after FACTIVE. Sucralfate should not be taken within 2 hours of FACTIVE. (See **CLINICAL PHARMACOLOGY.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long term studies in animals to determine the carcinogenic potential of gemifloxacin have not been conducted.

Photocarcinogenesis: Gemifloxacin did not shorten the time to development of UVR-induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photocarcinogenic in this model. These mice received oral gemifloxacin and concurrent irradiation with simulated sunlight 5 days per week for 40 weeks followed by a 12-week treatment-free observation period. The daily dose of UV radiation used in this study was approximately 1/3 of the minimal dose of UV radiation that would induce erythema in Caucasian humans. The median time to the development of skin tumors in the hairless mice was similar in the vehicle control group (36 weeks) and those given up to 100 mg/kg gemifloxacin daily (39 weeks). Following repeat doses of 100 mg/kg gemifloxacin per day, the mice had skin gemifloxacin concentrations of approximately 7.4 μg/g. Plasma levels following this dose were approximately 1.4 μg/mL in the mice around the time of irradiation. There are no data on gemifloxacin skin levels in humans, but the mouse plasma gemifloxacin levels are in the expected range of human plasma Cmax levels (0.7-2.6 μg/mL, with an overall mean of about 1.6 μg/mL) following multiple 320 mg oral doses.

Mutagenesis: Gemifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in an Ames *Salmonella* reversion assay. It did not induce micronuclei in the bone marrow of mice following intraperitoneal doses of up to 40 mg/kg and it did not induce unscheduled DNA synthesis in hepatocytes from rats which received oral doses of up to 1600 mg/kg. Gemifloxacin was clastogenic *in vitro* in the mouse lymphoma and human lymphocyte chromosome aberration assays. It was clastogenic *in vivo* in the rat micronucleus assay at oral and intravenous dose levels (≥800 mg/kg and ≥40 mg/kg, respectively) that produced bone marrow toxicity. Fluoroquinolone clastogenicity is apparently due to inhibition of mammalian topoisomerase activity which has threshold implications.

Impairment of Fertility: Gemifloxacin did not affect the fertility of male or female rats at AUC levels following oral administration (216 and 600 mg/kg/day) that were approximately 3- to 4-fold higher than the AUC levels at the clinically recommended dose.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing at 450 mg/kg/day), rats (oral dosing at 600 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day) at AUC levels which were 2-, 4- and 3-fold those in women given oral doses of 320 mg. In rats, this growth retardation appeared to be reversible in a pre- and postnatal development study (mice and rabbits were not studied for the reversibility of this effect). Treatment of pregnant rats at 8-fold clinical exposure (based upon AUC comparisons) caused fetal brain and ocular malformations in the presence of maternal toxicity. The overall no-effect exposure level in pregnant animals was approximately 0.8 to 3-fold clinical exposure.

The safety of gemifloxacin in pregnant women has not been established. Gemifloxacin should not be used in pregnant women unless the potential benefit to the mother outweighs the risk to the fetus. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers: Gemifloxacin is excreted in the breast milk of rats. There is no information on excretion of gemifloxacin into human milk. Therefore, gemifloxacin should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

Pediatric Use: Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including gemifloxacin, cause arthropathy and osteochondrosis in immature animals. (See **WARNINGS.**)

Geriatric Use: Of the total number of subjects in clinical studies of gemifloxacin, 30% (2064) were 65 and over, while 12% (779) were 75 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse event rate for this group was similar to or lower than that for younger subjects with the exception that the incidence of rash was lower in geriatric patients compared to patients less than 40 years of age.

ADVERSE REACTIONS

In clinical studies, 6775 patients received daily oral doses of 320 mg gemifloxacin. In addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of gemifloxacin in clinical pharmacology studies. The majority of adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity.

Gemifloxacin was discontinued because of an adverse event (possibly or probably related) in 2.2% of patients, primarily due to rash (0.9%), nausea (0.3%), diarrhea (0.3%), urticaria (0.3%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an adverse event at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.3%), vomiting (0.3%) and rash (0.3%).

Drug-related adverse events, classified as possibly or probably related with a frequency of ≥1% for patients receiving 320 mg of gemifloxacin versus comparator drug (beta-lactam antibiotics, macrolides or other fluoroquinolones) are as follows: diarrhea 3.6% vs. 4.6%; rash 2.8% vs. 0.6%; nausea 2.7% vs. 3.2%; headache 1.2% vs. 1.5%; abdominal pain 0.9% vs. 1.1%; vomiting 0.9% vs. 1.1%; dizziness 0.8% vs. 1.5%; and taste perversion 0.3% vs. 1.9%.

Gemifloxacin appears to have a low potential for photosensitivity. In clinical trials, treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.

Additional drug-related adverse events (possibly or probably related) in >0.1% to 1% of patients who received 320 mg of gemifloxacin were: abdominal pain, anorexia, arthralgia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, hyperglycemia, insomnia, leukopenia, moniliasis, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

Other adverse events reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in ≤0.1% of patients were: abnormal urine, anemia, asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, flushing, gastroenteritis, granulocytopenia, hot flashes, increased GGT, leg cramps, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, pneumonia, thrombocytopenia, tremor, vertigo, and vision abnormality.

In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), the incidences of rash were as follows (Table 3):

Table 3. Incidence of Rash by Clinical Indication in Patients Treated with Gemifloxacin

	ABECB (5 days) N = 2284		CAP (7 days) N = 643	
	n/N	%	n/N	%
Totals	27/2284	1.2	26/643	4.0
Females, < 40 years	NA*		8/88	9.1
Females, ≥ 40 years	16/1040	1.5	5/214	2.3
Males, < 40 years	NA*		5/101	5.0
Males, ≥ 40 years	11/1203	0.9	8/240	3.3

*insufficient number of patients in this category for a meaningful analysis.(See **PRECAUTIONS**).

Laboratory Changes: The percentages of patients who received multiple doses of gemifloxacin and had a laboratory abnormality are listed below. It is not known whether these abnormalities were related to gemifloxacin or an underlying condition.

Clinical Chemistry: increased ALT (1.5%), increased AST (1.1%), increased creatine phosphokinase (0.6%), increased potassium (0.5%), decreased sodium (0.3%), increased gammaglutamyl transferase (0.5%), increased alkaline phosphatase (0.3%), increased total bilirubin (0.3%), increased blood urea nitrogen (0.3%), decreased calcium (0.2%), decreased albumin (0.3%), increased serum creatinine (0.2%), decreased total protein (0.1%) and increased calcium (<0.1%).

CPK elevations were noted infrequently: 0.8% in gemifloxacin patients vs. 0.4% in the comparator patients.

Hematology: increased platelets (0.9%), decreased neutrophils (0.5%), increased neutrophils (0.5%), decreased hematocrit (0.3%), decreased hemoglobin (0.2%), decreased platelets (0.2%), decreased red blood cells (0.1%), increased hematocrit (0.1%), increased hemoglobin (0.1%), and increased red blood cells (0.1%).

In clinical studies, approximately 7% of the gemifloxacin treated patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 10% showed a further elevation of their ALT at the on-therapy visit and 5% showed a further elevation at the end of therapy visit. None of these patients demonstrated evidence of hepatocellular jaundice. For the pooled comparators, approximately 6% of patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 7% showed a further elevation of their ALT at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

In a clinical trial where 638 patients received either a single 640 mg dose of gemifloxacin or 250 mg bid of ciprofloxacin for 3 days, there was an increased incidence of ALT elevations in the gemifloxacin arm (3.9%) vs. the comparator arm (1.0%). In this study, two patients experienced ALT elevations of 8 to 10 times the upper limit of normal. These elevations were asymptomatic and reversible.

OVERDOSAGE

Any signs or symptoms of overdosage should be treated symptomatically. No specific antidote is known. In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage; the patient should be carefully observed and treated symptomatically with appropriate hydration maintained. Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400 mg/kg) of gemifloxacin to rodents included ataxia, lethargy, piloerection, tremor, and clonic convulsions.

DOSAGE AND ADMINISTRATION

FACTIVE can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of FACTIVE is 320 mg daily, according to the following table (Table 4).

Table 4. Recommended Dosage Regimen of FACTIVE

INDICATION	DOSE	DURATION
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily	5 days
Community-acquired pneumonia (of mild to moderate severity)	One 320 mg tablet daily	7 days

The recommended dose and duration of FACTIVE should not be exceeded (see Table 2).

Renally Impaired Patients: Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. Table 5 provides dosage guidelines for use in patients with renal impairment:

Table 5. Recommended Doses for Patients With Renal Impairment

Creatinine Clearance (mL/min)	Dose
>40	See Usual Dosage
≤40	160 mg q24h

Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) should receive 160 mg q24h.

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

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

Women: 0.85 x the value calculated for men

Use in Hepatically Impaired Patients: No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Use in Elderly: No dosage adjustment is recommended.

HOW SUPPLIED

FACTIVE (gemifloxacin mesylate) is available as white to off-white, oval, film-coated tablets with breaklines and GE 320 debossed on both faces. Each tablet contains gemifloxacin mesylate equivalent to 320 mg of gemifloxacin.

320 mg Unit of Use (CR*) 5's	NDC 67707-320-05
320 mg Unit of Use (CR*) 7's	NDC 67707-320-07
320 mg Hospital Pack (NCR**) 30's	NDC 67707-320-30

*Child Resistant ** Not Child Resistant

STORAGE

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. Degeneration of articular cartilage occurred in juvenile dogs given at least 192 mg/kg/day gemifloxacin in a 28-day study (producing about 6 times the systemic exposure at the clinical dose), but not in mature dogs. There was no damage to the articular surfaces of joints in immature rats given repeated doses of up to 800 mg/kg/day.

Some quinolones have been reported to have proconvulsant properties that are potentiated by the concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs). Gemifloxacin alone had effects in tests of behavior or CNS interaction typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the active metabolite of the NSAID, fenbufen, followed by 80 mg/kg gemifloxacin.

Dogs given 192 mg/kg/day (about 6 times the systemic exposure at the clinical dose) for 28 days, or 24 mg/kg/day (approximately equivalent to the systemic exposure at the clinical dose) for 13 weeks showed reversible increases in plasma ALT activities and local periportal liver changes associated with blockage of small bile ducts by crystals containing gemifloxacin.

Quinolones have been associated with prolongation of the electrocardiographic QT interval in dogs. Gemifloxacin produced no effect on the QT interval in dogs dosed orally to provide about 4 times human therapeutic plasma concentrations at Cmax, and transient prolongation after intravenous administration at more than 4 times human plasma levels at Cmax. Gemifloxacin exhibited weak activity in the cardiac I_{kr} (hERG) channel inhibition assay, having an IC_{50} of approximately 270 μM.

Gemifloxacin, like many other quinolones, tends to crystallize at the alkaline pH of rodent urine, resulting in a nephropathy in rats that is reversible on drug withdrawal (oral no-effect dose 24 mg/kg/day).

Gemifloxacin was weakly phototoxic to hairless mice given a single 200 mg/kg oral dose and exposed to UVA radiation. However, no evidence of phototoxicity was observed at 100 mg/kg/day dosed orally for 13 weeks in a standard hairless mouse model, using simulated sunlight.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

FACTIVE (320 mg once daily for 5 days) was evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in three pivotal double-blind, randomized, actively-controlled clinical trials (studies 068, 070, and 212). The primary efficacy parameter in these studies was the clinical response at follow-up (day 13 to 24). The results of the clinical response at follow-up for the principal ABECB studies demonstrate that FACTIVE 320 mg PO once daily for 5 days was at least as good as the comparators given for 7 days. The results are shown in Table 6 below.

Table 6. Clinical Response at Follow-Up (Test of Cure): Pivotal ABECB Studies

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
Study 068		
FACTIVE 320 mg x 5 days	86.0 (239/278)	1.2 (-4.7, 7.0)
Clarithromycin 500 mg bid x 7 days	84.8 (240/283)	
Study 070		
FACTIVE 320 mg x 5 days	93.6 (247/264)	0.4 (-3.9, 4.6)
Amoxicillin/clavulanate 500 mg/125 mg tid x 7 days	93.2 (248/266)	
Study 212		
FACTIVE 320 mg x 5 days	88.2 (134/152)	3.1 (-4.7, 10.7)
Levofloxacin 500 mg x 7 days	85.1 (126/148)	

Community Acquired Pneumonia (CAP)

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of community acquired pneumonia in adults consisted of three double-blind, randomized, actively-controlled clinical studies (studies 011, 012, and 049) and one open, actively-controlled study (study 185). In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the studies, pivotal study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for FACTIVE. Pivotal study 011 compared a 7-day course of FACTIVE with a 10-day treatment course of amoxicillin/ clavulanate (1g/125 mg tid) and clinical success rates were similar between treatment arms. The results of comparative studies 049, 185, and 012 were supportive although treatment duration could have been 7 to 14 days. The results of the clinical studies with a fixed 7-day duration of gemifloxacin are shown in Table 7:

Table 7. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7 Day Duration of Treatment

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
Study 011		
FACTIVE 320 mg x 7 days	88.7 (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 500 mg/125 mg tid x 10 days	87.6 (99/113)	
Study 061		
FACTIVE 320 mg x 7 days	91.7 (154/168)	(86.1, 95.2)
Study 287		
FACTIVE 320 mg x 7 days	89.8 (132/147)	(84.9, 94.7)

* For uncontrolled studies, the 95% CI around the success rate is shown

The combined bacterial eradication rates for patients treated with a fixed 7-day treatment regimen of FACTIVE are shown in Table 8:

Table 8. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies with a Fixed 7-day Duration of Treatment

Pathogen	n/N	%
S. pneumoniae	68/77	88.3
M. pneumoniae	21/22	95.5
H. influenzae	30/35	85.7
C. pneumoniae	13/14	92.9
*K. pneumoniae**	11/13	84.6
M. catarrhalis	10/10	100

*Subjects with *Klebsiella pneumoniae* included in this table were from non-comparative studies 061 and 287. Ten of these subjects had mild disease, two had moderate disease, and one had severe disease. Both failures were in subjects with mild disease (one of these had a bacteriologic recurrence).

FACTIVE was also effective in the treatment of CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP*). Of 22 patients with MDRSP treated for 7 days, 19 (86.5%) achieved clinical and bacteriological success at follow-up. The clinical and bacteriological success for the 22 patients with 22 MDRSP isolates are shown in Table 9.

*MDRSP: Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Table 9. Clinical and Bacteriological Success for 22 Patients Treated with FACTIVE in Studies with a 7-day Duration of Treatment for MDRSP

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N[a]	%	n/N[b]	%
Penicillin-resistant	11/11	100	11/11	100
2nd generation cephalosporin-resistant	14/14	100	14/14	100
Macrolide-resistant[c]	16/19	84.2	16/19	84.2
Trimethoprim/sulfamethoxazole-resistant	16/16	100	16/16	100
Tetracycline-resistant	13/16	81.3	13/16	81.3

a) n = the number of patients successfully treated; N = number of patients with MDRSP (from a total of 22 patients)

b) n = the number of bacteriological isolates successfully treated; N = number of isolates studied (from a total of 22 isolates)

c) Macrolide antibiotics tested include clarithromycin and erythromycin

Cutaneous Manifestations (Rash)
In clinical trials of 6,775 patients, the incidence of rash was higher in patients receiving gemifloxacin than in those receiving comparator drugs (see **PRECAUTIONS** and **ADVERSE REACTIONS**). Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days, see Table 2).

To further characterize gemifloxacin-associated rash, a clinical pharmacology study was conducted. The study enrolled 1,011 healthy female volunteers less than 40 years of age. Subjects were randomized to receive either FACTIVE 320 mg po daily or ciprofloxacin 500 mg po twice daily for 10 days. The objective of the study was to assess the characteristics of rash. The majority of rashes in subjects receiving FACTIVE were maculopapular and of mild to moderate severity; 7% of the rashes were reported as severe, and severity appeared to correlate with the extent of the rash. In 68% of the subjects reporting a severe rash and approximately 25% of all those reporting rash, >60% of the body surface area was involved; the characteristics of the rash were otherwise indistinguishable from those subjects reporting a mild rash. The histopathology was consistent with the clinical observation of uncomplicated exanthematous morbilliform eruption. There were no documented cases of hypersensitivity syndrome or findings suggestive of angioedema or other serious cutaneous reactions.

The majority of rash events (81.9%) occurred on days 8 through 10 of the planned 10 day course of gemifloxacin; 2.7% of rash events occurred within one day of the start of dosing. The median duration of rash was 6 days. The rash resolved without treatment in the majority of subjects. Approximately 19% received antihistamines and 5% received steroids, although the therapeutic benefit of these therapies is uncertain.

In the second part of this study after a 4 to 6 week wash out period, subjects developing a rash on gemifloxacin were treated with ciprofloxacin or placebo; 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash when treated with placebo. The characteristics of rash in subjects receiving ciprofloxacin following gemifloxacin were similar to those described in subjects who only received ciprofloxacin. The cross sensitization rate to other fluoroquinolones was not evaluated in this clinical study. There was no evidence of sub-clinical sensitization to gemifloxacin (i.e. subjects who had not developed a rash to gemifloxacin in the first part of the study were not at higher risk of developing a rash to gemifloxacin with a second exposure).

There was no relationship between the incidence of rash and systemic exposure (Cmax and AUC) to either gemifloxacin or its major metabolite, N-acetyl gemifloxacin.

REFERENCES 1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003. **2.** National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Eighth Edition. Approved Standard NCCLS Document A2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January 2003.

DATE OF REVISION AUGUST 2004

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OSCIENT PHARMACEUTICALS

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Licensed from LG Life Sciences, Ltd. Seoul, Korea

70011424

Patient Information

FACTIVE®

(gemifloxacin mesylate) Tablets

This leaflet summarizes the most important information about FACTIVE. Read the Patient Information that comes with FACTIVE each time you get a new prescription. There may be new information. This leaflet does not list all benefits and risks of treatment and does not take the place of talking with your healthcare provider about your condition or your treatment. FACTIVE can only be prescribed by a healthcare professional. If you would like more information, talk with your healthcare provider or pharmacist.

What is FACTIVE?
FACTIVE is an antibiotic. It is used to treat adults 18 years or older with bronchitis or pneumonia (lung infections) caused by certain bacteria (germs).

Sometimes, other germs called viruses infect the lungs. The common cold is a virus. FACTIVE, like other antibiotics, does not treat viruses.

FACTIVE tablets are white to off white and imprinted with GE 320 on both sides.

Who should not take FACTIVE?
- **Do not take FACTIVE if you are allergic to any of the ingredients in FACTIVE or to any antibiotic called a "quinolone".** If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, stop taking FACTIVE and call your healthcare professional. The ingredients in FACTIVE are listed at the end of this leaflet. Ask your healthcare provider or pharmacist if you need a list of quinolones.

FACTIVE may not be right for you. Tell your healthcare provider if you:

- are pregnant, planning to become pregnant, or are breast feeding. The effects of FACTIVE on unborn children and nursing infants are unknown;
- or any family members have a rare heart condition known as congenital prolongation of the QTc interval;
- have low potassium or magnesium levels;
- have a slow heart beat called bradycardia;
- have had a recent heart attack;
- have a history of convulsions;
- have kidney problems.

FACTIVE has not been studied in children under the age of 18. Quinolones may cause joint problems (arthropathy) in children.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and dietary supplements. **Be sure to tell your healthcare provider if you take:**

- medicines for your heart rhythm called "antiarrhythmics"
- erythromycin
- medicines for your mental health called "antipsychotics" or "tricyclic antidepressants"
- medicines called "corticosteroids", taken by mouth or by injection
- medicines called diuretics such as furosemide and hydrochlorothiazide.

How should I take FACTIVE?

- Take 1 FACTIVE tablet a day for 5 or 7 days, exactly as prescribed.
- Take FACTIVE at the same time each day.
- FACTIVE can be taken with or without food.
- Swallow the FACTIVE tablet whole, and drink plenty of fluids with it. Do not chew the FACTIVE tablet.
- If you miss a dose of FACTIVE, take it as soon as you remember. **Do not take more than 1 dose of FACTIVE in a day.**
- To make sure all bacteria are killed, take all the medicine that was prescribed for you even if you begin to feel better.
- Call your healthcare provider if your condition does not improve while taking FACTIVE.

Do not take the following medicines within 3 hours before FACTIVE or 2 hours after FACTIVE. They may interfere with the absorption of FACTIVE and may prevent it from working properly:

- antacids that contain magnesium or aluminum
- ferrous sulfate (iron)
- multivitamin that contains zinc or other metals
- Videx® (didanosine)

FACTIVE should be taken at least 2 hours before sucralfate.

(continued on next page)

What are possible side effects of FACTIVE?

FACTIVE is generally well tolerated. The most common side effects with FACTIVE include diarrhea, rash, nausea, headache, vomiting, stomach pain, dizziness, and a change in the way things taste in your mouth. If you get a rash while taking FACTIVE, stop FACTIVE, and call your healthcare provider right away. Do not drive or operate heavy machinery until you know how FACTIVE affects you. FACTIVE can make you dizzy.

FACTIVE and other quinolone antibiotics may cause the following serious side effects:

- a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and result in sudden death. You should call your healthcare provider right away if you have any symptoms of prolongation of the QTc interval including heart palpitations (a change in the way your heart beats) or fainting spells;
- central nervous system problems including body shakes (tremors), restless feeling, lightheaded feelings, confusion, and hallucinations (seeing or hearing things that are not there);
- tendon problems including tendonitis or rupture ("tears") of a tendon. If you experience pain, swelling, or rupture of a tendon, stop taking FACTIVE and call your healthcare professional;
- phototoxicity. This can make your skin sunburn easier. Do not use a sunlamp or tanning bed while taking FACTIVE. Use a sunscreen and wear protective clothing if you must be out in the sun.

These are not all the side effects you may experience with FACTIVE. If you get any side effects that concern you, call your healthcare provider.

General information about the safe and effective use of FACTIVE: Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use FACTIVE for a condition for which it was not prescribed. Do not give FACTIVE to other people, even if they have the same symptoms that you have. It may harm them. **Keep FACTIVE and all medicines out of the reach of children.**

What are the ingredients in FACTIVE?
Active ingredient: gemifloxacin

Inactive ingredients: crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide.

DATE OF REVISION
AUGUST 2004

FACTIVE is a registered trademark of LG Life Sciences.

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Manufactured for:
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Seoul, Korea

Appendix B:

Medical Officer's Review of NDA 21-376 (4/2002)

Medical Officer's Review of NDA 21-376

Factive® (gemifloxacin mesylate) 320 mg tablet in Acute Bacterial Sinusitis, 5-Day regimen

IDENTIFYING INFORMATION

Applicant identification

GlaxoSmithKline Pharmaceuticals
One Franklin Plaza,
P.O.Box 7929
Philadelphia, PA 19101
Phone: (215) 751-3836
Fax: (215) 751-4926
Contact Person: Edward M. Yuhas, Ph.D.
Associate Director, US Regulatory Affairs

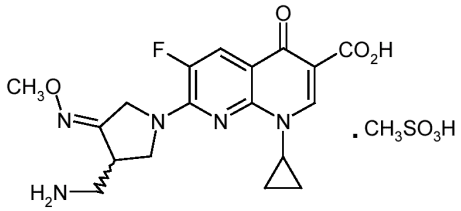
Submission/review dates

Date of submission: June 14, 2001
CDER stamp date: June 14, 2001
Date review begun: December 15, 2001
Date review completed: April 8, 2002
User fee #: 4137

Drug identification

Generic name: gemifloxacin mesylate
Trade name: FACTIVE® Tablets
Chemical name: (±)-7-[3-(aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 7^4 -(Z)-(O-methyloxime), monomethanesulfonate
Other names used during development: SB-265805, LB20304a

Chemical Structure:



Molecular formula: $C_{18}H_{20}FN_5O_4 \bullet CH_4O_3S$
Molecular weight: 485.49
Pharmacologic category: fluoronaphthyridone antimicrobial agent
Dosage form: Tablet
Strength: 320 mg
Route of administration: Oral

CLINICAL REVIEW

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Clinical Review for NDA 21-376

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Factive® (gemifloxacin mesylate) is a fluoronaphthyridone antimicrobial agent, a member of the quinolone class. Factive® was previously reviewed for the indication of acute bacterial sinusitis (ABS) at a dose of 320 mg po daily for 7 days. This previously reviewed 7-day treatment regimen was one of the indications in NDA 21-158. NDA 21-158 received an action of not approvable on December 15, 2000. In NDA 21-158, gemifloxacin was found to have satisfactory evidence in the treatment of ABS at the dose of 320 mg po daily for 7 days. However, the safety profile of gemifloxacin (frequent rash, insufficient information on the potential for cross-sensitization and the potential for more serious dermatologic adverse events including hypersensitivity reactions and the potential for hepatic toxicity, possibly as a result of hypersensitization) prevented a satisfactory benefit risk profile from being attained for gemifloxacin for the indications in NDA 21-158 including the 7-day ABS regimen. The Applicant is gathering additional data to further address these deficiencies and plans to resubmit NDA 21-158.

In NDA 21-376, the Application that is the subject of this review, the Applicant is seeking an indication for the use of gemifloxacin for the treatment of ABS using a 5-day treatment regimen for gemifloxacin (gemifloxacin 320 mg po daily for 5 days) in patients 18 years of age and older. The efficacy data in NDA 21-376 for the 5-day gemifloxoacin regimen provides satisfactory evidence of the efficacy of gemifloxacin 320 mg po daily for 5 days in the treatment of ABS due to *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. GlaxoSmithKline (GSK) is seeking approval for treatment of acute bacterial sinusitis using a 5-day course.

The safety data from the two 5-day sinusitis studies in NDA 21-376 is somewhat limited in scope (one non-comparative study and one study comparing gemifloxacin 5 days vs. gemifloxacin 7 days). NDA 21-376 also cross-references NDA 21-158 which provides a more substantial safety database for gemifloxacin. The review of this larger body of evidence of the safety of gemifloxacin raised concerns regarding the rates of rash observed, especially in pre-menopausal women, the potential for cross-sensitization to other quinolones, the potential for hypersensitivity and more serious dermatologic reactions and hepatic toxicity. While the rates of rash were lower with a 5-day gemifloxacin treatment regimen, the data from NDA 21-376 are not sufficient to address the concerns raised regarding the aforementioned safety issues for gemifloxacin. Concerns still remain regarding the high rates of rash observed with gemifloxacin, cross-sensitization to other quinolone antimicrobials, and the potential for hepatic toxicity, despite the shorter duration of therapy of 5-days in NDA 21-376.

It is the recommendation of the reviewing MO that NDA 21-376 receive an action of **not approvable** because the risks associated with gemifloxacin therapy outweigh its benefits. The notable safety issues that have led to an unsatisfactory risk benefit profile include the following:

- The high rate of gemifloxacin-associated rash.
- The potential for cross-sensitization to other fluoroquinolones.
- The likelihood that the high rate of gemifloxacin-associated rash will result in patients being labeled as "quinolone allergic" resulting in the restriction of the quinolone class of antibiotics as a therapeutic option for individuals exposed to gemifloxacin.
- For the proposed indication of ABS, there isn't an unmet medical need that warrants the risks of gemifloxacin therapy.
- In addition there are concerns that attempts to limit the duration of Factive® therapy may be met with limited success. Therefore realistically the likelihood that patients will receive durations of therapy beyond 5 or 7 days should be considered.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

The MO is recommending an action of not approval for NDA 21-376 as noted in the preceding section "Recommendation on Approvability." Therefore no specific recommendations for postmarketing studies are provided. However, if the Applicant should in the future be able to demonstrate a satisfactory risk/benefit profile for gemifloxacin such that it was approved, the following type of study should be considered: A large safety study to further investigate the adverse events associated with gemifloxacin in an actual use situation. The study should include information on the duration of gemifloxacin therapy, indication of use, patient demographics, patient drug allergy history, along with a detailed description of the adverse event.

While the high rate of gemifloxacin-associated rash is greatest in pre-menopausal women, rates of rash for other patient populations are higher for gemifloxacin than for its comparators. Therefore at the present time, it isn't clear that risk-management strategies could be successfully employed that would effectively mitigate the risks of gemifloxacin-associated rash. No specific risk management strategies are recommended at this time for gemifloxacin in the setting of the MOs recommendation for an action of not approvable for NDA 21-376.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

CLINICAL REVIEW

In NDA 21-376, the Applicant submitted two clinical trials, Study-186 & Study-206, to support treatment of ABS for 5 days. Results of the efficacy and safety of these two studies are summarized in the following sections.

5-day Clinical Program in ABS
Source: NDA 21-376 Vol. 4/17, Table 8G1 p:12

Study	Treatment Regimen	Duration	N*	Geographic Region
186	gemifloxacin 320mg qd gemifloxacin 320mg qd	5 days 7 days	220 203	Europe, Canada
206	gemifloxacin 320mg qd	5 days	469	N. America, Europe, Costa Rica

* N= number of patients randomized (Study 186) or enrolled (Study 206) to treatment

Study-186 was a double-blind, double-dummy, randomized, multicenter, parallel group study. The clinical sites that participated in the study were in Europe and Canada. The total number of patients enrolled was 423 patients (11 patients were excluded from site #246 in The Netherlands after an internal audit by the Applicant called the quality of the data into question). The mean age of patients in the two arms of the study was 40. years, and the majority of patients in the study were White (98%). The primary population of interest was the Clinical Per Protocol population at the Follow-Up visit.

Study-206 was an open-label, multicenter, non-comparative trial. The clinical sites that participated were in the USA, Canada, Costa Rica, and Europe. There were 469 patients enrolled in the study (8 patients were excluded from site #012 in Louisiana, USA after the FDA had initiated disqualification proceedings against the investigator). The mean age of patients was 38 years, and the majority of patients in the trial were White (93%). The primary population of interest was the ITT bacteriology population at Follow-Up (F/U).

B. Efficacy

Study-186 compared 5-day vs. 7-day gemifloxacin for the treatment of acute bacterial sinusitis. This was a double blind, prospective, parallel study. The primary endpoint was Clinical Response at F/U. Gemifloxacin has not been approved for use in the USA. **Study-206** was an open-label study using a 5-day course of gemifloxacin for the treatment of ABS. This study was a bacteriological study that involved sinus puncture aspirates. The primary endpoint in the study was bacteriological response at F/U.

The Applicant submitted two studies under NDA 21-158 (Study-009 & Study-010) to demonstrate the safety and efficacy of 7-day gemifloxacin course for the treatment of ABS. In studies 009 & 010 gemifloxacin demonstrated its efficacy in the treatment of ABS using a 7-day course of gemifloxacin 320 mg po qd. These results supported the Applicants use of the 7-day gemifloxacin regimen as the comparator for the 5-day studies under this current NDA, NDA 21-

376. Of note is the Agency's Points-to-Consider document that stipulates that one of the two studies should establish the superiority or equivalence of the drug under study to an approved product. In this instance the comparator drug is the 7-day gemifloxacin regimen.

Study-186: Summary of Efficacy Results			
	5-day gemifloxacin 320 mg qd	7-day gemifloxacin 320 mg qd	Treatment Difference (95% CI)
Enrolled	N=220	N=203	
Received Medication (ITT)	N=218	N=203	
Withdrawn	N=9 (4.1%)	N=8 (3.9%)	
Clinical PP at F/U	N=181	N=175	
Clinical success	N=158 (87.3%)	N=152 (86.9%)	0.44% (-6.54, 7.41)
Bacteriology ITT	N=20	N=22	
Bacteriology PP at F/U	N=18	N=21	

Although gemifloxacin 320 mg po qd for 7days is not an approved indication for the treatment of ABS, as noted in the non approvable letter for NDA 21-158, sufficient evidence for the efficacy of a 7-day course gemifloxacin was demonstrated.

Study-206: Summary of Efficacy Results		
	5-day gemifloxacin 320 mg qd	Treatment Difference (95% CI)
Enrolled	N=469	
Received Medication (ITT)	N=469	
Withdrawn	N=17 (3.6%)	
Bacteriology ITT	N=236	
Success at F/U	N=203 (86.0%)	(81.59, 90.44)
Bacteriology PP at F/U	N=216	
Success at F/U	N=195 (90.3%)	(86.33, 94.23)
Pathogen Eradication Bacteriology ITT at F/U		
All pathogens	N=236/275 (85.8%)	
S. pneumoniae	N=88/101 (87.1%)	
H. influenzae	N=44/50 (88.0%)	
M. catarrhalis	N=15/15 (100%)	
**S. aureus*	N=9/12 (75%)	

*The criteria in the CDER Draft Guidance for ABS studies requires 10-20 cases of *S. aureus*. On review the Applicant's data included 9 acceptable cases (>10^4 cfu/ml & pure culture) for further review; 4/9 isolates were suggestive of contamination (the 4 isolates were collected at two centers #504 (#206.504.28799/28809 & #503 (#206.503.28767/28769). One sample had no WBCs on microscopy, and 2 isolates from the same center had similar MICs). Therefore the applicant did not meet the necessary criteria for *S. aureus* cases to permit the inclusion of *S. aureus* among the pathogens listed in the ABS indication.

C. Safety

In the integrated summary of safety for NDA 21-376, the Applicant combined all patients in Study-206 with patients who received gemifloxacin for 5 days in Study-186, and reported on safety for the combined cohort of patients which totaled 687 patients. This was compared to the 7-day treatment arm of Study-186 which included a total of 203 patients. The total number of patients analyzed for safety was 890 patients. Adverse events (AEs) were reported for the period of On-Therapy to 30-days post therapy completion. Twenty nine percent (200/687) of patients in the 5-day gemifloxacin treatment arm experienced at least one AE vs. forty percent (82/203) patients in the 7-day gemifloxacin treatment arm. Patients who were suspected to have drug-related AEs were observed in 14% (95/687) of patients in the 5-day treatment group and in 21% (43/203) patients in the 7-day treatment group.

The most common AEs observed in the 5-day group were nausea, diarrhea, dizziness and headache, whereas the most common AEs observed in the 7-day group were nausea, diarrhea, rash, somnolence, and fatigue. Most AEs were graded as either mild or moderate in severity. Six patients were reported to have a serious AE in the 5-day arm, and 1 patient had a serious AE in the 7-day arm. The 5-day arm serious AEs were: serum sickness (This is a confounded case, the patient had positive acute mycoplasma titers. In NDA 21-158 serum sickness was not reported in any of the studied subjects), miscarriage, depression & suicide attempt, high grade fever secondary to pneumonia, viral infection, 2 patients reported injuries (one had a traumatic leg fracture leg and the other had a foreign body in the maxillary sinus). Vertigo that was considered unrelated to the study medication was the only serious AE reported in the 7-day arm. The patient had a history of vertigo prior to enrollment.

AEs related to “skin and appendages” were associated with female gender and age. In Study-186 there were 42 patients who reported a skin and appendage AE. Fourteen of the 42 (33%) patients were in the 5-day treatment arm and 28 (67%) patients in the 7-day treatment arm. Most patients with skin and appendage AEs were in the age group 30-46. Of the 42 patients 29 (69%) were females.

In Study-206 there were 20 AEs related to the skin and appendages. These events occurred in 15 female (75%) and 5 male patients. Fifty percent of these AEs occurred in subjects between the ages of 20-27 years of age. Phototoxicity reactions were not reported in patients who received gemifloxacin.

Five patients in the 5-day arm reported a severe AE, one patient reported dermatitis related to study drug. Six patients in the 7-day arm reported a severe AE, 3 of which had a skin & appendage related AE.

Laboratory abnormalities classified as AEs were uncommon during the study. A few patients with normal baseline laboratory values showed mild liver function changes (elevation <3X normal levels) during the study. The safety review for NDA 21-158 indicates that the potential for liver injury is possible following exposure to gemifloxacin. Elevation in liver enzymes was observed when patients were treated with gemifloxacin 640 mg for urinary tract infection.

Although the applicant is requesting gemifloxacin 320 mg po qd for 5-days, the potential risk of liver injury may be higher in patients with liver and renal dysfunction. There were no clinically significant renal function (BUN/Creatinine) abnormalities. Clinically significant hematologic abnormalities were infrequent; the most common change from baseline was an increased platelet count or low hemoglobin. There were no hypoglycemic events noted and none of the patients experienced a "temafloxacin syndrome". Two patients in total had an elevated CPK suspected to be related to gemifloxacin use. The safety review for NDA 21-158 did not identify any trends related to hemoglobin levels, platelet count, CPK values, or serum glucose levels in patients who received gemifloxacin vs. the comparators. EKGs were not performed in Studies 186 and 206 to look for QT interval effects.

Seven of the 890 patients from both studies were withdrawn. One patient from the 7-day treatment group had vertigo which was unrelated to the study drug, the other patients were in the 5-day arm (2 patients had an elevated baseline bilirubin level, 1 patient had a leg fracture, 1 patient had a rash, 1 patient had high grade fever later diagnosed with pneumonia, and one patient had nausea and gastritis).

Although the safety data for the 5-day course of gemifloxacin 320 mg did not show an increased rate of AEs, the MO is concerned that the occurrence of an increased rate of rash that could herald serious dermatologic AEs and the occurrence of increased liver toxicity that was observed in NDA 21-158. These events could occur in the population at large, at a higher rate than observed in the setting of a clinical trial. It is also likely that the use of gemifloxacin would result in more frequent drug associated AEs (e.g., gemifloxacin associated rash) leading to patients being labeled as "quinolone allergic" and removing quinolones from the therapeutic armamentarium for such individuals. It is the opinion of the MO that the risk/benefit ratio for gemifloxacin does not justify its approval for the 5-day course of therapy in the treatment of ABS.

D. Dosing

The proposed dose of gemifloxacin for Acute Bacterial Sinusitis is gemifloxacin 320 mg po qd for five days, taken with or without food.

E. Special Populations

The use of gemifloxacin in special populations is discussed under section IX of this review. In summary more than 95% of subjects enrolled in NDA 21-376 were white and more than 90% were in the age group 18-65 years of age. Thirteen patients in the 5-day arm were 16-18 years of age, one AE was reported in that group. The 5-day arm included 39 patients ≥65 years of age, 12 of those patients reported an AE. The 7-day arm included 9 patients ≥65 years of age, 6 of those patients reported an AE. Due to the small numbers of patients between the ages of 16-18 and ≥65 years in NDA 21-376, the Applicant was unable to provide a meaningful analyses of age-related

differences. Data from NDA 21-158 included over one thousand patients ≥65 years of age. The reader is referred to NDA 21-158 for details of these analyses.

Currently the proposed labeling for gemifloxacin is Pregnancy category C. Pregnant or nursing women were excluded from the sinusitis studies. Patients with mild baseline abnormalities in liver and renal function were allowed to enroll in the sinusitis studies. Although, the Applicant reported that patients with liver dysfunction at baseline were more likely to report an AE during the On-Therapy plus 30 days post-therapy (29%, 200/687), the proportion of patients with AEs was less than the proportion of patients reported in NDA 21-158 (63%, 67/107).

The proposed labeling that the Applicant submitted recommends no change in dosage for patients with mild or moderate hepatic impairment. Modification of the dosage is recommended for patients with creatinine clearance <40 mL/min.

Clinical Review

I. Introduction and Background

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

Text in the Arial font is copied verbatim from the Applicant's submission

Factive® (gemifloxacin mesylate) is a fluoronaphthridone compound, a member of the quinolone class of antibacterial agents. The applicant, GlaxoSmithKline (GSK) is seeking marketing approval for gemifloxacin 320 mg orally once daily for 5 days for the treatment of Acute Bacterial Sinusitis (ABS) under NDA 21-376. Gemifloxacin is not currently approved for any indication in the USA. A separate NDA, NDA 21-158, was submitted in 1999 for Factive® (gemifloxacin) for the indications of:

Acute Bacterial Exacerbation of Chronic Bronchitis (AECB)
Acute Bacterial Sinusitis (ABS)
Community Acquired Pneumonia (CAP)
Uncomplicated Urinary Tract Infections (UTI)
Acute Pyelonephritis (AP)

The Applicant received a non approvable letter for all of the requested indications for NDA 21-158 on December 15, 2000. The issues cited in the non approvable letter were:

- Insufficient information about gemifloxacin's potential risks that are posed by the increased incidence of rash.
- Evidence of potential liver toxicity when gemifloxacin was used at dosages exceeding 320 mg.
- The application did not have adequate information to support the indication for Acute Pyelonephritis.
- The application did not include sufficient numbers of Penicillin Resistant *S. pneumoniae* isolates to support labeling for the indications of CAP, ABS or AECB.
- The application did not include additional studies that would support labeling for "severe CAP."
- A Macrolide-Resistant *S. pneumoniae* (MRSP) labeling claim may not convey a meaningful public health benefit, and therefore there is insufficient evidence to justify the approval of a labeling claim for MRSP.
- The Agency provided the Applicant with a revised list of breakpoints for

S. pneumoniae and *H. influenzae* that would be used in the label.

Proposed Labeling (Indications and Usage, Dosage and Administration, Special Populations Sections For ABS) for FACTIVE® (gemifloxacin mesylate) tablets:

INDICATIONS AND USAGE

Factive is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Acute bacterial sinusitis caused by *Streptococcus pneumoniae* (including clarithromycin-resistant strains); *Haemophilus influenzae; Moraxella catarrhalis; Klebsiella pneumoniae, Staphylococcus aureus.*

DOSAGE AND ADMINISTRATION

Factive can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of *Factive* is 320 mg daily, according to the following table.

INDICATION	DOSE	DURATION
Acute bacterial sinusitis	One 320 mg tablet daily	5 days

Pregnancy: Teratogenic Effects. Pregnancy Category C. Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing), rats (oral dosing) and rabbits (IV dosing) at AUC levels that were 1.8, 4.4 and 3.4-fold those in women given oral doses of 320 mg. In rats, this growth retardation appeared reversible (mice and rabbits were not studied for the reversibility of this effect). Treatment of pregnant rats at 8.8-fold clinical exposure (oral dosing) caused maternal toxicity and fetal brain and ocular malformations. The overall no-effect exposure level in pregnant animals was 0.8 to 2.6-fold the average clinical exposure.

The safety of gemifloxacin in pregnant women has not been established. Gemifloxacin should not be used in pregnant women unless the potential benefit to the mother outweighs the risk to the fetus.

Nursing Mothers

Gemifloxacin is excreted in the breast milk of rats. There is no information on excretion of gemifloxacin into human milk. Therefore, gemifloxacin should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

Pediatric Use

Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including gemifloxacin, cause arthropathy in immature animals. (See **WARNINGS**)

Geriatric Use

Of the total number of subjects in clinical studies of gemifloxacin, 29% (1127) were 65 and over, while 11% (439) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

B. State of Armamentarium for Indication(s)

Text in the Arial font is applied verbatim from the PDR

A number of antibiotics are approved for the indication of ABS. The length of therapy for ABS may vary by agent, but has traditionally been 10-14 days. Courses of antibiotics shorter in duration than the traditional 10-14 day course may provide better compliance and similar efficacy; however, the benefits of shorter courses are not clear in light of the fact that most patients (~69%) with ABS note symptomatic improvement on their own in the absence of antimicrobial therapy[1] .

CIPRO (ciprofloxacin tablets, suspension, intravenous)

INDICATIONS AND USAGE

CIPRO® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

[1] AHCPR. Diagnosis and treatment of acute bacterial rhinosinusitis. Rockville (MD): Agency for Health Care Policy and Research; 1999. (This study is a pooled meta-analysis of English-language articles indexed in Medline from 1966 to May 1998)

Acute Sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae,* or *Moraxella catarrhalis.*

LEVAQUIN (levofloxacin tablets, injection)

INDICATIONS AND USAGE

LEVAQUIN Tablets/Injection are indicated for the treatment of adults (>/=18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. LEVAQUIN Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Acute maxillary sinusitis due to *Streptococcus pneumoniae* , *Haemophilus influenzae* , or *Moraxella catarrhalis.*

AVELOX (moxifloxacin tablets)

INDICATIONS AND USAGE

AVELOX Tablets are indicated for the treatment of adults (>/= 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.
Acute Bacterial Sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*

TEQUIN (gatifloxacin tablets, injection)

INDICATIONS AND USAGE

TEQUIN (gatifloxacin) is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below. (See DOSAGE AND ADMINISTRATION.)
Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenza*e.

CEFTIN (cefuroxime axetil tablets)

INDICATIONS AND USAGE

NOTE: CEFTIN TABLETS AND CEFTIN FOR ORAL SUSPENSION ARE NOT BIOEQUIVALENT AND ARE NOT SUBSTITUTABLE ON A MG/MG BASIS (SEE CLINICAL PHARMACOLOGY **).**

CEFTIN Tablets: CEFTIN Tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:
Acute Bacterial Maxillary Sinusitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (non-beta-lactamase-producing strains only). (See CLINICAL STUDIES section.)
NOTE: In view of the insufficient numbers of isolates of beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* that were obtained from clinical trials with CEFTIN Tablets for patients with acute bacterial maxillary sinusitis, it was not possible to adequately evaluate the effectiveness of CEFTIN Tablets for sinus infections known, suspected, or considered potentially to be caused by beta-lactamase-producing *Haemophilus influenzae* or *Moraxella catarrhalis* .

LORABID (loracarbef capsules, suspension)

INDICATIONS AND USAGE

Lorabid is indicated in the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.
Acute Maxillary Sinusitis † caused by *S. pneumoniae, H. influenzae* (non-(beta)-lactamase-producing strains only), or *M. catarrhalis* (including (beta)-lactamase-producing strains). Data are insufficient at this time to establish efficacy in patients with acute maxillary sinusitis caused by (beta)-lactamase-producing strains of *H. influenzae.*

†NOTE: In a patient population with significant numbers of (beta)-lactamase-producing organisms, loracarbef's clinical cure and bacteriological eradication rates were somewhat less than those observed with a product containing a (beta)-lactamase inhibitor. Lorabid's decreased potential for toxicity compared to products containing (beta)-lactamase inhibitors along with the susceptibility patterns of the common microbes in a given geographic area should be taken into account when considering the use of an antimicrobial (*see* CLINICAL STUDIES section).

VANTIN (cefpodoxime proxetil tablets, suspension)

INDICATIONS AND USAGE

Cefpodoxime proxetil is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.
Acute maxillary sinusitis caused by *Haemophilus influenzae* (including beta-lactamase producing strains), *Streptococcus pneumoniae* , and *Moraxella catarrhalis* .

CEFZIL (cefprozil tablets, suspension)

INDICATIONS AND USAGE

CEFZIL (cefprozil) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:
Acute Sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including (beta)-lactamase-producing strains) and *Moraxella (Branhamella) catarrhalis* (including (beta)-lactamase-producing strains).

OMNICEF (cefdinir capsules, suspension)

INDICATIONS AND USAGE

OMNICEF (cefdinir) capsules and OMNICEF (cefdinir) for oral suspension are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.
Acute Maxillary Sinusitis caused by *Haemophilus influenzae* (including (beta)-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including (beta)-lactamase producing strains).

BIAXIN (clarithromycin tablets, suspension)

INDICATIONS AND USAGE

BIAXIN Filmtab tablets and BIAXIN Granules for oral suspension are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions as listed below:

Adults (BIAXIN Filmtab tablets and Granules for oral suspension):

Acute maxillary sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

AUGMENTIN (amoxicillin/clavulanate potassium)

INDICATIONS AND USAGE

Augmentin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Sinusitis--caused by (beta)-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*

AMOXIL (amoxicillin capsules, tablets, chewable tablets, suspension)

INDICATIONS AND USAGE

Amoxil (amoxicillin) is indicated in the treatment of infections due to susceptible (ONLY (beta)-lactamase-negative) strains of the designated microorganisms in the conditions listed below:
Infections of the ear, nose, and throat due to *Streptococcus* spp. ((alpha)- and (beta)-hemolytic strains only), *Streptococcus pneumoniae, Staphylococcus* spp., or *H. influenzae*

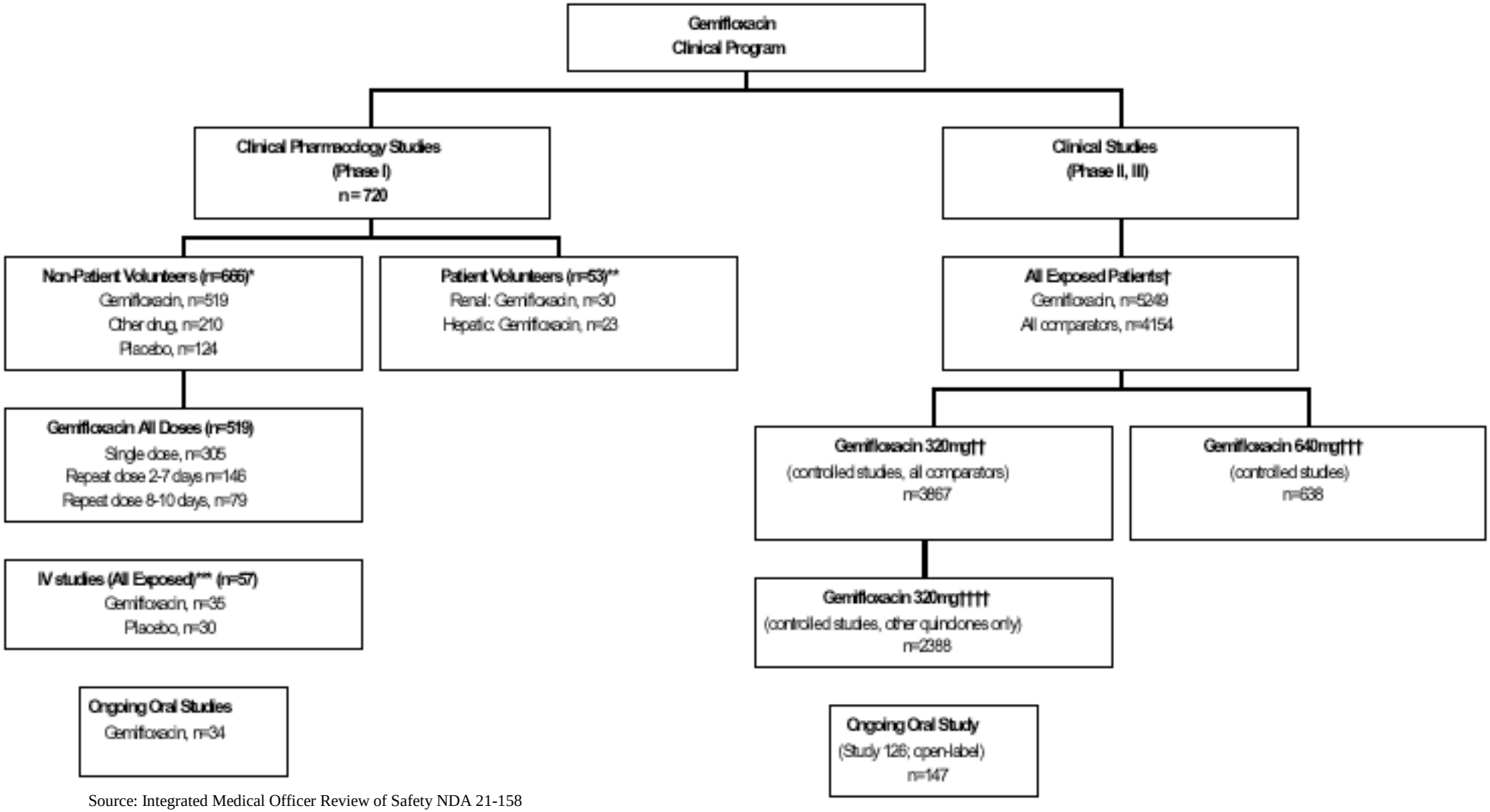
C. Important Milestones in Product Development

Initial manufacturing and analysis of gemifloxacin was carried out by LG Chemical Ltd. (Teajon, Korea). The gemifloxacin drug formulation was a racemic mixture of *d*- and *l*-isomers either as free base or the mesylate salt. Both enantiomers are active *in-vitro* against gram-positive bacteria. In June 24, 1997 a pre-IND meeting took place between the FDA and GSK, which led to the submission of IND 53-908 on August 6, 1997. The proposed discussed indications in the submission were for acute exacerbation of chronic bronchitis (AECB), sinusitis (ABS), community acquired pneumonia (CAP), urinary tract infections (UTI) and skin and soft tissue infections.

On December 15, 2000 the Applicant submitted NDA 21-158 requesting gemifloxacin use in: acute exacerbation of chronic bronchitis (AECB), acute bacterial sinusitis (ABS), community acquired pneumonia (CAP), acute pyelonephritis and uncomplicated urinary tract infections (UTI).The submission received a not approvaable letter dated December 15, 2000. The letter cited **a)** clinical safety deficiencies, which included the potential risks posed by the high incidence of rash in the clinical trials, liver toxicity at doses of gemifloxacin that exceeded 320 mg, **b)** clinical efficacy deficiencies for the indication of Acute Pyelonephritis, **c)** labeling issues concerning Community Acquired Pneumonia (duration of therapy for longer than 7 days, Penicillin-Resistant *S. pneumoniae* (PRSP) and Macrolide-Resistant *Streptococcus pneumoniae* claims) and setting breakpoints for *S. pneumoniae* and *Hemophilus* species. NDA 21-376 was submitted on June 14, 2001 for the indication of ABS using a 5-day course of gemifloxacin.

The clinical programs from NDA 21-158, including the number of patients enrolled in each study to evaluate the safety of oral gemifloxacin, are illustrated in **Figure-2**. In summary, approximately 9000 patients were enrolled in 14 clinical studies (>5200 patients received gemifloxacin, of those, around 3900 patients received the 320 mg dose and 640 patients received the 640 mg dose). The comparator agents used in the studies in NDA 21-158 included beta-lactams (penicillins & cephalosporins), macrolides (clarithromycin), and quinolones (levofloxacin, trovafloxacin,ciprofloxacin, and ofloxacin). A minority of patients received more than 10 days of study drug.

Figure 2 Summary of Clinical Program to Evaluate Safety of Oral Gemifloxacin (cut off: 9/30/99)



Source: Integrated Medical Officer Review of Safety NDA 21-158

The ABS indication in NDA 21-158 is for gemifloxacin 320 mg once daily for 7 days. There were two clinical studies in NDA 21-158 that examined the efficacy of gemifloxacin in ABS. Study-009 examined gemifloxacin 320 mg once daily for 7 days versus cefuroxime axetil 250 mg twice daily for 10 days. Study-010 examined the efficacy of gemifloxacin 320 mg once daily for 7 days compared to trovafloxacin 200 mg once daily for 10 days. Study-010 was a clinical study conducted abroad, and Study-009 was a microbiological study conducted abroad and in the USA. Table-3 lists the major characteristics of both trials.

Table-3 Acute Bacterial Sinusitis: Principal Studies

Study	Treatment Regimen	Duration	N*	USA (n)	Geographic Region
Principal controlled studies (randomized, double blind, double dummy, and parallel group)					
009[a] 62 centers	gemifloxacin 320mg po qd	7 days	338	(147)	N. America, Europe
	cefuroxime axetil 250mg po bid	10 days	339	(144)	
010 74 centers	gemifloxacin 320mg po qd	7 days	202	(0)	Europe
	trovafloxacin 200mg po qd	10 days	200	(0)	

* N= number of patients randomized to treatment

[a] In Study 009, patients underwent sinus puncture with aspiration for culture at screening

Adapted from Applicant's Table 8.G.49 from NDA 21-158, Vol. 1.8.095, p. 133.

Source: Tables 3,4,5 were taken verbatim from Medical Officers Review for NDA 21-158, Acute Bacterial Sinusitis Indication

Studies 009 & 010, both demonstrated non-inferiority of gemifloxacin 320 mg po qd for 7 days to its comparators at the test-of-cure visit (day 17 to 24). Study-009 also found that patients treated with gemifloxacin had equivalent rates of Bacterial Response – a secondary endpoint – as the comparator cefuroxime axetil Table-4.

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Table-4 Clinical and Bacteriological Response at Follow-Up: Principal ABS Studies 009 and 010 (NDA 21-158)

Adapted from NDA 21158

	Study 009		Study 010	
	Gemifloxacin 320 mg po qd (7 days)	**Cefuroxime 250 mg po bid (10 days)**	**Gemifloxacin 320 mg po qd (7 days)**	**Trovafloxacin 200 mg po qd (10 days)**
Clinical PP Follow-Up				
N	284	296	158	162
Success, n (%)	249 (87.7)	263 (88.9)	143 (90.5)	148 (91.4)
Failure, n (%)	35 (12.3)	33 (11.1)	15 (9.5)	14 (8.6)
Treatment difference, %*	-1.2		-0.9	
95% CI	-6.4, 4.1		-7.1, 5.4	
Bacteriological Response PP Follow-Up (Per Patient)**				
N	138	141	13	15
Success, n (%)	129 (93.5)	290 (93.6)	11 (84.6)	13 (86.7)
Failure, n (%)	9 (6.5)	9 (6.4)	2 (15.4)	2 (13.3)
Treatment difference, %*	-0.1		-2.1	
95% CI	-5.9, 5.6		-28.1, 24.0	

* Gemifloxacin minus comparator.

** In Study 010, only patients at study centers in France underwent sinus endoscopic culturing at Screening. This was done at the request of the French Regulatory Authorities. (Note: bacteriology in Study 009 was determined by maxillary sinus puncture at Screening)

In addition, Study-009 provided the microbiologic data in support of the ABS indication Table-5. Note that there was sufficient clinical evidence of activity for *S. pneumoniae* and *H. influenza* only. The study did not provide sufficient evidence of clinical activity to support *K. pneumoniae, S. aureus, M. catarrhali*s, and penicillin-resistant *S. pneumoniae*.

Table 5. Pre-Therapy Pathogens Eradicated or Presumed Eradicated at Follow-Up: Principal ABS Study 009

	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin 320 mg po qd		Cefuroxime 250 mg po bid		Gemifloxacin 320 mg po qd		Cefuroxime 250 mg po bid	
Follow-Up	**N=138**		**N=141**		**N=165**		**N=156**	
	n/N*	**%**	***n/N****	**%**	***n/N****	**%**	***n/N****	**%**
All Pathogens	142/153	(92.8)	144/155	(92.9)	157/185	(84.9)	152/173	(87.9)
S. pneumoniae	54/55	(98.2)	54/58	(93.1)	58/66	(87.9)	57/64	(89.1)
H. influenzae	27/29	(93.1)	31/31	(100.0)	29/37	(78.4)	33/36	(91.7)
K. pneumoniae	13/15[a]	(86.7)	17/18	(94.4)	15/18	(83.3)	18/19	(94.7)
S. aureus	14/15[b]	(93.3)	8/9	(88.9)	14/17	(82.4)	8/11	(72.7)
M catarrhalis	7/7	(100.0)	6/6	(100.0)	9/9	(100.0)	6/6	(100.0)

Adapted from Applicant's Table 8.G.60 from NDA 21-158, Vol. 1.8.095, p.155.
Note: failures at end of therapy are carried forward into the follow-up analysis by applying the following algorithms:
(1) failures and 'unable to determines' at end of therapy are added to the denominator at follow-up
(2) successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.
* *n/N* = number of pathogens eradicated or presumed eradicated / number of pathogens.
** Bacteriology PP population at follow-up.

MO Comment: [a] All but one of the *K. pneumoniae* isolates were derived from a single center where 85% of the patients had *K. pneumoniae* isolated – contamination is a likely explanation for this unique finding
[b] Only 10 of the *S. aureus* isolates were in pure culture at a quantity of 10^4 cfu/mL, only 4 of these 10 patients had WBCs at a quantity of moderate or greater on gram stain. Three of these 10 patients had symptoms of less than 7 days duration.

Regulatory Guidance for the Indication of Acute Bacterial Sinusitis

IDSA/FDA[2]

Guidelines for conducting clinical trials to treat ABS were developed in 1992. Under these guidelines, patients included in clinical trials of ABS should meet the following criteria:

- Clinical criteria to support diagnosis of ABS such as fever, headache, malar tenderness, nasal discharge, and symptoms lasting < 4 weeks.
- Localizing studies to support clinical findings such as radiography, ultrasonography, or CT.
- Microbiologic criteria established through direct aspiration or injection wash of the sinus cavity.

The guidelines recommend performing two clinical trials in ABS. One study should involve sinus aspiration or wash in all patients enrolled. In addition, the study should provide specific microbe identification for at least 20 cases each of the major pathogens isolated in ABS (*S. pneumoniae, H. influenzae, and M. catarrhalis*). In the second study, sinus aspirate and radiography are not required but are strongly recommended for all patients who fail to have an adequate clinical response. Patients should be followed up clinically and with one of the

[2] Chow AW, et al., General guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Clinical Infectious Diseases 1992;15(Suppl):S62-S88.

imaging studies suggested earlier for at least 2 weeks after completion of study drug treatment.

Points to Consider Document (PTC)[3]

The PTC document recommends two clinical studies. The first study should establish equivalence or superiority to an approved product using rigorous case definitions and specific clinical and imaging entry criteria and endpoints as the primary effectiveness parameters. A sinus puncture is not required unless a patient is judged a therapeutic failure. It is preferable that this study is performed in the USA.

A second study performed as an open-label trial would include microbiology flora from sinus puncture aspirates to establish successful microbial, clinical, and imaging outcomes in at least 100 patients. As a minimum, the study should establish successful outcomes in at least 25 patients with *S. pneumoniae*, 25 patients with *H. influenzae*, and 15 patients with *M. catarrhalis*. Similar to the first study, a sinus puncture aspirate is strongly recommended in those patients that fail to respond to treatment and are judged to be therapeutic failures. This study may be performed by at least two investigators in different geographic regions, and the total contribution by any one center should not exceed 55% of evaluable patients. The PTC also recommends a "restricted" listing as "not a product for first line therapy" if the study drug failed to eradicate the major bacterial pathogens associated with ABS. The rational for this restriction is based on the nature of empiric treatment for ABS and the need for true first-line therapies to be efficacious against the major bacterial pathogens of ABS.

FDA\CDER Draft Guidance on ABS

In 1998, CDER produced an ABS Draft Guidance Document for industry on developing antimicrobial agents for the treatment of ABS. The recommendations in the Draft Document are similar to the IDSA/FDA guidelines whereby two clinical trials should be performed. One study should be a statistically adequate and well-controlled multicenter trial that uses rigorous case definitions and imaging criteria to establish study eligibility and endpoint outcomes. Inclusion criteria for the study are a clinical diagnosis of ABS (signs & symptoms lasting longer than 7 days but less than 28 days). Patients with a history of allergic rhinitis should be identified upon entry so that they may be analyzed separately. Sinus puncture is not a requirement for this study. Patients are required to attend at least an entry visit, on-therapy visit, and a post-therapy (Test-of-Cure) visit 1-2 weeks after completion of therapy. The Test-of-Cure visit should include a clinical evaluation and an imaging study similar to what was used at study entry. Clinical failures are identified as non-responders after 72 hours of therapy and require a sinus puncture study to document bacterial pathogens not adequately treated in the trial.

[3] http://www.fda.gov/cder/guidance/infections.htm#sinusitis.

A second study that includes clinical and imaging criteria similar to the first study should be conducted in at least 100 patients; however, this study should include a sinus aspirate for all patients at study entry. The purpose of this study is to measure clinical, imaging, and microbial outcomes. The Draft Guidance recommends the following numbers of bacterial pathogens as a minimum to establish the efficacy of an antimicrobial in the treatment of ABS:

H. influenza >25 patients
S. pneumoniae >25 patients
M. catarrhalis >25 patients
S. aureus >10 patients (pathogen in ABS when bacterial count is $\geq 10^4$ CFU/ml, and isolated in pure culture).

In addition, documentation for microbiological diagnosis should include a Gram stain of the sinus aspirate looking at bacterial morphology, WBC's, semiquantitative, quantitative bacterial cultures, and antimicrobial susceptibility testing.

D. Other Relevant Information

Factive® has been approved in New Zealand, but the Applicant has not marketed the in New Zealand as of March 25, 2002. GSK has applications pending in other countries. Human clinical experience with gemifloxacin is limited to NDA clinical studies. There is no post-marketing experience to report on for gemifloxacin at this time.

E. Important Issues with Pharmacologically Related Agents

Safety related concerns for the quinolones include their adverse effects that may be related to a class event or may be peculiar to each agent. Examples of class effect is the occurrence of QT interval changes, potential for phototoxicity, tendon related disorders; where as agent related AEs include "temafloxacin syndrome", liver failure as noted with trovafloxacin, dysglycemic reactions observed with gatifloxacin use. For a more comprehensive review the reader is referred to Section IV-D of this review. Other potential concerns relate to class overuse leading to acquisition of resistance by bacteria.[4]

[4] Chen D, et al. The Canadian Bacterial Surveillance Network: Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N Engl J Med 1999;341:233-9.

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

Chemistry/Manufacturing and Controls: Please refer to Dr. Milton Sloan's Chemist Review of NDA 21-158, and NDA 21-376.

Pharmacology/Toxicology: Please refer to Dr. Stephen Hundley's Pharmacology Review of NDA 21-158 (nonclinical metabolism and pharmacokinetics) and Dr. Amy Ellis's review (Dr. Ellis is the primary pharmacology/toxicology reviewer of studies submitted in support of NDA 21-158).

Repeat dose toxicity studies in rats revealed crystal nephropathy in the distal and collecting tubules with evidence of inflammatory cells, Dog studies also revealed an inflammatory cell infiltration consistent with a diagnosis of cholangitis/pericholangitis. In hairless mice gemifloxacin was less potent than other quinolones tested at inducing phototoxicity.

Microbiology: Please refer to Dr. Peter Dionne's Microbiology Review for NDA 21-158, and NDA 21-376. Gemifloxacin has lower MICs against *S. pneumoniae* compared to other quinolones; however, at the recommended human dose gemifloxacin's AUC value is only about ¼ that of most other quinolones. This effect largely counter balances the drug's lower MICs. Similarly, gemifloxacin exhibits lower MICs for most gram-positive bacteria, but again these lower MICs are largely offset by the correspondingly lower MICs attained by gemifloxacin.

In one animal study, gemifloxacin efficacy was studied in an experimentally induced pulmonary infection with different *S. pneumoniae* or *H. influenzae* strains. Some of these strains exhibited quinolone resistance and it was observed that gemifloxacin therapy (dosing and time of initiation) had to be altered in order to achieve similar outcomes to when fully quinolone susceptible strains were used.

The activity of gemifloxacin against gram-negative enteric organisms is, at best, equivalent to most other quinolones and during treatment some species may have MIC_{90} values above achievable serum or tissue levels of the drug. Therefore gemifloxacin activity against gram-negative enteric rods is borderline at best. Gemifloxacin has good activity against gram-negative respiratory tract pathogens (i.e. *H. influenzae* and *M. catarrhalis).* Gemifloxacin has poor activity against most anaerobes.

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III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

All clinical pharmacology studies were previously submitted in NDA 21-158. No new pharmacokinetic issues were raised in NDA 21-376. The clinical data supporting this new 5-day course for ABS was filed under NDA 21-376.

A brief summary of the pharmacokinetic data from NDA 21-158 follows. After a repeated daily dose of gemifloxacin 320 mg, the absolute tablet bioavailability is 71%, mean Cmax was 1.6 ± 0.51 μg/ml, AUC(0-24) was 9.9 ±3.1 μg●hr/ml. The mean plasma T ½ at steady-state in adults for gemifloxacin is 7 ±2 hr. Food has no appreciable effect on absorption. Gemifloxacin is 60-70% protein bound. It is minimally metabolized by the liver (<10%) and is excreted mostly unchanged in the urine 30-40% and feces 60%.

Patients with impaired renal function (CrCL is < 40 mL/min) require a dose adjustment to 160 mg q24 hr; this includes patients on hemodialysis or CAPD. No change in dose is required for patients with mild or moderate liver disease. Adequate data is not currently available to provide recommendations for dosing in patients with severe liver disease. Age, gender, and body weight have no effect on PK. Similar to the other quinolones, coadministration of gemifloxacin with antacids and other cationic products significantly reduces the oral bioavailability of gemifloxacin. When gemifloxacin is coadministered with probenecid, renal clearance of gemifloxacin is significantly reduced.

B. Pharmacodynamics

No new pharmacodynamic issues were raised with this supplement. All clinical pharmacology studies were previously submitted in NDA 21-158. A brief summary of pharmacodynamic data from NDA 21-158 follows. Phase II studies of gemifloxacin using different dose regimens in humans (80 mg, 160 mg, 320 mg once daily) provided evidence to support the 320 mg qd dose. These Studies (Study-001 & Study-002) are briefly described.

Study-001: gemifloxacin 80 mg, 160 mg, 320 mg once daily was compared to ofloxacin in the treatment of acute exacerbation of chronic bronchitis (AECB). Although the three dosages of gemifloxacin were equally effective as the comparator with regards to clinical efficacy, bacteriological efficacy was superior in the 320 mg dose.

Study-002: gemifloxacin 160 mg and 320 mg once daily were compared to a quinolone comparator for the treatment of uncomplicated skin & skin structure infections. Although the 320 mg dose of gemifloxacin demonstrated higher

clinical success the study was under powered and the results were inconclusive. The Applicant's rationale for selecting 320 mg in phase III trials was based upon results of microbiology and clinical studies in conjunction with known PK parameters in humans and susceptibility tests *in vitro*.

IV. Description of Clinical Data and Sources

A. Overall Data

GSK's submission for NDA 21-376 included 17 volumes. The NDA was also available electronically through the EDR and includes the data sets as SAS transport files.

B. Tables Listing the Clinical Trials

Overview of studies submitted for NDA 21-376

Study	Type of study	Dose	*N	Geographic region
186	Randomized, double-blind, double-dummy, parallel group	Gemifloxacin 320 mg qd X 7 days Gemifloxacin 320 mg qd X 5 days	203 220	Europe, Canada
206[a]	Open-label, single group	Gemifloxacin 320 mg qd X 5 days	469	N. America, Europe, Costa Rica

*N= number of patients randomized to treatment

[a] In study 206, patients underwent sinus puncture with aspiration for culture at screening

Adapted from Study 186, Table 10.01; Study 206, Table 10.01

***MO Comment**: Studies 009 & 010 under NDA 21-158 were used by the applicant to establish the efficacy for gemifloxacin 320 mg po qd for 7 days for the treatment of ABS and to use the gemifloxacin 7-day course as the comparator for Study-186.*

C. Postmarketing Experience

As of February 27, 2002 gemifloxacin has been approved in New Zealand, but GSK has chosen not to market gemifloxacin in New Zealand. GSK is waiting for approval in additional regions before initiating marketing. Human clinical experience with gemifloxacin is limited to NDA clinical studies. There is no post-marketing experience to report on for gemifloxacin at this time.

D. Literature Review

Literature review on safety:

The following is a synopsis of quinolone related adverse effects[5,6] :

- Dermatologic: rash, photosensitivity, urticaria, pigmentation
- Temafloxacin/HUS syndrome: fever, chills, hemolysis, renal dysfunction, coagulopathy
- Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea, anorexia
- Hepatic: liver enzyme abnormalities, hepatitis, jaundice, hepatic failure
- Renal: azotemia, crystalluria, hematuria, nephritis, renal failure
- Musculoskeletal: arthropathy, tendon disorders including rupture
- Arthropathy – juvenile animals
- Cardiovascular: QT prolongation and ventricular arrhythmias, hypotension
- Metabolic: dysglycemic reactions
- CNS: seizures, dizziness, sleep disturbances, headaches, mood changes, confusion, psychosis
- Drug interactions

V. Clinical Review Methods

A. How the Review was Conducted

NDA 21-376 included two clinical studies in ABS. Both were reviewed in detail. The efficacy data from each study was reviewed separately. The analyses are reviewed under section VI-C of this review. The section of the review addressing Safety (Section VII) describes the combined safety data for Study-186 & Study-206.

The available electronic case report forms and narratives were reviewed when the MO needed more information about a patient in relation to understanding clinical events, ineligibility, unevaluability, or/and verifying data in context of the study. A random sample of 20% of cases from Study-186 and 10% of cases from Study-206 were reviewed to validate and evaluate patient data as described in the Applicant's submission. The MO reviewed inclusion, exclusion criteria, patient assessments, evaluability, and outcomes and found only minor differences that did not affect the overall conclusions from the Applicant's analyses. Because there were only minor differences in the assessment of the random samples, and these minor differences were unlikely to affect the conclusions from the data, the Applicant's analyses were accepted. The analyses and tabulations that follow are derived from the Applicant's study report. The MO conducted additional exploratory analysis to address questions that arose during the review of the NDA.

[5] Blum MD, Graham DJ. Temafloxacin Syndrome. Clinical Infectious Diseases 1994;18:946-950.
[6] Lipsky BA, Baker CA. Flouroquinlone Toxicity Profiles: A Review Focusing on Newer Agents. Clinical Infectious Diseases 1999;28:352-364.

B. Overview of Materials Consulted in Review

- Electronic NDA 21-376 submission folders.
- NDA 21-376 Division File Documents
- NDA 21-158 Division File Documents
- IND 53-908 Volume 1/18
- MO Reviews in IND 53-908, and for indication of ABS in NDA 21-158

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Data from two sites were excluded from the study. The first site was in the Netherlands (Dr. Passage), an internal audit conducted by the applicant found the data from that site unreliable. The other site is in Louisiana (Dr. Deabate), the Agency considered the data from that site unsuitable for inclusion due to protocol violations (NIDPOE letter issued 4/13/01).

During the conduct of Study-206, the applicant conducted an audit of specific investigator sites (centers: 042 Fresno USA, 501 Budapest Hungary, 605 Krakow Poland). The audits were carried out by Worldwide Regulatory Compliance-GCP a GSK independent division that monitors compliance of clinical trials conducted by GSK.

DSI inspection: On March 13, 2002 Dr. Jose Carreras from the FDA's Bioresearch Monitoring Program submitted a letter confirming the favorable inspection of two clinical sites related to NDA 21-376. The sites inspected were in Corpus Christi, Texas (principal investigator was Dr. Cesar A. Albarracin) and in Fresno, California (principal investigator was Dr. Sudeep Singh).

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Studies 206 & 186 were conducted in accordance to accepted ethical standards. Both trials used an informed consent form that had to be signed prior to any patient receiving the study medication. The applicant carried out the trials under accepted international standards that protect human subjects from undue harm during the conduct of clinical studies. The Applicant's field monitors obtained written IRB approvals from all study sites at the time of study initiation.

E. Evaluation of Financial Disclosure

The Applicant's Certificate of Financial Disclosure is in accordance with the Agency regulations 21 CFR 54.2. There were 7 investigators who did not complete the Financial Disclosure form, despite due diligence exerted by the Applicant. Four investigators from Study-206 disclosed a financial interest in GSK (Retirement plan, Stock in a group pension/profit sharing plan). There was no evidence that the investigators with a financial interest biased the data results.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The Applicant submitted results of two clinical studies (Study-186 & Study-206) to support the indication for a 5-day course of oral gemifloxacin 320 mg daily.

Study-186: This study was a double-blind, randomized, parallel group, comparative study of patients with ABS. The purpose of the study was to establish the efficacy of gemifloxacin 320 mg once daily for 5 days vs. the comparator gemifloxacin 320 mg once daily for 7 days. The primary efficacy parameter was "clinical response" at the follow-up visit. Sinus puncture aspirates were not performed in Study-186.

Most patients enrolled in the study were white (>97%). Female subjects comprised 57% of the population. "Clinical Response" at follow-up for gemifloxacin in the 5-day treatment group was 83.5% for the ITT population and 87.3% for the Clinical Per Protocol population, both rates were similar to the 7-day treatment groups. The point estimate for the treatment difference of the Clinical PP population at follow-up was 0.44 and the 95% CI was (-6.54, 7.41) well within the lower bound for the study's specified delta of –15. The secondary efficacy endpoints corroborated the primary efficacy endpoint.

Study-206: This was an open-label, non-comparative, multicenter study using oral gemifloxacin 320 mg once a day for 5 days in the treatment of ABS. The protocol specified primary efficacy parameter for Study-206 was bacteriological eradication at F/U in the Bacteriology ITT population. Almost 60% of the subjects enrolled were females and the majority of patients were white 93%. The average age was 38 years, with a range from 16-81 years of age. All patients had a sinus puncture procedure done at entry; pathogens were recovered from 236/469 (50%) patients.

This study demonstrated that a 5-day course of gemifloxacin had a bacteriological success rate of 86% (203/236 patients) in the Bacteriology ITT population at F/U and 90% (195/216 patients) in the Bacteriology PP population at F/U.

Study-206 Per pathogen success rates at Follow-Up.

Pathogen identified	Bacteriology ITT	Bacteriology PP
S. pneumoniae N=101	88/101 (87.1%)	85/91 (93.4%)
H. influenzae N=50	44/50 (88%)	43/46 (93.5%)
M. catarrhalis N=15	15/15 (100%)	15/15 (100%)
**S. aureus* N=12	9/12 (75%)	7/9 (77.8%)

*MO analyses: The criteria in the CDER Draft Guidance for ABS studies requires 10-20 cases of *S. aureus*. On review the Applicant's data included 9 acceptable cases of *S. aureus* (>10^4 cfu/ml & pure culture) for further review; 4/9 isolates were suggestive of contamination (they were collected at the same center #504 & #503, no WBCs in one sample, and isolates from same center had similar MICs). Therefore the applicant did not meet the necessary quota for *S. aureus* cases to support the inclusion of *S. aureus* within the ABS indication.

Patients with a history of allergic rhinitis had a success rate of 69% (22/236) in the Bacteriology ITT population at F/U, whereas patients who did not have a history of allergic rhinitis had a success rate of 89% (181/236). The applicant's analysis of the secondary efficacy endpoints corroborates the success rates noted in the primary endpoint.

MO Comment: *In the Indications & Usage section of the Applicant's proposed labeling, the applicant is requesting: the indication for ABS caused by S. pneumoniae (including clarithromycin-resistant strains), H. influenzae, M. catarrhalis, K. pneumoniae, and S. aureus. It should be noted that K. pneumoniae is not an organism typically associated with ABS. The reader is referred to NDA 21-158 for a discussion of why the evidence for a K. pneumoniae is not sufficient to support inclusion of K. pneumoniae within the ABS indication. Based on the MO's analysis, the number of S. aureus cases that were submitted were not sufficient to support a labeling claim.*

In conclusion the MO is in agreement with the applicant's assessment of efficacy for the proposed treatment of ABS using gemifloxacin 320 mg po qd for 5 days, based on the data presented in the applicant's submission. Patients with allergic rhinitis, the majority of which were from the USA, have a lower response rate suggesting that these patients may be more difficult to treat, take longer to resolve, or have disease that is not responsive to antimicrobial therapy (the underlying etiology may not be solely a bacterial infection). The MO recommends that label for the ABS indication include *S. pneumoniae, H. influenzae*, and *M. catarrhalis,* as the organisms listed in the ABS indication.

B. General Approach to Review of the Efficacy of the Drug

The Applicant's submission for NDA 21-376 includes two principal studies for treatment of ABS (Table-2):

CLINICAL REVIEW

Table-2 Overview of studies submitted

Study	Type of study	Dose	*N	Geographic region
186	Randomized, double-blind, double-dummy, parallel group	Gemifloxacin 320 mg qd X 7 days Gemifloxacin 320 mg qd X 5 days	203 220	Europe, Canada
206[a]	Open-label, single group	Gemifloxacin 320 mg qd X 5 days	469	N. America, Europe, Costa Rica

*N= number of patients randomized to treatment
[a] In study 206, patients underwent sinus puncture with aspiration for culture at screening
Adapted from Study 186, Table 10.01; Study 206, Table 10.01

- Study-186 is a randomized, double blind, double-dummy, parallel group study intended to establish the clinical response to oral gemifloxacin 320 mg once daily for 5 days compared to gemifloxacin 320 mg once daily for 7 days.
- Study-206 is an open-label, non-comparative study intended to primarily assess for bacteriological response to oral gemifloxacin 320 mg once daily for 5 days.

A detailed review of Study-186 and Study-206 is presented followed by an integrated summary of the efficacy results.

MO Comment: *The MO reviewed a 20% random sample of patients in Study-186 and approximately 10% of patients in Study-206. The sample was provided by the FDA's Statistical Reviewer Dr. Cheryl Dixon. In conclusion, after a detailed review of Studies 186 & 206, the MO concludes that the Applicant's analyses for efficacy is satisfactory for both studies. In addition, the MO performed exploratory analysis when warranted.*

C. Detailed Review of Trials by Indication

Study-186:

A Double-Blind, Randomized, Multicenter, Parallel Group Study to Compare the Efficacy and Safety of Oral Gemifloxacin 320mg Once Daily for 5 Days Versus Oral Gemifloxacin 320mg Once Daily for 7 Days for the Treatment of Acute Bacterial Sinusitis (ABS).

Study dates: 23 November 1999 through 30 March 2000

Investigators & Centers: Fifty nine centers participated in the study, mostly from Europe (Belgium, Germany, Italy, Finland, Ireland, Netherlands), two centers were in Lithuania, and 1 center in Estonia.

Objectives: To evaluate the safety and demonstrate non-inferiority of gemifloxacin 320 mg oral dose once daily for 5 days versus gemifloxacin 320 mg oral dose once daily for 7 days in the treatment of adults with ABS.

Study Drug and Dosing Schedule: Gemifloxacin is produced as a white, film-coated, oval tablet. Each tablet contains gemifloxacin-S mesylate salt 400 mg, which is equivalent to gemifloxacin 320 mg pure free base. Batch numbers for gemifloxacin and the placebo tablets used in the study are detailed in **Table-6**

Table-6 Appearance, Formulation and Dosage Strength of Drugs used in Study-186.

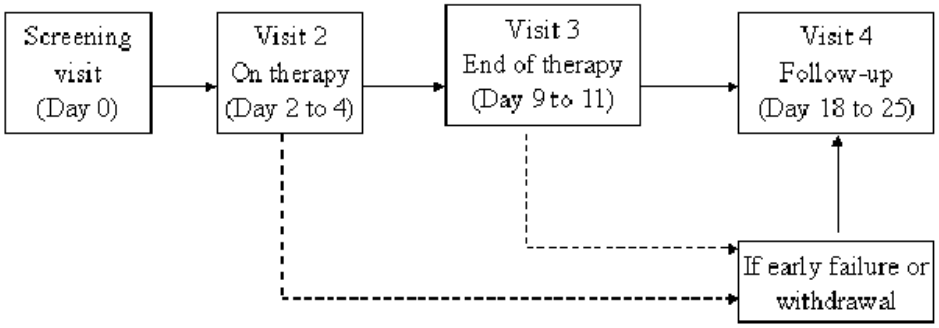
Study Drug	Appearance	Formulation	Dose	Batch Numbers
Gemifloxacin	White, film-coated, oval	Tablet	320 mg	N99116
Gemifloxacin-Placebo	White, film-coated, oval	Tablet	-	U99098

Bottle labels provided instructions for tablet schedule administration. Each patient received two bottles; the first bottle label asked the patient to take one tablet every morning on days 0-4, the second bottle (dispensed only at the on-therapy visit days 2-4) label asked the patient to take one tablet every morning for day 5 and 6.

Adequacy of Comparator: The comparator in this study was gemifloxacin 320 mg po daily for 7-days. The non approvable letter from the Agency dated December 15, 2000 notes that NDA 21-158 demonstrated non-inferiority of gemifloxacin 320 mg po daily for 7-days to approved comparators (cefuroxime and trovafloxacin) for the treatment of patients with ABS.

Study Design:
Study-186 was a multicenter, randomized, double-blind, parallel group, comparative phase III study of patients with ABS designed to study the safety and efficacy of gemifloxacin 320 mg once daily for 5 days versus gemifloxacin 320 mg once daily for 7 days in patients 18 years of age and older with ABS. Male or female patients were included in the study. Patients were divided into two groups, Group-A received the 5-day course and Group-B received the 7-day course. Patients were randomized using an automated telephone system (ClinPhone®). Patients were required to return for evaluation for a total of 4 visits over a span of 3 weeks to evaluate their clinical and radiological response to treatment as shown in Figure-2. Visit 4, the Follow-up visit at Day 18-25 was the time point for the primary efficacy assessment, Clinical Response (scored as success or failure).

Figure-2 Study-186 Schedule of Assessments
(Adapted from NDA 21-376, Vol. 11/17 3.2, p: 0814)



Sample Size: The estimated sample size was 400 patients. Included within this estimated sample size is an estimated rate of 25% for non-evaluability. Assuming a successful clinical rate of 80% for group A & B and a power of 90% to detect a difference in response rates between the two treatment groups (gemifloxacin 5-day minus gemifloxacin 7-day) of no less than –15% at the lower bounds of the two-sided 95% confidence interval. It is expected that 25% of patients in the protocol would be ineligible and therefore 400 patients were recruited to provide 300 (150 patients in each arm) evaluable patients.

Protocol Overview:

Text taken verbatim from NDA 21-376 is in the Arial font

Inclusion Criteria:

Male or female patients were included in this study, if they:

1) Have respiratory signs symptoms for at least 7 days, but less than and including 28 days duration, as defined by purulent/mucoid nasal discharge or purulence in the nasal cavity on examination) and at least one *major* or two *minor* criteria [7,8] .

- *Major criteria* include: facial pain/pressure/tightness over affected sinus(es), facial congestion/fullness, or nasal obstruction/blockage

- *Minor criteria* include: tooth pain, earache, non-vascular headache (within the last 24 hours), sore throat, cough, halitosis, fever (≥38.0º C oral, ≥38.5° C tympanic or ≥39.0° C rectal)[9] change in perception of smell or periorbital swelling.

2) Have radiologically confirmed (i.e,via Water's view x-ray or CAT scan) ABS of the affected sinus(es) (i.e. sinus opacification and/or an air-fluid level), within 72 hours before the time of randomization. Patients with mucosal thickening only will not be allowed to participate in the study.

3) Have purulent nasal discharge on Day 0 (screening visit) of the study.

4) Male or female patients,18 years of age or over.

5) Patient has consented to initial sinus endoscopy and will consent to repeat sinus endoscopy of the affected sinus(es) or rhinoscopy **(selected centers only**) if a clinical treatment failure or recurrence.

***MO Comment**: CDER Draft Guidance Document on developing antimicrobial agents for ABS recommends a repeat sinus puncture study for all clinical nonresponders at 72 hours*

6) Have an ABS, which is suitable for treatment with oral antibacterial therapy.

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[7] Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngology – Head and Neck Surgery*. 1992;117(Supp):S1-S7.

[8] Shapiro FF, Rachelefsky GS. Introduction and definition of sinusitis. *J Allergy and Clin Immun* 1992;90(Supp):417-418.

[9] Fever is defined as oral temperature ≥38.0° C, ≥38.5° C tympanic or rectal temperature ≥39.0° C as measured in the clinic or by the patient in previous 12 hours

7) Have provided written and dated informed consent to participate in the study.

8) Are willing and able to comply with the protocol.

9) Female patients of childbearing potential must have a negative urine pregnancy test measuring HCG (human chorionic gonadotrophin) prior to enrollment.

Exclusion Criteria

Male or female patients were excluded from this study, if they:

1) Have suspected or demonstrated previous hypersensitivity reactions to quinolone antibacterials.

2) Have received antibacterial therapy within 7 days prior to enrollment.

3) Are participating in another clinical trial or have received or anticipate receiving an investigational drug, vaccine, or medical device (non-government approved) within 30 days (or 5 half-lives, whichever is longer) prior to the first dose of study medication or during the conduct of the study (NB 16 weeks for Ireland).

4) Have a life threatening or serious unstable underlying disease which is likely to preclude evaluation of response to an antibacterial in ABS *(e.g*., cystic fibrosis, immunosupression, sepsis)

5) Have a concomitant infection that would preclude the evaluation of response to a quinolone in ABS *(e.*g., tooth abscess).

6) Have intraorbital or intracranial condition that would interfere with the interpretation of radiological images of the affected sinus(es) *(e.g*., previous surgery or a congenital abnormality of the head and neck).

7) Patients are immunocompromised or HIV positive with a CD4 count of <500 cells/mm^3 .

8) Are currently receiving or scheduled to receive corticosteroids at doses greater than 10mg/day of prednisone or equivalent.

9) Have had prior endoscopic sinus surgery, including Caldwell-Luc procedure, within 6 months (prior septal deviation repair, turbinate resection or rhino/turboplasty surgeries not involving the actual sinuses are allowed).

10) Have nasal polyp disease extending proximal to the middle turbinate.

11) Require hospitalization, parenteral antibacterial therapy, or have signs and symptoms of a disseminated infection.

12) Have a history of chronic sinusitis *(i.e*., three or more previous episodes/exacerbations of sinusitis in the preceding 12 months or one episode/exacerbation of sinusitis in the preceding 3 months, or continuing symptoms lasting longer than 28 days).

13) Patient is a female who is pregnant [10] , lactating, or planning a pregnancy during the study, or are of child bearing potential and are not using an accepted method of birth control *(i.*e., surgically sterile, intra-uterine contraceptive device, diaphragm or condom in combination with contraceptive cream, jelly or foam, oral contraceptive plus barrier contraception, other hormonal delivery systems plus barrier contraception)[11]

14) Have known or suspected renal impairment and/or known creatinine clearance of less than 40 mL/min.

15) Have known or suspected severe hepatic impairment or alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase levels three times the upper limit of normal or bilirubin levels of 1.5 times the upper limit of normal.

16) Patient is currently receiving treatment or medication for epilepsy, convulsions or myasthenia gravis.

17) Patient has a clinical history of hemolytic crisis or known glucose-6-phosphate dehydrogenase (G6PD) deficiency.

18) Patients with active alcohol or drug abuse.

19) Are concurrently receiving sucralfate and/or tubular secreting inhibitors (e.g. probenecid).

20) Have previously been enrolled in this study or any other involving gemifloxacin.

MO Comment: *The MO reviewed the inclusion/exclusion criteria and found them in general acceptable and in accordance with the criteria defined in the Agency's Draft Guidance document.*

[10] Patient has a positive urine pregnancy test at screening.

[11] Some antibacterials are known to react with oral contraceptives or hormonal delivery systems and hence reduce their effectiveness. As a precaution against loss of effectiveness patients should remain on their hormonal contraception but additional barrier contraception is required during the study period and the remainder of the menstrual cycle coincident with the last dose of study medication.

MO Comment: *In NDA 21-158 gemifloxacin 320 mg po qd for 7-days was non-inferior to comparators in the treatment of ABS, and hence is an appropriate comparator to gemifloxacin 320 mg po qd for 5-days in terms of efficacy, but not for safety purposes (comparing gemifloxacin to gemifloxacin for safety is not an ideal way to assess safety).*

Study Procedures: Patients who met the eligibility criteria and signed informed consent were randomized (1:1) into treatment Group-A (oral gemifloxacin 320 mg once daily for 5 days) or Group-B (oral gemifloxacin 320 mg once daily for 7 days). The investigator obtained a medical history and performed a physical examination. An imaging study (sinus radiography or CT-scan) was performed to assess the presence of radiographic evidence of ABS. Sinus endoscopy was permitted in this protocol. All women were required to provide a urine sample for a pregnancy test. In addition, all women of child bearing age provided a serum sample for a pregnancy (HCG) test. The study involved a total of four visits that took place over a period of 25 days. Procedures and evaluations scheduled for each visit are listed in **Table-7.**

Table 7 Outline of Study Procedures
Source: NDA 21-376. Vol. 8/17, Table-3, p:32

Study Procedure	Preliminary visit	On-Therapy Visit	End of Therapy Visit	follow-up Visit
Visit No.	1	2	3	4
Day	0	2-4	9-11	18-25
Signed/dated Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographic Data	X			
Medical History/Physical Examination*	X			
Clinical Examination**	X	X	X	X
Vital Signs	X	X	X	X
Radiological Examination	X			X
Sinus Endoscopy or rhinoscopy	X		X¹	X²
Blood sample (hematology, clinical chemistry)#	X		X	
Pregnancy Test+	X			
Prior/Concomitant Medication	X	X	X	X
Baseline Signs/Symptoms, AEs	X	X	X	X
Assessment of Compliance		X	X	
Call to ClinPhone	X	X	X	X
Study Conclusion Reason				X

* Including history of sinusitis and episodes of respiratory allergies.

** Including clinical examination of ears, nose, throat & teeth.
Vital signs to include temperature, BP, pulse and respiration rate.

Hematology includes hemoglobin, hematocrit, red/white cell counts, platelet count, reticulocytes and differential.
Clinical chemistry includes alkaline phosphatase, AST, ALT, BUN, LDH, albumin, total bilirubin, total protein, calculated creatinine clearance, serum creatinine, creatine kinase, glucose, calcium, sodium and potassium.
† Sinus aspiration via sinus endoscopy or rhinoscopy will be performed at selected sites only.
¹ Secondary efficacy: Bacteriological success or failure at EOT or F/U
² Repeated once only at the time of clinical failure/recurrence/withdrawal
+ Urine and serum HCG test for all females of child bearing potential.

Reasons for Withdrawal:

Patients were allowed to withdraw from the study at any time for any reason, similarly investigators were allowed to withdraw patients from the study at any time. Investigators had to document in the CRF the reason for withdrawal. Also, investigators had to make every effort to obtain a Follow-Up visit (F/U) for a safety assessment on all patients who withdraw or prior to F/U Visit-4. The reasons for study withdrawal were:

1. **Adverse Experience:** Patient has any adverse experience deemed sufficiently severe to warrant withdrawal. This must be recorded in the CRF and all adverse events followed-up until resolution.

2. **Insufficient therapeutic effect:** In the opinion of the investigator there has been a clinical failure of study medication and further antibacterial treatment is required for ABS.

3. **Patient is lost to follow up:** e.g. present at EOT visit, but absent at FU visit.

4. **Protocol Deviation:** Including non-compliance, dosing regimen or visit schedule.

5. **Other:** Patient becomes pregnant, or patient withdraws consent or requests cessation of treatment.

Evaluability Criteria:

After determination of inclusion/exclusion criteria for the study and informed consent, any patient who received at least one dose of study medication was considered as a member of the Intent-to-treat (ITT) population.

In the study protocol the Applicant defined 27 protocol violations (PV). A violation related to patient safety only did not result in exclusion from the analysis. Patients were excluded from the PP population from the time a PV occurred. The PV's list was as follows:

PV 1. An inclusion criterion was marked 'No'.

PV 2. An exclusion criterion was marked 'Yes'.

PV 3. The patient did not satisfy the protocol specified age range *(Not applied; this was an inclusion criterion that was considered not to impact upon efficacy).*

PV 4. The patient was female of child-bearing potential but did not have a negative urine pregnancy test prior to enrolment. *(Not applied; this was an exclusion criterion to ensure patient safety and was considered not to impact upon efficacy).*

PV 5. The patient had a known or suspected hypersensitivity reaction to quinolone antibacterials. *(Not applied; this was an exclusion criterion to ensure patient safety and was considered not to impact upon efficacy).*

PV 6. The patient had a concomitant infection which would preclude the evaluation of response to study medication in ABS (e.g. tooth abscess). *(Applied on an individual patient basis where the infection was judged to affect efficacy assessment).*

PV 7. Patient has received antibacterial therapy within seven days of study entry (prophylaxis for other indications excepted, however this must be stopped on study entry) or patient has received antibacterial therapy during the study period (other than for treatment of the disease under study). *(Applied for oral, IV, IM or other systemic antibacterial therapy only; not applied where antibacterial therapy was given for clinical failure or clinical recurrence*).

PV 8. The patient had known or suspected creatinine clearance of less than 40 mL/min {*Creatinine clearance was changed to <40ml/min from <30ml/min because of an amendment}. (Not applied; this was an exclusion criterion to ensure patient safety and was considered not to impact upon efficacy).*

PV 9. The patient participated in another clinical trial or received an investigational drug, vaccine or medical device (non-government approved) within 30 days (or five half lives, whichever is longer) prior to the first dose of study medication or during the conduct of the study. *(Applied for unlicensed medications for which impact on efficacy could not be determined).*

PV 10. The patient had previously been enrolled in this study or any other gemifloxacin study. *(Not applied for healthy volunteers).*

PV 11. The patient received a protocol prohibited concomitant medication (e.g. corticosteroids at a dose of >10mg per day of prednisone or equivalent, sucralfate, or tubular secretion inhibitors (e.g. probenecid)). *(Not applied for the following medications: prednisone or equivalent given for treatment failure; single intra-articular injection of steroid; sucralfate; probenecid).*

PV 12. The patient had known severe hepatic impairment or alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase levels greater than three times the upper limit of normal, or bilirubin levels greater than one and a half times the upper limit of normal. *(Not applied; this was an exclusion criterion to ensure*

patient safety and was considered not to impact upon efficacy).

PV 13. The patient had a life-threatening or serious unstable underlying disease (e.g. history of epilepsy, convulsions, myasthenia gravis G6PD deficiency, HIV positive with a CD4 count of <500cells/mm3, cystic fibrosis, immunosuppression, sepsis). *(Applied on an individual patient basis where the disease was judged to affect efficacy assessment).*

PV 14. The patient has active alcohol or drug abuse*.(Applied).*

PV 15. The patient had a history of tendonitis while taking fluoroquinolones. *(Not applied; this was an exclusion criterion to ensure patient safety and was considered not to impact upon efficacy).*

PV 16. The patient suffered an adverse experience or baseline event which might compromise treatment evaluation. *(Applied on an individual patient basis where the adverse experience/baseline event was judged to affect efficacy assessment).*

PV 17. The patient did not demonstrate sufficient compliance with study medication *(i.e. 80% - 120%)* and/or did not receive 100% of the required medication over the first 72 hours. (Applied).

PV 18. The patient did not demonstrate compliance with the protocol specified visit schedule *(Applied - All four protocol-specified windows were extending prior to breaking the blind, i.e. Screening, Day -4 - 0; on-therapy, Day 1-6; end of therapy, Day 7-14 and follow-up, Day 16 -35; patients returning early as failures/recurrences were not excluded).*

PV 19. The patient did not have a clinical diagnosis of ABS (i.e. purulent/mucoid nasal discharge or purulence, specific major and minor signs and symptoms of infection). *(Applied).*

PV 20. The patient did not have a positive radiological confirmation of ABS (i.e. pre-treatment air-fluid level and/or sinus opacification). *(Applied -confirmatory X-rays were permitted up to five days prior to the start of study medication).*

PV 21. The patient had a clinical outcome of unable to determine. *(Applied).*

PV 22. Patients who's method of radiological examination, i.e. X-ray or CAT Scan, is different at Follow-Up from Screening. *(Applied).*

PV 23. Patient had nasal polyp disease extending proximal to the middle

turbinate. *(Applied on an individual patient basis where Medical History/baseline event was judged to affect efficacy assessment).*

PV 24. Patient required hospitalization, parenteral antibacterial therapy, or had signs and symptoms of a disseminated infection. *(Applied).*

PV 25. Patient had a history of chronic sinusitis (i.e., three or more previous episodes/exacerbations of sinusitis in the preceding 12 months or one episode/exacerbation of sinusitis in the preceding 3 months, or continuing symptoms lasting longer than 28-days). *(Applied).*

PV 26. Patient had intraorbital or intracranial complications that would interfere with the interpretation of radiological images of the affected sinus(es) (e.g., previous surgery of a congenital abnormality of the head and neck). *(Applied on an individual patient basis where Medical History/baseline event was judged to affect efficacy assessment).*

PV 27. The patient had an initial pathogen bacteriological outcome of unable to determine for one or more initial pathogens. *(Applied).*

***MO Comment**: The MO finds the evaluability criteria as presented in the protocol and their application acceptable. The adjudicated events in the study were all adjudicated prior to breaking the blind for Study-186.*

Efficacy Endpoints: The primary efficacy endpoint in the study was clinical response (success or failure) at Follow-Up (day 16-35). For a summary of the criteria used to determine clinical outcome at End-of-Therapy (EOT) and Follow-Up (F/U) see **Table-8** below.

Table-8 Criteria for Determining Clinical Outcome at End of Therapy and Follow-Up
(Applicant's Table-4 NDA 21-376, Vol. 8/17, p:039)

Visit	Clinical Outcome	Criteria
End of Therapy (Visit 3, Day 9-11)	Clinical success	Sufficient improvement or resolution of the signs and symptoms of ABS recorded at screening such that no additional antibacterial therapy was indicated for ABS.
	Clinical failure	Insufficient improvement or deterioration of signs and symptoms of ABS recorded at screening such that additional antibacterial therapy was indicated for ABS.
	Unable to determine	An assessment of clinical outcome could not be made (e.g., the patient was lost to follow-up or did not consent to clinical examination).
Follow-Up (Visit 4, Day 18-25)	Follow-up clinical success	Sustained improvement or resolution of signs and symptoms of ABS for patients who were clinical successes at the end of therapy visit, such that no additional antibacterial therapy was indicated for ABS
	Clinical recurrence	Reappearance or deterioration of signs and symptoms of ABS for patients who were clinical successes at the end of therapy, such that additional antibacterial therapy was indicated for ABS.
	Unable to determine	An assessment of clinical outcome could not be made (e.g. the patient was lost to follow-up or did not consent to clinical examination).

The Applicant also defined secondary efficacy parameters These included:

- Bacteriological response at EOT
- Bacteriological response at F/U
- Combined clinical and radiological response at F/U.
- Clinical response at end-of-therapy (Day 7-14).

The analysis for the secondary efficacy results was limited to the PP EOT and ITT populations. Other efficacy parameters included by the applicant were: Therapeutic Response (defined as a combination of clinical and bacteriological). This parameter was only calculated for patients who had both clinical and microbiological endpoints.

MO Comment: *F/U & EOT are identified by the Applicant in Figure-2 as Visit-4 on day 18-25 and Visit-3 on day 9-11. Both visits were extended to day 16-35 (F/U) and day 7-14 (EOT) prior to breaking study blind, to maximize the number of evaluable patients. Similarly the Screening and On-Therapy windows were extended The MO finds the practice of extending the windows to maximize patient evaluability acceptable without compromising the quality of the data being collected.*

MO Comment: *Two countries (Germany & Lithuania) in Study-186 performed microbiological sampling using sinus endoscopy aspirates. As per the Agency's Draft Guidance Document on developing antimicrobial agents for ABS, bacteriologic sampling during sinus endocscopy procedures is not a validated alternative to sinus puncture aspirate, and therefore results obtained by this method are difficult to interpret.*

Bacteriologic Response at End-of-Therapy

Bacteriologic response at End-of-Therapy (Visit 3) was determined based on defined bacteriologic outcomes. Determination for bacteriologic response was only applicable to select centers in Lithuania and Germany. Analysis for bacteriologic outcome included patients who had at least one initial pathogen **Table-9**. These outcomes were as follows:

- *Bacteriological Eradicatio*n: Elimination of the initial pathogen documented by culture of the repeat sinus aspirate.

- *Presumed Bacteriological Eradicatio*n: A repeat sinus aspiration was not clinically indicated based upon the resolution of signs and symptoms of infection and the patient's clinical outcome was 'clinical success'.

- *Bacteriological Persistenc*e: Continued presence of the initial pathogen in the repeat sinus aspirate.

- *Presumed Bacteriological Persistenc*e: In the absence of a repeat sinus aspirate, persistence of the initial pathogen was assumed if the patient's clinical outcome was 'clinical failure'.

- *Unable to Determin*e: An assessment of bacteriological outcome could not be made.

The Applicant defined Superinfection and Colonization as follows:

*Superinfectio*n: A new pathogen was identified at the end of therapy in a symptomatic patient requiring additional antibacterial therapy, i.e., a clinical failure.

*Colonizatio*n: A new pathogen was identified at the end of therapy in a non-symptomatic patient who did not require additional antibacterial therapy, i.e., a clinical success.

Bacteriological response at the End-of-Therapy included information on bacteriologic outcomes, colonization and superinfection as defined above. From that information Bacteriological Response was classified as Success or Failure as follows:

- *Succes*s: All initial pathogens were eradicated or presumed eradicated, without superinfection, but with or without colonization.

- *Failur*e: Persistence or presumed persistence of one or more of the initial pathogens, a superinfection or an assessment of unable to determine for one or more initial pathogens.

Bacteriologic Response at Follow-Up

Bacteriological response at Follow-Up (Visit-4) was determined in selected centers in Lithuania and Germany according to the following categories (**Table-9**):

- *Follow-Up Bacteriological Eradicatio*n: The initial pathogen was eradicated or presumed eradicated at the end of therapy and was still eradicated at follow-up.

- *Follow-Up Presumed Bacteriological Eradicatio*n: The initial pathogen was eradicated or presumed eradicated at end of therapy, a repeat sinus endoscopy was not indicated and the patient's clinical outcome was 'follow-up clinical success'.

- *Bacteriological Recurrenc*e: The initial pathogen was eradicated or presumed eradicated at end of therapy but reappeared at follow-up.

- *Presumed Bacteriological Recurrenc*e: The initial pathogen was eradicated or presumed eradicated at end of therapy, a repeat sinus endoscopy was not taken and the patient's clinical outcome was 'clinical recurrence'.

*Unable to Determin*e: An assessment of bacteriological outcome could not be made.

A new pathogen was identified at Follow-Up in patients who had an initial pathogen at study entry, the Follow-Up response was assigned as:

- *New Infectio*n: A new pathogen was identified at follow-up in a symptomatic patient requiring additional antibacterial therapy, i.e., a clinical recurrence.

- *Colonizatio*n: A new pathogen was identified at follow-up in a non-symptomatic patient who did not require additional antibacterial therapy, i.e., a follow-up clinical success.

Bacteriological response at F/U included information on bacteriologic outcomes, new infection and colonization as defined above. From that information Bacteriological Response was classified as Success or Failure as follows:

- *Success*: All initial pathogens were eradicated or presumed eradicated at the follow-up assessment, without any new infections, but with or without colonization.

- *Failure*: Recurrence of one or more of the initial pathogens at the follow-up assessment, a new infection, an assessment of unable to determine for one or more initial pathogens or the end of therapy bacteriological response was failure.

Combined Clinical and Radiologic Response at Follow-Up

Imaging studies consisted of an X-ray (Water's view) or CT-scan. A radiologist assessed the study as:

- *Improved*: Complete or substantial resolution of radiological signs of ABS.

- *Unchanged*: No change in the baseline radiological signs of ABS.

- *Worse*: Worsening of one or more radiological signs of ABS and/or the appearance of new radiological signs of ABS.

- *Unable to Determine*: An assessment of radiological outcome could not be made (e.g. the patient was lost to follow-up or patient did not have an identical radiographic procedure performed at screening and follow-up).

To assess the Combined clinical & radiologic response, the Applicant defined the following categories:

- *Success*: The clinical response at follow-up was 'success' and the radiological outcome was 'improved' or 'unchanged'.

- *Failure*: The clinical outcome at end of therapy was 'failure' or the clinical outcome at follow-up was 'recurrence' and/or the radiological outcome was 'worse'.

- *Unable to determine*: Either the clinical outcome at end of therapy or follow-up was 'unable to determine' and the radiological outcome was 'improved', 'unchanged' or 'unable to determine'; or the clinical response was 'success' and the radiological outcome was 'unable to determine'.

Clinical Response at End-of-Therapy

A patient's clinical response at End-of-Therapy depends on the clinical outcome at End-of-Therapy. Patients were excluded from the PP population if their clinical outcome was "unable to determine." The Applicant then defined clinical response as follows:

- *Success*: The patient's clinical outcome at end of therapy was 'clinical success'.

- *Failure*: The patient's clinical outcome at end of therapy was 'clinical failure' or 'unable to determine'.

Therapeutic Response at Follow-Up

Therapeutic response includes clinical and bacteriological response. Patients included were from selected centers in Lithuania and Germany only. Therapeutic response was defined as:

- *Success*: Both the clinical and bacteriological response of 'success' at follow-up.

- *Failure*: The clinical and/or bacteriological response was 'failure' at follow-up.

MO Comment: *Centers in Germany and Lithuania performed bacteriologic assessments using sinus endoscopy. This method for sampling sinus contents has not been validated according to the Agency's Draft Guidance on developing antimicrobial agents for the treatment of ABS. Bacteriologic cultures obtained by sinus endoscopy are difficult to interpret due to potential contamination from the nasal cavity during sampling.*

Statistical Considerations

The Applicant used two-sided 95% confidence interval testing to analyze the primary efficacy parameter- clinical response at Follow-Up. Assuming a successful clinical response rate of 80% for Group A & Group B and a power of 90% to detect a difference in response rates between the two treatment groups of no less than –15% (gemifloxacin 5-day minus gemifloxacin 7-day). The estimated sample size was 400 patients per group. Included within this estimated sample size is an estimated rate of 25% for non-evaluability.

Validation for the primary efficacy analysis was also assessed using three different methods:

1. Principal analysis was repeated for the Intent-to-Treat (ITT) population.
2. Logistic regression to include categorical covariates for country and history of allergic rhinitis.
3. Multiple imputation on the ITT population if more than 5% of patients were missing data. This method is used to evaluate the impact of missing data on the analysis.

The principle method used to analyze secondary efficacy variables was comparison of proportions between treatment groups for the PP population, and their respective 95% confidence intervals.

There were 4 patient populations that were described in the analyses:

Intent-to-treat (ITT): All randomized patients who took at least one dose of study medication.

Bacteriology ITT: All randomized patients who took at least one dose of study medication and had at least one pre-therapy pathogen identified at screening (centers in Lithuania and Germany only).

Clinical PP: This population excluded patients who violated the protocol to an extent that could bias efficacy results. The Clinical PP population was a subset of the ITT population.

Bacteriology PP: This population included patients who were included in the Clinical PP population and who had at least one pre-therapy pathogen identified at screening. The Bacteriology PP population was a subset of the Bacteriology ITT population.

Study Results

Population

A total of 423 patients were randomized to receive study medication; however, only 421 patients received at least one dose of medication. The two patients who were randomized but never received study medication were in the gemifloxacin 5-day treatment group. Neither of the two patients met the inclusion criteria for radiographic evidence of sinusitis. All patients were randomized via ClinPhone® prior to review of their X-rays. Thus the ITT population is comprised of 421 patients. A large proportion of patients who were recruited for the study were from Germany. **Table-10** provides a summary of patient distribution by country, randomization and study completion.

Table 10 Number of Patients Who Were Randomized (R) and Who Completed (C) the Study, by Country (ITT Population)
Source: NDA 21-376. Vol. 9/17, Table 10.02b, 10.03., p:139

	No. of Patients Treatment Group			
	Gemifloxacin 320mg qd for 5 days N=218		Gemifloxacin 320mg qd for 7 days N=203	
Country	R	C	R	C
Belgium	21	21	12	12
Canada	39	37	37	36
Estonia	4	4	4	4
Finland	9	7	8	8
Germany	83	80	82	78
Ireland	3	3	2	2
Italy	10	8	8	6
Lithuania	13	13	1	4
Netherlands	36	36	36	35
Total	218	209	203	195

Patient disposition for all patients is summarized in **Table-11.** Most patients in each treatment group attended the End-Of-Therapy visit (99% of patients), and the Follow-Up visit (96% of patients).

Table-11 Patient Disposition (All Randomized Patients) Study-186
Source: Vol. 9/17, Table 10.01; p:138.

	Treatment Group	
	Gemifloxacin 320mg qd for 5 days	Gemifloxacin 320mg qd for 7 days
Population	n	n
Randomized	220	203
Received Study Medication (ITT)*	218	203
Completed Study	209	195
Clinical PP End of Therapy	189	184
Clinical PP Follow-Up	181	175[#]
Bacteriology ITT**	20	22[##]
Bacteriology PP End of Therapy	18	21
Bacteriology PP Follow-Up	18	21

* These patients comprised the safety population.
** Centers in Lithuania and selected centers in Germany
[#] Patient 186.138.31659 in the seven day treatment group was included in the Clinical PP population with only five days signs and symptoms of ABS. This patient was a clinical success at follow-up.
[##] Patient 186.281.31554 in the seven day treatment group should have been included in the Bacteriology ITT population.

CLINICAL REVIEW

Demographic and Baseline Characteristics

Demographic and baseline characteristics for the ITT population are listed in **Table-12**. Most patients were white >97%. There was a slight preponderance of females in both treatment arms. The mean age of patients was approximately 40 years in both arms of the study. Demographic characteristics for the clinical PP population were similar to the ITT population. The number of patients in the Clinical PP population was 181 patients in the 5-day group and 175 patients in the 7-day group.

Table-12 Demographic Characteristics (ITT Population) Study-186
Source: . Vol. 9/17, Table 10.14a and 10.15a, p:186

	Treatment Group	
	Gemifloxacin 320mg qd for 5 days	Gemifloxacin 320mg qd for 7 days
Demographic Characteristic	N=218	N=203
Gender n (%)		
Male	93 (42.7)	85 (41.9)
Female	125 (57.3)	118 (58.1)
Age (yr.)		
Mean (SD)	41.4 (14.6)	39.7 (13.9)
Range	18 - 78	18 - 80
Race n (%)		
White	213 (97.7)	199 (98.0)
Black	1 (0.5)	3 (1.5)
Oriental	1 (0.5)	0
Other*	3 (1.4)	1 (0.5)
Weight (kg)		
Mean (SD)	73.6 (15.9)	75.0 (15.4)
Range	47 - 135	36.1 - 130
Height (cm)		
Mean (SD)	170 (8.5)	171 (8.8)
Range	150 - 200	150 - 194

*Other included Mediterranean, Asian, East Indian and Peruvian. Applicant's Table 15 from NDA 21-376, Vol. 8/17, p 073

Clinical characteristics at screening for the ITT population are listed in **Tables 13 & 14**. Patients in the Clinical PP population had similar Major & Minor characteristics at screening as the ITT population. The radiographic characteristics of the ITT population at screening are listed in **Table-15**. Greater than 98% of patients in both treatment groups had an abnormal reading. At least 94% of patients in both groups had air/fluid levels and/or sinus opacification on their screening X-ray. Patients who had mucosal thickening alone were not included in the study. Ten percent of patients in the 5-day treatment group and 14% in the 7-day treatment group had a history of allergic rhinitis.

Table-13 Number (%) of Patients with Major Criteria of ABS at Screening (ITT Population)
Source: Applicant Table-19, Vol. 8/17, p 078

	Treatment Group			
	Gemifloxacin 320mg qd for 5 days N=218		Gemifloxacin 320mg qd for 7 days N=203	
Sign/Symptom	n	(%)	n	(%)
Nasal Discharge				
Clear	0		2	(1.0)
Mucoid	18	(8.3)	19	(9.4)
Purulent	199	(91.3)	180	(88.7)
Nasal Cavity Purulence	189	(86.7)	184	(90.6)
Facial Pain/Pressure/Tightness				
Present with Pressure	94	(43.1)	91	(44.8)
Evident Upon Movement	70	(32.1)	77	(37.9)
Facial Congestion/Fullness	176	(80.7)	170	(83.7)
Nasal Obstruction/Blockage	186	(85.3)	179	(88.2)

Table-14 Number (%) of Patients with Minor Criteria of ABS at Screening (ITT Population)
Source: Applicant Table-21, Vol. 8/17, p 079

	Treatment Group			
	Gemifloxacin 320mg qd for 5 days N=218		Gemifloxacin 320mg qd for 7 days N=203	
Sign/Symptom	n	(%)	n	(%)
Tooth Ache	64	(29.4)	81	(39.9)
Earache	78	(35.8)	76	(37.4)
Periorbital Swelling	69	(31.7)	67	(33.0)
Non-Vascular Headache	157	(72.0)	148	(72.9)
Sore Throat	86	(39.4)	85	(41.9)
Cough	155	(71.1)	125	(61.6)
Halitosis	56	(25.7)	55	(27.1)
Fever	70	(32.1)	64	(31.5)
Change in Perception of Smell	138	(63.3)	138	(68.0)

Table-15 Sinus X-ray/CAT Scan Abnormalities at Screening (ITT Population)
Source: Applicant Table-17, Vol. 8/17, p 076

	Treatment Group			
	Gemifloxacin 320mg qd for 5 days N=218		Gemifloxacin 320mg qd for 7 days N=203	
	n	(%)	n	(%)
Sinus X-ray/CAT Scan Performed	218	(100.0)	203	(100.0)
Abnormal Image Results	217	(99.5)	199	(98.0)
Abnormality				
Air Fluid Level	84	(38.5)	72	(35.5)
Sinus Opacification	159	(72.9)	149	(73.4)
Air Fluid Level and/or Sinus Opacification	206	(94.5)	191	(94.1)
Other*	103	(47.2)	98	(48.3)

*Verbatim terms reported by the investigators included: Mucosal thickening and partial opacification of maxillary and ethmoidal sinuses, mucosal thickening, frontal sinusitis, mucosal hypertrophy, normal, presumption of cystic structure, partial mucous swelling, swelling sinus maxillaris mucosal membrane, slight density increase in the left frontal which may be due to chronic sinusitis, clear, hyperplasia of sinus mucosal, ossification, cyst, cisti asole nascente, left antrum with only 1.5cm air collection, right only half opacified, inclusion cyst and edemous mucosa.

MO Comments: The rate of patients with allergic rhinitis in Study-186 is less than the rate in Study-206. This may be due to the study location. Study-186 did not recruit patients from the USA where rates of allergic rhinitis are high compared to other countries. The MO reviewed a random 20% sample of subjects enrolled in the study, and concurs that they satisfied the major and minor criteria for enrollment . Both groups A & B in the study were sufficiently comparable at baseline.

Withdrawals

The ITT population was 421 patients. A total of 17/421 (4%) patients withdrew from the study. Nine out of 17 patients were in the gemifloxacin 5-day treatment arm. The most common reason for withdrawal was “lost to follow-up” followed by “inadequate therapeutic response” as noted in **Table-16**. Three patients in both treatment arms were withdrawn due to adverse effects, 2/3 were in the gemifloxacin 5-day group.

Table-16 Number (%) of Patients who Completed the Study or who were Withdrawn, by the Reason for Study Withdrawal (ITT Population) (Study-186)
Source: Applicant Table-10, Vol. 8/17, p 068

	Treatment Group			
Study Conclusion Reason	Gemifloxacin 320mg qd for 5 days N=218		Gemifloxacin 320mg qd for 7 days N=203	
	n	(%)	n	(%)
COMPLETED STUDY*	209	(95.9)	195	(96.1)
Withdrawal Reason**				
Adverse Experience	2	(0.9)	1	(0.5)
Insufficient Therapeutic Effect	3	(1.4)	0	
Protocol Deviation	1	(0.5)	1	(0.5)
Lost to Follow-up	3	(1.4)	6	(3.0)
Other Reasons	0		0	
TOTAL WITHDRAWN	9	(4.1)	8	(3.9)

*Patients were considered to have completed the study if they completed the seven-day treatment phase and returned for the end of therapy and follow-up visits.
**This table shows withdrawals occurring at any time during the study.

MO Comments: *The majority of patients were able to complete the study. The number of patients withdrawn from either arm of the study was low. Two patients were withdrawn from the 5-day treatment arm due to an adverse event. Patient #186-143-31464 suffered a leg fracture 4 days after completing the 5-day course of therapy. The investigator classified the event as unrelated to study drug. Patient #186-274-32384 developed a generalized rash on the 4th day on-therapy but was able to complete the 5-day course. His rash was classified as moderate, lasted for 7 days, and did not require corrective therapy. The only patient who had to be withdrawn in the 7-day treatment arm due to an adverse event had a history of vertigo that was unrelated to study medication, which recurred and required surgical intervention.*
Three patients were withdrawn due to an insufficient therapeutic effect in the 5-day treatment arm compared to none in the 7-day treatment arm: The three patient records show: Patient #186-273-32361 had a history of allergic rhinitis, and was started on levofloxacin one day after completing a 5-day course of gemifloxacin. Patient #186-291-31544 did not have allergic rhinitis. She took 3 doses of gemifloxacin, and began doxycycline on the 2nd day of her 5-day gemifloxacin treatment. Patient #186-292-31531 did not have allergic rhinitis, took gemifloxacin for 3 days, and at the EOT visit was switched to doxycycline. Although these findings are interesting, the numbers are too small to conclude anything.

Patients Excluded For Non-evaluability

Forty eight patients were non-evaluable at EOT (29/48 [60%] gemifloxacin 5-day treatment arm), and 65 patients were non-evaluable (37/65 [57%] gemifloxacin 5-day treatment arm) from the Clinical PP population at F/U. The most frequently cited reasons for exclusion were: “unable to determine”, “medication compliance”, and “visit compliance”. Reasons for patient non-evaluability by treatment group are summarized in**Table-17.**

Table 17 Number (%) of Patients Excluded from the Clinical PP Population at End of Therapy and Follow-Up, by Reason
Source: Applicant Table-13, Vol. 8/17, p 071

	Treatment Group			
	Gemifloxacin 320mg qd for 5 days		Gemifloxacin 320mg qd for 7 days	
PV Criteria*	N=218		N=203	
End of Therapy	n	(%)	n	(%)
PV 2 (exclusion criterion marked yes)	1	(0.5)	1	(0.5)
PV 6 (complicating infection)	2	(0.9)	0	
PV 7 (antibacterial 7 days prior to entry or received antibacterial therapy during the study period (other than for treatment of the disease under study))	0		1	(0.5)
PV 10 (previously enrolled in study)	3	(1.4)	0	
PV 11 (prohibited concomitant medication)	0		1	(0.5)
PV 13 (serious underlying disease)	0		1	(0.5)
PV 17 (medication non-compliance)	6	(2.8)	3	(1.5)
PV 18 (visit non-compliance)	2	(0.9)	1	(0.5)
PV 19 (no clinical diagnosis of ABS)	1	(0.5)	0	
PV 20 (no radiological confirmation of ABS)	14	(6.4)	12	(5.9)
PV 21 (patients with an outcome of UTD)	5	(2.3)	2	(1.0)
PV 22 (patient with different methods of radiological examination)	0		1	(0.5)
Total Number of Patients Excluded**	29	(13.3)	19	(9.4)
Follow-Up	n	(%)	n	(%)
PV 2 (exclusion criterion marked yes)	1	(0.5)	1	(0.5)
PV 6 (complicating infection)	2	(0.9)	0	
PV 7 (antibacterial 7 days prior to entry or received antibacterial therapy during the study period (other than for treatment of the disease under study))	3	(1.4)	3	(1.5)
PV 10 (previously enrolled in study)	3	(1.4)	0	
PV 11 (prohibited concomitant med.)	2	(0.9)	2	(1.0)
PV 13 (serious underlying disease)	0		1	(0.5)
PV 17 (medication non-compliance)	6	(2.8)	3	(1.5)
PV 18 (visit window non-compliance)	5	(2.3)	1	(0.5)
PV 19 (no clinical diagnosis of ABS)	1	(0.5)	0	
PV 20 (no radiological confirmation of ABS)	14	(6.4)	12	(5.9)
PV 21 (patients with an outcome of UTD)	6	(2.8)	8	(3.9)
PV 22 (patient with different methods of radiological examination)	0		1	(0.5)
Total Number of Patients Excluded**	37	(17.0)	28	(13.8)

Note: some patients may have had more than one protocol violation.
** Patients can violate more than one PV Criteria, hence Total is not necessarily the sum of the 'n' column.
Key: UTD = Unable to determine

The number and protocol violations that lead to exclusion for the Bacteriological ITT population are listed in **Table-18**. There were a total of 78 eligible patients collected from select centers in Germany and Lithuania. 36/78 patients (46%) were excluded leaving 42 patients in the

Bacteriological ITT population. Three patients were excluded from the Bacteriology PP population at End-of-Therapy and at Follow-Up.

MO Comment:. Centers in Lithuania and Germany provided bacteriologic sinus samples from patients using sinus endoscopy as required by European regulatory guidance in those two countries. Sinus puncture aspirates are the accepted method for determining the bacteriologic etiology in ABS studies as described in the Agency's Draft Guidance document. Therefore the Applicant's bacteriologic data should be interpreted with caution.

Table 18 Number (%) of Patients Excluded From the Bacteriology PP Population at End of Therapy and Follow-Up, by Reason
Source: Applicant Table-14, Vol. 8/17, p 073

	Treatment Group			
	Gemifloxacin 320mg qd for 5 days		Gemifloxacin 320mg qd for 7 days	
PV Criteria		N=20	N=22	
End of Therapy	n	(%)	n	(%)
PV 2 (exclusion criterion marked yes)	0		1	(4.5)
PV 11 (prohibited concomitant medication)	0		1	(4.5)
PV 13 (serious underlying disease)	0		1	(4.5)
PV 19 (no clinical diagnosis of ABS)	1	(5.0)	0	
PV 20 (no radiological confirmation of ABS)	1	(5.0)	0	
Total Excluded**	**2**	**(10.0)**	**1**	**(4.5)**
Follow-up	n	(%)	n	(%)
PV 2 (exclusion criterion marked yes)	0		1	(4.5)
PV 11 (prohibited concomitant medication)	0		1	(4.5)
PV 13 (serious underlying disease)	0		1	(4.5)
PV 19 (no clinical diagnosis of ABS)	1	(5.0)	0	
PV 20 (no radiological confirmation of ABS)	1	(5.0)	0	
Total Excluded**	**2**	**(10.0)**	**1**	**(4.5)**

Note: some patients may have had more than one protocol violation.
** Patients can violate more than one PV Criteria, hence Total is not necessarily the sum of the 'n' column.

Treatment Compliance

The Applicant calculated % Compliance as: $\frac{\text{Number of tablets taken x 100}}{\text{Scheduled number of days on treatment}}$

Patients were considered compliant with the study medication if their early treatment compliance (defined as 100% Compliance in the first 72 hours of therapy) and their total percentage compliance was in the range of 80-120%. Study participants in both arms of the study were 98% compliant with study medication. Compliance is summarized in **Table-19**.

Table 19 Number (%) of Patients Compliant with Study Medication (ITT Population)
Source: Applicant Table-29, Vol. 8/17, p 090

	Treatment Group			
	Gemifloxacin 320mg qd for 5 days N=218		Gemifloxacin 320mg qd for 7 days N=203	
	n	(%)	n	(%)
Early Compliance	218	(100.0)	202	(99.5)
Percentage Compliance				
80% - 120%	212	(97.2)	200	(98.5)
Unknown	1	(0.5)	2	(1.0)
Overall Compliance	212	(97.2)	200	(98.5)
Treatment Difference % (gemifloxacin 5d – gemifloxacin 7d)	**-1.27**			
95% CI	**-4.01, 1.46**			
P Value	**0.51**			

Efficacy Results

The primary efficacy parameter was Clinical Response at Follow-Up (Day 16-35) in the Clinical PP population. Results for the following five secondary efficacy parameters were also analyzed:

- Clinical Response at End of Therapy
- Bacteriological Response at End of Therapy
- Combined Clinical and Radiological Response at Follow-Up
- Bacteriological Response at Follow-Up
- Other: Therapeutic Response

Primary Efficacy Results:

Clinical Response at Follow-Up

The Clinical Success rate for the Clinical PP population is provided in **Table-20**; Patients in both the gemifloxacin 5-day and 7-day treatment arms had an 87% Clinical Success rate. The 95% confidence interval for the difference in success rates was –7.78, well within the lower bound of the study's specified delta of –15. Similar results were reported for the ITT population.

Table-20 Clinical Response at Follow-Up (Clinical PP and ITT Follow-Up Populations)
Source: Applicant Table-30, Vol. 8/17, p 092

	Treatment Group Gemifloxacin 320mg qd for 5 days	Gemifloxacin 320mg qd for 7 days
Clinical PP Follow-Up Population	N=181	N=175
Success, n (%)	158 (87.3)	152 (86.9)
Failure, n (%)	23 (12.7)	23 (13.1)
Treatment difference % (gemi 5d – gemi 7d)	**0.44**	
95% CI	**-6.54, 7.41**	
ITT Population	N=218	N=203
Success, n (%)	182 (83.5)	171 (84.2)
Failure*, n (%)	36 (16.5)	32 (15.8)
Treatment difference % (gemi 5d – gemi 7d)	**-0.75**	
95% CI	**-7.78, 6.28**	

*Patients with an outcome of unable to determine at end of therapy were considered to have a response of failure at follow-up.

Secondary Efficacy Results

Clinical Response at End-of-Therapy (day 7-14): Success rates for the Clinical PP population were 93% in the 5-day treatment group and 96% in the 7-day group. The success rates for the ITT population were 89% in the 5-day treatment group and 96% in the 7-day group. However, analysis for both the Clinical PP and the ITT populations was not powered to demonstrate non-inferiority for secondary end-points. **Table-21** lists Clinical Response at End-of-Therapy.

MO Comment: *The MO agrees that secondary endpoints were not statistically powered to demonstrate non-inferiority in this study.*

Table 21 Clinical Response at End of Therapy (ITT and Clinical PP End of Therapy Populations)
Source: Applicant Table-31, Vol. 8/17, p 093

	Treatment Group Gemifloxacin 320mg qd for 5 days	**Gemifloxacin** 320mg qd for 7 days
Clinical PP End of Therapy Population	**N=189**	**N=184**
Success, n (%)	176 (93.1)	177 (96.2)
Failure, n (%)	13 (6.9)	7 (3.8)
Treatment difference % (gemi 5d – gemi 7d)	**-3.07**	
95% CI	**-7.63, 1.47**	
ITT Population	**N=218**	**N=203**
Success, n (%)	194 (89.0)	194 (95.6)
Failure*, n (%)	24 (11.0)	9 (4.4)
Treatment difference % (gemi 5d – gemi 7d)	**-6.58**	
95% CI	**-11.60, -1.55**	

*Includes five patients in the gemifloxacin 5-day treatment group and two patients in the gemifloxacin 7-day treatment group with an outcome of unable to determine.

CLINICAL REVIEW

Bacteriologic Response at Follow-Up

A limited number of centers in Germany and Lithuania obtained samples for evaluation and these were obtained through sinus endoscopy. The small number of isolates reported 39 in total, limits their usefulness in analysis. The most common organism isolated was *S. pneumoniae* 6 in the gemifloxacin 5-day group and 7 *S. pneumoniae* in the gemifloxacin 7-day group. **Tables-22** provides a summary of bacteriological outcome for all initial pathogens at the Follow-up visit, and **Table-23** lists a summary of patient Bacteriological Response.

MO Comment: *The primary limiting reason to the usefulness of the bacteriological samples provided in this study is the method in which they were collected, i.e. via sinus endoscopy, which has not been validated according to the Agency's ABS Draft Guidance. A secondary limiting factor is the small number of isolates that is reported from two countries only.*

Table-22 Initial Screening Pathogen Bacteriological Outcome at Follow-Up (For All Pathogens Combined and Key Pathogens) (Bacteriology PP Follow-Up Population)
Source: Applicant Table-33, Vol. 8/17, p 96

		Treatment Group			
		Gemifloxacin 320mg qd for 5 days N=18		Gemifloxacin 320mg qd for 7 days N=21	
Initial Pathogen	**Bacteriological Outcome**	**n**	**(%)**	**n**	**(%)**
All Pathogens	*(n)*	20	(100.0)	22	(100.0)
	Presumed Eradication	20	(95.2)	19	(86.4)
	Eradication	0		3	(13.6)
	Missing#	1	(4.8)	0	
S. pneumoniae	*(n)*	6	(100.0)	7	(100.0)
	Presumed Eradication	6	(100.0)	5	(71.4)
	Eradication	0		2	(28.6)
H. influenzae	*(n)*	4	(100.0)	2	(100.0)
	Presumed Eradication	4	(100.0)	1	(50.0)
	Eradication	0		1	(50.0)
S. aureus	*(n)*	2	(100.0)	2	(100.0)
	Presumed Eradication	2	(66.7)	2	(100.0)
	Missing#	1	(33.3)	0	
M. catarrhalis	*(n)*	1	(100.0)	1	(100.0)
	Presumed Eradication	1	(100.0)	1	(100.0)

(n)=Total number of pathogens. A patient could have more than one pathogen, hence the (n) total are larger than the total number N.
n(%)=number (%) of pathogens with a particular outcome
An outcome of missing indicates that the patient had a bacteriological response of failure at the end of therapy visit.
Note: Only those pathogens that were eradicated or presumed eradicated at follow-up have an initial pathogen outcome at follow-up

Table-23 Per Patient Bacteriological Response at Follow-Up (Bacteriology PP Follow-Up Population)
Source: Applicant Table-35, Vol. 8/17, p 98

	Treatment Group		
	Gemifloxacin 320mg qd for 5 days		Gemifloxacin 320mg qd for 7 days
Bacteriology PP Follow-Up Population	**N=18**		**N=21**
Success, n (%)	17 (94.4)		19 (90.5)
Failure, n (%)	1 (5.6)		2 (9.5%)
Treatment difference % (gemi 5d – gemi 7d)		**3.97**	
95% CI		**-12.45, 20.39**	

Bacteriological Efficacy Results at End-of-Therapy:

The Bacteriological efficacy results are presented in **Table-24**. In brief, the number of patients in the Bacteriology PP population was limited to 18 patients in the 5-day treatment arm and 21 patients in the 7-day treatment arm. All the *S. pneumoniae* isolates (13 in both arms) were susceptible to penicillin. Bacteriological eradication or presumed eradication was achieved in all patients who had one of the three major organisms associated with ABS.

MO Comment: The successful bacteriologic response rate for the three major respiratory pathogens was 100% at EOT. However, these results were obtained by as yet unvalidated culturing methodologies (sinus endoscopy). In addition to the questions raised by the methods by which culturing was performed, the number of patients with pathogenic organisms was too small to draw any conclusions. Aside from these technical limitations there were no apparent major deficiencies noted.

Table-24 Initial Screening Pathogen Bacteriological Outcome at End of Therapy (For All Pathogens and Key Pathogens) (Bacteriology PP End of Therapy Population)
Source: Applicant Table-36, Vol. 8/17, p 100

		Gemifloxacin 320mg qd for 5 days N=18		Gemifloxacin 320mg qd for 7 days N=21	
Initial Pathogen	**Bacteriological Outcome**	**n**	**(%)**	**n**	**(%)**
All Pathogens	*(n)*				
	Presumed Eradication	19	(90.5)	21	(95.5)
	Eradication	1	(4.8)	1	(4.5)
	Persistence	1	(4.8)	0	
S. pneumoniae	*(n)*				
	Presumed Eradication	6	(100.0)	6	(85.7)
	Eradication	0		1	(14.3)
H. influenzae	*(n)*				
	Presumed Eradication	3	(75.0)	2	(100.0)
	Eradication	1	(25.0)	0	
S. aureus	*(n)*				
	Presumed Eradication	2	(66.7)	2	(100.0)
	Persistence	1	(33.3)	0	
M. catarrhalis	*(n)*				
	Presumed Eradication	1	(100.0	1	(100.0)

(n)=Total number of pathogens
n(%)=number (%) of pathogens with a particular outcome

Combined Clinical and Radiological Response at Follow-Up

Table-25 provides a summary of results for the combined Clinical and Radiological Response for the Clinical PP and the ITT populations at Follow-Up. The lower bound of the 95% confidence interval for the treatment difference for the combined clinical and radiological response rate is within the delta of –15. However, statistically the study was not powered to demonstrate non-inferiority for the multiple secondary end-points. In the Clinical PP population. The combined clinical and radiological success rate was 83.4% (Clinical PP) and 78.9% (ITT) populations in the gemifloxacin 5-day arm and 80% (Clinical PP) and 77.8% (ITT) populations in the gemifloxacin 7-day treatment arm.

Table-25 Combined Clinical and Radiological Response at Follow-Up (Clinical PP Follow-Up and ITT Populations)
Source: Applicant Table-32, Vol. 8/17, p 94

	Treatment Group Gemifloxacin 320mg qd for 5 days	**Gemifloxacin 320mg qd for 7 days**
Clinical PP Follow-Up Population	**N=181**	**N=175**
Success, n (%)	151 (83.4)	140 (80.0)
Failure, n (%)	25 (13.8)	25 (14.3)
Unable to Determine, n (%)	5 (2.8)	10 (5.7)
Treatment difference % (gemi 5d – gemi 7d)	3.43	
95% CI	-4.60, 11.45	
ITT Population	**N=218**	**N=203**
Success, n (%)	172 (78.9)	158 (77.8)
Failure, n (%)	33 (15.1)	26 (12.8)
Unable to Determine, n (%)	13 (6.0)	19 (9.4)
Treatment difference % (gemi 5d – gemi 7d)	1.07	
95% CI	-6.81, 8.94	

Other parameters evaluated:

The Applicant also evaluated Therapeutic Response at Follow-Up for patients who had both clinical and microbiological endpoints. Briefly the Therapeutic Response was 17/18 (94%) in the 5-day group and 19/21 (90%) in the 7-day group.

MO Comment: *There were too few patients for whom a therapeutic response could be assessed because most patients did not have microbiologic sampling.*

CLINICAL REVIEW

Treatment Failures:

Treatment Failures were reported at the End-of-Therapy and Follow-Up visits. A summary **Table-26** is provided for reference. Thirteen patients out of a total of 189 in the 5-day treatment arm and 7/184 patients in the 7-day treatment arm were labeled clinical failures at EOT.

Among the failed patients in the 5-day treatment arm who had a repeat culture: Patient #186.136.31683 initially had *S. aureus* that was also isolated (sample collected via sinus endoscopy) at EOT. The organism was susceptible to gemifloxacin. Another patient #186.142.31842 had *H. influenzae* that was susceptible to gemifloxacin at screening. On F/U the patient grew *S. pneumoniae* that was susceptible to gemifloxacin. All cultures from this patient were obtained via a nasopharyngeal swab. The Applicant excluded this patient because the definition for ABS was not met.

Among the failed patients in the 7-day treatment arm who had a repeat culture: Patient #186.153.31436 had a nasopharyngeal culture at screening that was positive for *S. pneumoniae*. Subsequently *M. catarrhalis* was isolated at F/U. Both isolates were susceptible to gemifloxacin. Another patient #186.153.31445 in the 7-day treatment arm had *H. influenzae* isolated at screening, and subsequently *M. catarrhalis* was isolated at F/U. Both isolates from this patient were sensitive to gemifloxacin. Cultures were obtained via a nasopharyngeal swab.

Table-26 Treatment Failures ITT population

Visit #	Classification	5-day Gemifloxacin		7-day Gemifloxacin	
		n	(%)	n	(%)
End-of-Treatment	Clinical Failure	13/189	(6.9)	7/184	(3.8)
Follow-Up	Clinical Recurrence	23/181	(12.7)	23/175	(13.1)

***MO Comment**: The number of organisms isolated in patients who failed therapy is too small to draw conclusions. It is interesting that these patients had a culture obtained using a nasopharyngeal swab, a method of culturing which is of no value in clinical studies of primary ABS.*

Summary of Efficacy Results for Study 186

Study-186 was a multicenter, randomized, double blind, parallel group, comparative phase III study of adult patients with ABS in Europe and Canada. The study was designed to demonstrate the non-inferiority of gemifloxacin 320 mg once daily for 5 days versus gemifloxacin 320 mg once daily for 7 days. This study was primarily a clinical study of ABS and patients did not undergo a sinus puncture aspirate unless they were recruited from specific sites in Germany and Lithuania. The primary efficacy endpoint of the study was Clinical Response (Success or Failure) at the Follow-Up visit on Day 16-35. The Applicant estimated a sample size of 400, in order to achieve a 90% power to detect a difference (gemifloxacin 5 days minus gemifloxacin 7 days) at the lower bound of the 95% confidence interval within a delta of –15%.

The ITT population was limited to 421. There were 220 patients in the 5-day arm and 203 patients in the 7-day arm. The two groups had comparable baseline demographics and clinical characteristics. Withdrawal rates were similar in both groups and were limited to 17/421 (4%). The most frequent reason for withdrawal was related to “lost to follow up”. In the 5-day treatment arm there were 9/209 (4%) withdrawals: 3 patients had an inadequate therapeutic effect, 2 patients experienced adverse effects, 3 patients were lost to follow up, and 1 patient deviated from the protocol. In the 7-day treatment arm there were 8/203 (4%) patient withdrawals: 6 patients were lost to follow up, 1 patient deviated from the protocol, and 1 patient had an adverse event. Overall compliance with study drug was over 97% in both arms of the study.

Study-186 achieved its primary endpoint by demonstrating that gemifloxacin 320 mg po qd for 5 days is non-inferior to the comparator (gemifloxacin 320 mg po qd for 7 days) in both the ITT and the Clinical PP populations at F/U. In addition, the Combined Clinical & Radiological Response at Follow-Up and the Clinical Response at End-of-Therapy in the ITT and Clinical PP populations corroborated the results observed for the primary efficacy endpoint. The other secondary efficacy parameters including the Bacteriological Response at EOT and at F/U were not sufficiently powered for further analysis in this study. It is important to note that Study-186 was primarily a clinical study. The bacteriological isolates that were collected in the study used unvalidated methodologies and hence were not used to claim efficacy. Study-206 is a bacteriological study, that used validated methodologies for sampling sinus contents. The integrated efficacy review for Study-206 follows.

In summary, Study 186 provides evidence of non-inferiority of gemifloxacin 320 mg po qd for 5days compared to gemifloxacin 320 mg po qd for 7 days based on the Clinical Response rates at Follow-Up.

CLINICAL REVIEW

Detailed Review of Study

Study-206:

"An Open-Label, Multicenter, Single-Group Study to Assess the Bacteriological Eradication, Clinical Efficacy and Safety of Oral Gemifloxacin 320mg Once Daily for 5 days in the Treatment of Acute Bacterial Sinusitis (ABS)".

Study dates: 22 November 1999 through 4 April 2000.

Investigators & Centers: This study was conducted at 40 centers and included 27 centers from the USA, 1 center in Costa Rica, 4 centers in Hungary, and 8 centers in Poland.

Objectives:

1. To assess bacteriological eradication with oral gemifloxacin 320mg once daily for five days in the treatment of ABS.

2. To evaluate the clinical efficacy and safety of oral gemifloxacin 320mg once daily for five days in the treatment of ABS.

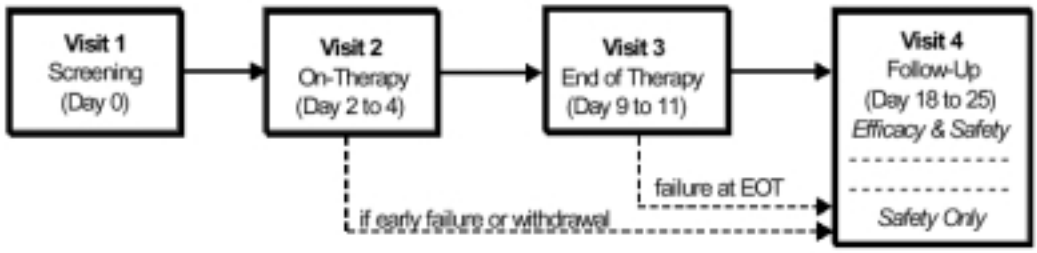
Study Drug and Dosing Schedule: Gemifloxacin is produced as a white, film-coated, oval tablet. Each tablet contains gemifloxacin-S mesylate salt 400 mg, which is equivalent to gemifloxacin 320 mg pure free base. Batch number for gemifloxacin used in the study was N99112.

Adequacy of Comparator: The protocol was an open-label, non-comparative study by design.

Study Design:
Study-206 was an open-label, prospective, multicenter, non-comparative, study of patients over the age of 16 years with ABS. The study goal was to enroll a minimum of 400 evaluable patients in centers in the USA, Mexico, Argentina, Hungary, and Poland. Patients were randomized using an automated telephone system (ClinPhone®) and were required to return for evaluation for a total of 4 visits over a span of 3 weeks to evaluate their clinical and bacteriological response to treatment as shown in (Figure-1)[12] . The Applicant's goal was to ensure a sufficient number of patients with the pre-therapy pathogens representative of ABS (50 *S. pneumoniae, 50 H. influenzae*, and 30 *M. catarrhalis*).

[12] Figure-1 Adapted from NDA 21376, p23/1804.

Figure 1 Schedule of Assessment



Protocol Overview:

Inclusion Criteria:

Male or female patients may be included in this study if the following criteria are met:

1) Patient is male or female aged 16 years.

2) Patient has purulent nasal discharge on Day 0 (screening visit) of the study.

3) Patient has respiratory signs and symptoms for at least 3 days (for severe cases), 7 days (for mild-to-moderate cases) but less than and including 28-days duration, as defined by purulent/mucoid nasal discharge or purulence in the nasal cavity on examination and at least one *major* or two *minor* criteria:

- *Major criteria* include: Facial pain/pressure/tightness over affected sinus(es), facial congestion/fullness, or nasal obstruction/blockage.
- *Minor criteria* include: Tooth pain, earache, non-vascular headache (Within previous 24 hours), sore throat, cough, halitosis, fever (Fever is defined as 38 ° C/100.4°F oral, 39°C/102.2°F rectal, or 38.5°C/101.2°F tympanic, as measured in the clinic or by the patient in the previous 12 hours), change in perception of smell, or periorbital swelling.

4) Patient has radiologically confirmed *(i.e*., via Water's view X-ray or a CAT [computed axial tomography] scan) ABS of the affected sinus(es) *(i.e*., sinus opacification and /or an air-fluid level), within 72 hours before the time of enrollment. Patients with mucosal thickening alone will not be allowed in the study.

5) Patient or parent/legal guardian has consented to initial sinus puncture and will consent to repeat sinus punctures of the affected sinus(es) if a clinical treatment failure

or recurrence.

6) Patient has an ABS infection which is suitable for treatment with oral antibacterial therapy.

7) Patient or parent/legal guardian is willing and able to comply with the protocol (including sinus puncture/aspiration of the sinus cavity).

8) Patient or parent/legal guardian has provided written and dated informed consent to participate in the study.

Exclusion Criteria:

Male or female patients must be excluded from this study, if any of the following criteria apply:

1) Patient has known or suspected hypersensitivity to quinolone antibacterials.

2) Patient has received antibacterial therapy within 7 days of study entry (prophylaxis for other indications excepted, however this must be stopped on study entry).

3) Patient is participating in another patient clinical trial or has received or anticipates receiving an investigational drug, vaccine, or medical device (non-government approved) within 30 days (or 5 half-lives, whichever is longer) prior to the first dose of study medication or during the conduct of the study.

4) Patient has a life-threatening or serious unstable underlying disease which is likely to preclude evaluation of response to an antibacterial in ABS *(e.g.*, cystic fibrosis, immunosuppression, sepsis).

5) Patient is HIV-positive with a CD 4 count of <500 cells/mm 3.

6) Patient is currently receiving or scheduled to receive corticosteroids at a dose greater than 10mg/day of prednisone (or the equivalent).

7) Patient has a concomitant infection which would preclude the evaluation of response to study medication in ABS *(e.*g., tooth abscess).

8) Patient has had prior endoscopic sinus surgery, including Caldwell-Luc procedure, within 6 months (prior septal deviation repair, turbinate resection, or rhino/turboplasty surgeries not involving the actual sinuses are allowed).

9) Patient has nasal polyp disease extending proximal to the middle turbinate.

10) Patient requires hospitalization, parenteral antibacterial therapy, or has signs and symptoms of a disseminated infection.

11) Patient has a history of chronic sinusitis *(i.e*., three or more previous episodes/exacerbations of sinusitis in the preceding 12 months or one episode/exacerbation of sinusitis in the preceding 3 months, or continuing symptoms lasting longer than 28 days).

12) Patient has intraorbital or intracranial complications that would interfere with the interpretation of radiological images of the affected sinus(es) *(e.g*., previous surgery of a congenital abnormality of the head and neck).

13) Patient is a female who is pregnant (Patient has a positive urine pregnancy test at screening) , lactating, or planning a pregnancy during the study, or a woman of childbearing potential and not using an accepted method of birth control *(i.*e., surgically sterile, intra-uterine contraceptive device, oral contraceptive plus barrier contraception, other hormone delivery systems plus barrier contraception, diaphragm or condom in combination with contraceptive cream, jelly, or foam). (Some antibacterials are known to react with oral contraceptives or other hormonal delivery systems and hence reduce their effectiveness. As a precaution against loss of effectiveness patients should remain on their hormonal contraception with additional barrier contraception for the duration of the study period and for the remainder of the menstrual cycle coincident with the last dose of study medication.

14) Patient has known or suspected creatinine clearance of less than 40 mL/min.

15) Patient has known or suspected severe hepatic impairment or alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase levels greater than three times the upper limit of normal, or bilirubin levels greater than one and a half times the upper limit of normal.

16) Patient is currently receiving treatment or medication for epilepsy, convulsions, or myasthenia gravis.

17) Patient has a clinical history of hemolytic crisis or known glucose-6-phosphate dehydrogenase (G6PD) deficiency.

18) Patient with active alcohol or drug abuse.

19) Patient is concurrently receiving sucralfate, or tubular secretion inhibitors *(e.*g., probenecid).

20) Patient has previously been enrolled in this study or any other gemifloxacin study.

21) Patient has a history of tendinitis while taking fluoroquinolones.

22) Patient is at risk of bacterial endocarditis or has significant valvular heart disease.

Study Procedures:

Patients who met the eligibility criteria and signed informed consent were enrolled in the study. Since there was no comparator in this study, all patients received gemifloxacin 320 mg po qd for 5 days. The protocol's visitation schedule for assessments was described earlier in Figure-1. A summary of study procedures can be found in **Table-27**.

A difference of Study-206 compared to Study-186 is the DNA analysis performed on a 10 mL blood sample collected during screening. The analysis was to determine if there were associations between particular genes and susceptibility to ABS. Permission to participate in the DNA study was optional. It required a consent form and the same confidentiality issues governing the study. Participating subjects had to be >18 years of age.

Bacteriological evaluation in the study required that all patients undergo sinus puncture aspirate at the Screening visit. In addition patients who were labeled as failures or had recurrence of disease at any time during the study or at the F/U visit were required to have another sinus puncture aspirate study at EOT or F/U. Sinus puncture was allowed using one of the following routes: via the canine fossa, via the lateral wall of the nasal cavity, or via the hard palate. The microbiologic assessment of the samples included performing a Gram stain, leukocyte count, and quantitative microbiology assessment.

Table-27 Outline of Study Procedures
(Source NDA 21376, Vol16/17, p:1301)

Visit No. **Day**	**Screening** **1** **(0)**	**On-Therapy** **2** **(2 to 4)**	**EOT** **3** **(9 to 11)**	**F/U** **4** **(18 to 25)**
Written Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographic Data	X			
Medical History	X			
Pregnancy Test	X			
Physical Examination	X			
Clinical Evaluation	X	X	X	X
Call to ClinPhone	X		X	X
Radiological Examination	X			X
Sinus Puncture/aspiration	X		X	X
Vital Signs (temp and sitting BP, pulse, and respiration rate)	X	X	X	X
Blood sample (hematology, clinical chemistry)	X		X	
Blood Sample for DNA Analysis	X			
Prior/Concomitant Medication	X	X	X	X
Baseline Signs/Symptoms, AEs	X	X	X	X
Medical Procedures		X	X	X
Assessment of Compliance		X	X	
Study Conclusion Reason				X

Reasons for Withdrawal:

Patients were withdrawn from the study if gemifloxacin was stopped by an investigator or if a patient did not return for follow up. Patients were also allowed to withdraw from participation at any time. Other reasons for withdrawal include: occurrence of a severe adverse effect, an insufficient therapeutic effect, or a protocol deviation.

Efficacy Endpoints:

The primary efficacy parameter used was Bacteriological Response (success or failure) at Follow-Up (Visit 4), described as Success or Failure and defined as:

- *Success*: All initial pathogens were eradicated or presumed eradicated at the follow-up assessment, without any new infections, but with or without colonization.

- *Failure*: Recurrence of one or more of the initial pathogens at the follow-up assessment, a new infection, an assessment of unable to determine for one or more initial pathogens, or the end of therapy bacteriological response was failure.

The Applicant categorized bacteriological outcome in patients as follows:

- *Follow-Up Bacteriological Eradication*: The initial pathogen was eradicated or presumed eradicated at the end of therapy and was still eradicated at follow-up.

- *Follow-Up Presumed Bacteriological Eradication*: The initial pathogen was eradicated or presumed eradicated at end of therapy, a repeat sinus aspiration was not indicated, and the patient's clinical outcome was "follow-up clinical success".

- *Bacteriological Recurrence*: The initial pathogen was eradicated or presumed eradicated at end of therapy but reappeared at follow-up.

- *Presumed Bacteriological Recurrence*: The initial pathogen was eradicated or presumed eradicated at end of therapy, a repeat sinus aspirate was not taken, and the patient's clinical outcome was "clinical recurrence".

- *Unable to Determine*: An assessment of bacteriological outcome could not be made.

If a new pathogen is identified at F/U the following categories were defined:

- *New Infection*: A new pathogen was identified at F/U in a symptomatic patient requiring additional antibacterial therapy, i.e., a clinical recurrence.

- *Colonization*: A new pathogen was identified at F/U in a non-symptomatic patient who did not require additional antibacterial therapy, i.e., a F/U

clinical success.

Patients were excluded from the bacteriology PP population if the initial pathogen response was "unable to determine". Also patients were described as a failure at the F/U visit if the patient was a "bacteriological failure at EOT."

Secondary efficacy parameters included:

- Bacteriological response (success or failure) at EOT (Visit 3).
  (Bacteriologic response at EOT for Study-206 is similar as previously described for Study-186).

- Clinical response (success or failure) at F/U (Visit 4).
  (Clinical response at F/U and EOT was determined by comparing the signs and symptoms obtained at Visit-1 and at Visit-3 and Visit-4. Clinical outcome was categorized as Success, Failure, or Unable to Determine according to the criteria described in **Table-28**.

A patient's Clinical Response at F/U was defined as Success if the F/U clinical evaluation was "F/U clinical success." Clinical Response was defined as Failure if at F/U the clinical evaluation was "clinical recurrence" or "unable to determine." At the EOT a patient's clinical outcome was Failure when he/she was marked "clinical failure" or "unable to determine." Patients identified as Failures (at EOT or F/U) were limited to the ITT population (Patients were excluded from the Clinical PP population if they had a clinical outcome of "unable to determine.")

- Clinical response (success or failure) at End-of-Therapy (Visit 3).
  (Patients who were a treatment failure at the On-Therapy visit were categorized with the EOT assessment).

- Combined clinical and radiological response (success, failure or unable to determine) at Follow-Up (Visit 4).

- Therapeutic response (success or failure) at Follow-Up (Visit 4).

- Therapeutic response (success or failure) at End-of-Therapy (Visit 3).

The last three secondary parameters are similar to what has been described in Study-186; with an additional parameter of therapeutic response at EOT.

Table-28 Criteria for Determining Clinical Outcome at End of Therapy and Follow- Up
Source: NDA 21376, Vol. 12/17, Table-2, p42

Visit	Clinical Outcome	Criteria
EOT (Visit 3, Day 9-11)	Clinical success	Sufficient improvement or resolution of the signs and symptoms of ABS recorded at screening such that no additional antibacterial therapy was indicated for ABS.
	Clinical failure	Insufficient improvement or deterioration of signs and symptoms of ABS recorded at screening such that additional antibacterial therapy was indicated for ABS.
	Unable to determine	An assessment of clinical outcome could not be made (e.g., the patient was lost to follow-up or did not consent to clinical examination).
Follow-Up (Visit 4, Day 18-25)	Follow-up clinical success	Sustained improvement or resolution of signs and symptoms of ABS for patients who were clinical successes at the end of therapy visit, such that no additional antibacterial therapy was indicated for ABS.
	Clinical recurrence	Reappearance or deterioration of signs and symptoms of ABS for patients who were clinical successes at the end of therapy, such that additional antibacterial therapy was indicated for ABS.
	Unable to determine	An assessment of clinical outcome could not be made (e.g., the patient was lost to follow-up or did not consent to clinical examination).

Note: For patients who withdrew before the end of therapy visit (Visit 3), clinical outcome was determined at the time of withdrawal.

Statistical Considerations:

This study was primarily a bacteriological study, therefore the Applicant planned to enroll of approximately 400 patients to ensure a sample size of 200 evaluable patients. The Applicant calculated point estimates for primary & secondary response rates. Confidence intervals were also calculated using the normal approximation to the binomial distribution. Point estimates and 95% confidence intervals were calculated and stratified for the primary efficacy variable by country and also by history of allergic rhinitis. The protocol indicated that a further analysis of the primary efficacy parameter by multiple imputation on the bacteriology ITT population would be carried out if there was more than 5% of patients with missing data.

Analysis Populations
The analysis populations for Study-206 are similar to what has already been described for Study-186. These populations were the ITT, Bacteriology ITT, Clinical PP, and the Bacteriology PP. The reader is referred to Study-186 for a detailed description of the study populations. Window

visit frames were similarly extended in Study-206 as described in the preceding protocol. Protocol violations for this study were the same as those described for Study-186. The ITT populations (Clinical and Bacteriology) were of primary interest in the protocol analysis, especially the Bacteriology ITT population, and was used to assess the safety and efficacy of gemifloxacin (In Study-186 the Clinical PP was the primary population analyzed). The PP populations (Clinical & Bacteriology) were primarily used to assess efficacy.

Study Results:

Population

Twenty-seven of the 40 centers that participated in the study were from the USA. There were 8 centers in Poland, 4 centers in Hungary, and 1 center in Costa Rica. A total of 469 patients were enrolled in the study and were considered part of the ITT population. The total number of patients who completed the study was 452, the remaining 17 patients were withdrawn from the study. **Table-29** provides a description of patient disposition by population:

Table-29 Patient Disposition (All Enrolled Patients)

Source: NDS 21376 Vol. 12/17, Table-5,p: 65

Population	Gemifloxacin 320mg qd n
Enrolled	469
Received Study Medication (ITT)*	469
Completed Study	452
Patients Withdrawn	17
Clinical PP End of Therapy	439
Clinical PP Follow-Up	433
Bacteriology ITT	236
Bacteriology PP End of Therapy	219
Bacteriology PP Follow-Up	216

Data Source: Section 10, Table 10.01; Appendix B, Listings B.01, B.03, B.04 and B.05.
* These patients comprised the ITT population for efficacy and safety.

MO Comment: *Most patients were recruited from Hungary (n=193), followed by Poland (n=142) and the USA (n=132). There were only two patients recruited from Costa Rica. Recruitment targets of 50 patients each for S. pneumoniae and H. influenzae were reached; however, the study failed to achieve the 30 patient target for M. catarrhalis despite enrolling 469 patients.*

Demographic and Baseline Characteristics

The majority of patients in the study were white (93%). The mean age was 37.6 years (range of 16-81 years), and gender distribution was 60% females 280/469, and 40% males 189/469. Both

ITT populations were comparable in their demographic characteristic rates **Table-30**. Similarly the demographic characteristics of the Bacteriology PP (F/U and EOT) and the Clinical PP (F/U and EOT) were comparable to the ITT populations.

Table-30 Demographic Characteristics (ITT Population and Bacteriology ITT Follow-Up Population) Source: NDA 21376, Vol. 12/17, Table-11, p:71.

Demographic Characteristic	Gemifloxacin 320mg qd ITT N=469	Gemifloxacin 320mg qd Bacteriology ITT N=236
Gender: n (%)		
Female	280 (59.7)	145 (61.4)
Male	189 (40.3)	91 (38.6)
Age (yr)		
Mean (SD)	37.6 (13.8)	37.2 (14.1)
Range	16-81	17-78
Race n (%)		
White	437 (93.2)	222 (94.1)
Black	15 (3.2)	7 (3.0)
Other*	17 (3.6)	7 (3.0)
Weight (kg)		
Mean (SD)	72.6 (15.8)	72.1 (15.8)
Range	37.1-136	43-136
Height (cm)		
Mean (SD)	170 (9.0)	170 (9.1)
Range	148-193	148-192

* Other included Hispanic and multiracial.

Imaging Characteristics

Most patients enrolled, 466/469 (99.4%) had findings on sinus imaging studies (x-ray or CAT) consistent with a diagnosis of sinusitis. Three patients had normal imaging findings, another 3 patients had only mucosal thickening. Those 6 patients were excluded from the per protocol analysis. **Table-31** describes the imaging findings in the study.

Table31 Sinus X-Ray or CAT Scan Abnormalities at Screening (ITT Population)
Source: NDA 21376, Vol. 12/17, Table-12, p:72

	Gemifloxacin 320mg qd N=469 n	(%)
Sinus X-Ray/CAT Scan Performed	469	(100.0)
Abnormal Image Results	466	(99.4)
Abnormality		
Air Fluid Level	196	(41.8)
Sinus Opacification	315	(67.2)
Air Fluid Level and /or Sinus Opacification	463	(98.7)
Other*	318	(67.8)

*Also includes mucosal thickening alone.

CLINICAL REVIEW

Clinical characteristics at Screening:

Fourteen percent of patients (67/469) in the ITT population had a history of allergic rhinitis, and this proportion remained unchanged for the Bacteriology ITT, and the PP populations. All patients had symptoms and signs of ABS within the defined period of 3-28 days prior to enrollment. Eligibility for Study-206 required that patients had to experience a purulent/mucoid nasal discharge and one major or two minor criteria at the time of screening. **Tables-32&33** describe the number and percentage of patients who satisfied the major and minor criteria in the ITT and Clinical PP populations:

Table-32 Number (%) of Patients with Major Criteria of ABS at Screening (ITT Population and Clinical PP Follow-Up Population)

Source: NDA 21376. Vol. 12/17, Table-14, p:74

	Gemifloxacin 320mg qd			
	ITT Population N=469		Clinical PP Population N=433	
Sign/Symptom	**n**	**(%)**	**n**	**(%)**
Nasal Discharge				
Absent	2	(0.4)	1	(0.2)
Clear	1	(0.2)	1	(0.2)
Mucoid	27	(5.8)	22	(5.1)
Purulent	439	(93.6)	409	(94.5)
Facial Pain/Pressure/Tightness				
Absent	75	(16.0)	71	(16.4)
Evident Upon Movement	115	(24.5)	98	(22.6)
Present with Pressure	226	(48.2)	214	(49.4)
Both	53	(11.3)	50	(11.5)
Facial Congestion/ Fullness	290	(61.8)	262	(60.5)
Nasal Obstruction/Blockage	415	(88.5)	384	(88.7)
Nasal Cavity Purulence	441	(94.0)	407	(94.0)

Table-33 Number (%) of Patients with Minor Criteria of ABS at Screening (ITT Population and Clinical PP Follow-Up Population)

Source: NDA 21376. Vol. 12/17, Table-15, p:75

	Gemifloxacin 320mg qd			
	ITT N=469		Clinical PP N=433	
Sign/Symptom	n	(%)	n	(%)
Tooth Ache	138	(29.4)	123	(28.4)
Earache	167	(35.6)	153	(35.3)
Periorbital Swelling	99	(21.1)	87	(20.1)
Non-Vascular Headache	360	(76.8)	336	(77.6)
Sore Throat	187	(39.9)	174	(40.2)
Cough	288	(61.4)	263	(60.7)
Halitosis	139	(29.6)	124	(28.6)
Unknown*	1	(0.2)	1	(0.2)
Fever	87	(18.6)	80	(18.5)
Change in Perception of Smell	221	(47.1)	201	(46.4)

*Unknown: Patient had no data recorded.

***MO Comment**: The MO reviewed in detail a 10% random sample of patients assigned from the study. In general patients satisfied the major and minor criteria as described in the study protocol.*

There were 15/469 (3.2%) patients who reported signs and symptoms of hyperglycemia at baseline and 10/469 (2.1%) patients who had anemia. Other baseline signs and symptoms that were reported at a rate of ~1% included: increased SGPT, leukopenia, hypertension, bilirubinemia, leukocytosis, and thrombocytopenia.

A significant proportion of patients received prior medications 61%. Concomitant medications were administered in 384/469 (82%). These were mainly anesthetics, analgesics, and female hormone preparations. Patients were excluded from the PP population analysis if they received prohibited prior and/or concomitant medications.

Bacteriology

All patients enrolled in the study had a sinus puncture procedure. Fifty percent 236/469 of patients had one or more pathogens identified. The other 50% (233/469) had no organisms identified or no sample taken (3/469). **Table-34** lists the number of organisms identified in the Bacteriology ITT population at screening.

Table-34 Number (%) of Pathogens Identified Per Patient at Screening (ITT Population)

Source: NDA 21376. Vol. 12/17, Table-16, p:76

	Gemifloxacin 320mg qd N=469	
	n	(%)
No. of Patients Sampled	466	(99.4)
No. of Patients with at Least One Pathogen*	236	(50.3)
Number of Pathogens		
None	230	(49.0)
1	200	(42.6)
2	33	(7.0)
3	3	(0.6)
Unknown**	3	(0.6)

*These patients comprised the ITT population.
**Unknown includes all patients where a sample is not taken.

Among the organisms that were isolated in sinus puncture specimens in the study, were *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureu*s, and *E. coli*. According to the Applicant these were the key pathogens identified in ABS. The Applicant considered *S. aureus* a pathogen when: gram positive cocci were observed in a gram stain, bacteria grew in pure culture, and the bacterial count was $\geq 10^4$ cfu/mL. *S. pneumoniae* was identified as the most common organism, it was isolated from 101 patients (42.8% of the Bacteriology ITT population). **Table-35** lists the organisms identified at Screening. Penicillin-resistant *S. pneumoniae* made up 8/101 (8%) of the total sample. One of those 8 patients failed treatment with gemifloxacin, although gemifloxacin MICs for *S. pneumoniae* in the study ranged from 0.002- 0.06 µg/mL. The gemifloxacin MICs for the penicillin resistant isolates ranged from 0.015- 0.03 µg/mL. Five of these penicillin-

resistant pneumococci were intermediately susceptible to ofloxacin. There were 20/101 pneumococcal isolates that were clarithromycin-resistant, one of these clarithromycin-resistant isolates failed therapy in a patient.

MO Comment: *The Agency's Draft Guidance Document for the development of antimicrobial agents for ABS considers S. aureus to be a pathogen in ABS when it is isolated in pure culture and the bacterial count is ≥10^4 cfu/mL in association with evidence on gram stain of supporting bacterial morphology and the presence of WBCs. The MO considers S. pneumoniae, H. influenzae, and M. catarrhalis as the key pathogens in ABS in accordance with the Draft Guidance document.*

MO Comment: *Ofloxacin susceptible S. pneumoniae have an ofloxacin MIC ≤ 2µg/mL and intermediately susceptible S. pneumoniae isolates have an MIC of 4µg/mL. All the S. pneumoniae isolates in the study were found to be susceptible to gemifloxacin. For a detailed discussion of the microbiology results the reader is referred to Dr. Peter Dionne's Microbiology Review .*

MO Comment: *The MO reviewed all S. aureus cases that were submitted to verify the Applicant's claim of efficacy for S. aureus. This is discussed in more detail in the Results section.*

Table-35 Number (%) of Patients with Key Pathogens Associated with ABS at Screening (Bacteriology ITT Population and Bacteriology PP Follow-Up Population)
Source: NDA 21376. Vole 12/17, Table-17, p:77

	Gemifloxacin 320mg qd			
	Bacteriology ITT Population N=236		Bacteriology PP Follow- Up Population N=216	
Pre-therapy Pathogen	n	(%)*	n	(%)*
S. pneumoniae	101	(42.8)	91	(42.1)
H. influenzae	50	(21.2)	46	(21.3)
M. catarrhalis	15	(6.4)	15	(6.9)
S. aureus	12	(5.1)	9	(4.2)
E. coli	12	(5.1)	12	(5.6)

*Note: Percentages are based on the total number of patients; some patients may have more than one pathogen.

Isolated organisms that were associated with ABS in this study showed the following MIC ranges to gemifloxacin: *H. influenzae* from 0.001-0.008 µg/mL, *M. catarrhalis* 0.004-0.03 µg/mL, *S. aureus* 0.008-8 µg/mL, and *E. coli* 0.004-0.25 µg/mL. There was one reported *S. aureus* isolate that was intermediately susceptible to vancomycin (MIC of 8 µg/mL) with an MIC of 0.03 µg/mL for gemifloxacin.

Withdrawals

Most patients 452/469 (96.4%) completed the study (i.e. received the 5-day treatment course of gemifloxacin). Of the 17 (3.6%) patients who were withdrawn, 11 were "lost to follow-up, 4 had an "adverse reaction", and 2 had a "protocol violation". Patients who suffered an adverse effect were all withdrawn within 7 days of enrollment into the study.

MO Comment: *The MO reviewed the four patients who were withdrawn because of an adverse event. Patient #206-501-34288 had a high bilirubin level on screening , the patient received only one tablet of gemifloxacin and was withdrawn. Patient #206-501-34338 also had a high bilirubin level on screening. This patient received three gemifloxacin doses prior to being withdrawn from the study because of the high bilirubin level at screening. At F/U the patient was labeled a success, but was excluded from the Per Protocol populations. Although the patient was excluded from the PP populations, reporting him as a success is not correct since he received another quinolone (ciprofloxacin) and his compliance rate is <80% (he received 3/5 gemifloxacin doses). Patient #206-602-28922 had a sinus puncture performed and grew pure Staph. Coag(-) >10^5 cfu/mL, many bacteria and WBCs were observed on microscopy. The patient completed 4 tablets of gemifloxacin therapy. Due to a high fever he required hospitalization and was treated with cefoperazone IV. The patient was ultimately given a diagnosis of pneumonia. Patient #206-607-28889 grew S. pneumoniae sensitive to gemifloxacin MIC 0.015 ug/mL. The patient took 3 doses of gemifloxacin and then was switched to cefuroxime due to nausea and gastritis which resolved as soon as she stopped the study medication.*

Patients Excluded for Non-evaluability

The Bacteriology ITT population was comprised of 236/469 patients (50.3%), the other 233 patients did not have a pathogen identified at screening and where thus excluded from that population. Another 17 patients were excluded from the Bacteriology PP population at EOT (219/469 patients), and an additional 3 patients were excluded from the Bacteriology PP population at F/U (216/469 patients).

Common reasons for exclusion were: "unable to determine-clinical", "unable to determine-bacteriological", "medication compliance", and "visit compliance". **Table-36** lists the reasons why patients were excluded from the Bacteriology PP population.

Table-36 Number (%) of Patients Excluded from the Bacteriology PP Populations, by Reason

Source NDA 21376. Vol. 12/17. Table-9, p:69

PV Criteria	Gemifloxacin 320mg qd N=236**	
End of Therapy	n	(%)
PV 2 (Exclusion Criteria Violated)	1	(0.4)
PV 7 (Other Antibacterial Treatment)	1	(0.4)
PV 11 (Concomitant Medication)	2	(0.8)
PV 17 (Medication Compliance)	7	(3.0)
PV 18 (Visit Compliance)	5	(2.1)
PV 20 (No Radiological Confirmation of ABS)***	2	(0.8)
PV 21 (Unable to Determine – Clinical)	7	(3.0)
PV 22 (Different method of radiological exam)	2	(0.8)
PV 25 (History of chronic sinusitis)	1	(0.4)
PV 27 (Unable to Determine – Bacteriological)	7	(3.0)
Total Excluded	17	(7.2)
Follow-Up		
PV 2 (Exclusion Criteria Violated)	1	(0.4)
PV 7 (Other Antibacterial Treatment)	4	(1.7)
PV 11 (Concomitant Medication)	2	(0.8)
PV 17 (Medication Compliance)	7	(3.0)
PV 18 (Visit Compliance)	5	(2.1)
PV 20 (No Radiological Confirmation of ABS)***	2	(0.8)
PV 21 (Unable to Determine – Clinical)	10	(4.2)
PV 22 Different method of radiological exam	2	(0.8)
PV 25 History of chronic sinusitis	1	(0.4)
PV 27 (Unable to Determine – Bacteriological)	10	(4.2)
Total Excluded	20	(8.5)

Note: some patients may have had more than one protocol violation.
**Bacteriology ITT population
***Included sinus opacification and/or air fluid level. Mucosal thickening alone was insufficient for inclusion.

Four hundred and thirty three patients of the 469 patients in the ITT population were in the Clinical PP population at F/U. Thirty (6.4%) patients were excluded at EOT and another 6 patients were excluded at F/U. The most common reasons for exclusion were: “unable to determine-clinical”, “medication compliance”, and “visit compliance”. **Table-37** lists the number and reason for exclusion from the Clinical PP populations.

Table-37 Number (%) of Patients Excluded From the Clinical PP Populations, by Reason

Source: NDA 21376. Vol. 12/17, Table-10, p:70

PV Criteria*	Gemifloxacin 320mg qd N=469	
End of Therapy	**n**	**(%)**
PV 2 (Exclusion Criterion Violated)	4	(0.9)
PV 7 (Other Antibacterial Treatment)	3	(0.6)
PV 11 (Concomitant Medication)	2	(0.4)
PV 17 (Medication Compliance)	8	(1.7)
PV 18 (Visit Compliance)	7	(1.5)
PV 20 (No Radiological Confirmation of ABS)**	6	(1.3)
PV 21 (Unable to Determine – Clinical)	9	(1.9)
PV 22 (Different method of radiological exam)	4	(0.9)
PV 25 (History of chronic sinusitis)	3	(0.6)
Total Excluded	**30**	**(6.4)**
Follow-Up		
PV 2 (Exclusion Criterion Violated)	4	(0.9)
PV 7 (Other Antibacterial Treatment)	6	(1.3)
PV 11 (Concomitant Medication)	3	(0.6)
PV 17 (Medication Compliance)	8	(1.7)
PV 18 (Visit Compliance)	8	(1.7)
PV 20 (No Radiological Confirmation of ABS)**	6	(1.3)
PV 21 (Unable to Determine – Clinical)	14	(3.0)
PV 22 (Different method of radiological exam)	4	(0.9)
PV 25 (History of chronic sinusitis)	3	(0.6)
Total Excluded	**36**	**(7.7)**

Note: some patients may have had more than one protocol violation.
**Included sinus opacification and /or air fluid level. Mucosal thickening alone was insufficient for inclusion.

MO Comment: *The MO agrees with the exclusions to the Clinical PP and Bacteriological PP populations.*

Treatment Compliance

Overall compliance to the study medication was defined similar to what has already been discussed in Study-186. The majority of patients 99% showed early compliance and ~98% of patients were in the 80-120% category. **Table-38** describes compliance rates in the ITT population. Patient attendance at the scheduled visits was 98% (461 patients) at EOT and 97% (456 patients) at F/U.

Table-38 Number (%) of Patients Compliant with Study Medication (ITT Population)

Source: NDA 21376. Vol. 12/17, Table-25, p:92

	Gemifloxacin 320mg qd N=469 n	(%)
Early Compliance		
Yes	465	(99.1)
No	2	(0.4)
Unknown	2	(0.4)
Percentage Compliance		
<40%	2	(0.4)
40% - <80%	2	(0.4)
80% - 120%	461	(98.3)
Unknown	4	(0.9)
Overall Compliance		
Yes	461	(98.3)
No	8	(1.7)

Efficacy Results

The 4 populations that were defined in the study were the ITT, Bacteriology ITT, Bacteriology PP, and Clinical PP populations. Efficacy results were first reported for the primary efficacy parameter-bacteriological response at F/U- followed by the secondary efficacy parameters:

- Bacteriological response at EOT
- Clinical response at EOT
- Therapeutic response at EOT
- Clinical response at F/U
- Combined clinical and radiological response at F/U
- Therapeutic response at F/U

Primary Efficacy Results:

Bacteriological Response

Bacteriological response at F/U was the primary efficacy parameter. The Applicant reports that the success rate in the ITT population was 203/236 (86%) patients, and in the Bacteriology PP population 195/216 (90%) patients. The higher success rate observed in the Bacteriology PP population was primarily because the non-evaluable patients were not included in the PP analyses whereas the non-evaluable patients with assessments of “unable to determine” were included in the denominator in the ITT analysis. **Table-39** provides the per patient Bacteriological response at F/U for the Bacteriology ITT and PP populations. A multiple imputation analysis for the primary efficacy parameters was not carried out due to the low proportion of patients, 1.3% (3/236), with a bacteriological outcome of “unable to determine” at F/U.

MO Comment: *The MO reviewed all cases from Center #503. There was a total of 42 patients enrolled at Center #503, in Hungary. Six of 42 patients had no growth on sinus aspirate. The MO observed that there was an instance when two patients (#206.503.28850/28847) had both S. pneumoniae and H. influenzae from sinus aspirate cultures that were reported on the same day and had similar MICs; a similar observation was noticed for two patients with S. aureus (#206.503.28767/28769) and S. pneumoniae (#206.503.34220/34219). This raises the potential of a lapse in infection control procedures, or a laboratory error. In addition, there were patients with unusual organisms for ABS isolated from their sinus aspirates (Pseudomonas, Stenotrophomonas, Citrobacter, Hafnia, E. coli, Klebsiella, Group B Strep.). The Division of Scientific Investigation was notified of the potential data error. Analysis of the data excluding patients from Center #503, revealed no difference in efficacy for the 3 important pathogens associated with ABS.*

Table-39 Per Patient Bacteriological Response at Follow-Up (Bacteriology ITT Populations and Bacteriology PP Follow-Up)
Source: NDA 21-376. Vol. 12/17, Table-26, p:94

	Gemifloxacin 320mg qd
Bacteriology ITT Population	**N=236**
Success, n (%)	203 (86.0)
Failure, n* (%)	33 (14.0)
95% CI for Success	81.59, 90.44
Bacteriology PP Follow-Up Population	**N=216**
Success, n (%)	195 (90.3)
Failure, n (%)	21 (9.7)
95% CI for Success	86.33, 94.23

*Patients with an outcome of unable to determine at end of therapy were considered to have a response of failure at follow-up

CLINICAL REVIEW

When the Applicant conducted an analysis by country, the success rate for patients showed some variation as described in the following **Table-40.**

Table-40 Per Patient Bacteriological Response At Follow-Up By Country (Bacteriology ITT and PP Population)
Source: NDS 21-376. Vol. 12/17, Table-41, p:117

	Gemifloxacin 320mg qd	
	Bacteriology ITT Population N=236	**Bacteriology PP Population N=216**
Costa Rica	n*	n*
Success, n (%)	2/2 (100.0%)	2/2 (100.0)
95% CI	**	**
Hungary		
Success, n (%)	96/112 (85.7)	93/105 (88.6)
95% CI	(79.23, 92.20)	(82.49, 94.66)
Poland		
Success, n (%)	58/62 (93.6)	58/59 (98.3)
95% CI	(87.43, 99.7)	(95.01, 100.0)
USA		
Success, n (%)	47/60 (78.3)	42/50 (84.0)
95% CI	(67.91, 88.76)	(73.84, 94.16)

*n= total number of patients in the country/country grouping
**Confidence Interval not calculated due to very small numbers

MO Comment: *The USA had the lowest rates for success, possibly secondary to the high number of patients with allergic rhinitis in contrast to other countries. Other unrecognized factors could also be responsible for the observed difference.*

The results for patients who did not have a history of allergic rhinitis revealed a higher success rate in both the Bacteriology ITT (88.7%) and the Bacteriology PP (93.1%) populations. Patients who did have a history of allergic rhinitis had a success rate of 68.8% in the Bacteriology ITT population and 72.4% in the Bacteriology PP population. In a further analysis of allergic rhinitis the Applicant noted that 22/50 patients recruited from USA centers had allergic rhinitis in the Bacteriology PP F/U population; 5/100 patients from Hungary, 1/58 patients from Poland, and 1/2 patients from Costa Rica had allergic rhinitis. Similarly in the Bacteriology ITT population 25/35 of patients who had allergic rhinitis were from the USA, and 1/2 from Costa Rica, 5/107 from Hungary, and 1/61 from Poland. Close to 40% of patients in the USA had allergic rhinitis. The success rate in USA patients with allergic rhinitis was 73% compared to a rate of 93% in patients who lacked a history of allergic rhinitis (Bacteriology PP at F/U). **Table-41** lists the Bacteriological Response at F/U for patients who had a history of allergic rhinitis by country.

Table-41 Per Patient Bacteriological Response At Follow-Up By History Of Allergic Rhinitis And Country:

Source: NDA 21376. Vol. 17/17. Table 2.1, p1798

Bacteriology Per-Protocol Follow-Up Population

Allergic Rhinitis	USA	Costa Rica	Hungary	Poland	ALL
Yes	16 / 22 (72.7%)	1 / 1 (100.0%)	3 / 5 (60.0%)	1 / 1 (100.0%)	21 / 29 (72.4%)
No	26 / 28 (92.9%)	1 / 1 (100.0%)	90 / 100 (90.0%)	57 / 58 (98.3%)	174 / 187 (93.0%)
ALL	42 / 50 (84.0%)	2 / 2 (100.0%)	93 / 105 (88.6%)	58 / 59 (98.3%)	195 / 216 (90.3%)

MO Comment: *Allergic rhinitis is common in the USA population presented in this study. Allergic rhinitis was reported in 32 patients in the Bacteriology ITT, 25 (78%) of those patients were from the USA. Other trials of ABS in the USA have also shown a higher rate of failure compared to other countries, due to the higher rates of allergic rhinitis in the USA.*

Principle pathogen outcomes

When all pathogens were combined, the eradication and presumed eradication rates was 85.8% in the Bacteriology ITT F/U and 90.5% in the Bacteriology PP F/U populations. Specific pathogen eradication and presumed eradication rates for the Bacteriology ITT F/U population were 87% for *S. pneumoniae*, 88% for *H. influenzae*, 100% for *M. catarrhalis*, 75% for *S. aureus*, and 92% for *E. coli*. Similar outcomes were observed for the Bacteriological PP F/U population, **Table-42**.

MO Comment*: The criteria in the CDER Draft Guidance for ABS studies requires 10-20 cases of S. aureus. On review the Applicant's data included 9 cases of S. aureus in the Bacteriology PP F/U population (>10^4 cfu/ml & pure culture) Four of the 9 isolates may have been cross-contaminated (the 4 isolates were collected at two centers #504 (#206.504.28799/28809) & #503 (#206.503.28767/28769). One sample had no WBCs on microscopy. The MO review includes 6 satisfactory isolates for S. aureus that may be used for an efficacy analysis. Therefore the applicant did not meet the requirements for S. aureus, in accordance with the Draft Guidance, to permit the inclusion of S. aureus among the listed pathogens in the ABS indication.*

Table-42 Initial Pathogen Bacteriological Outcome at Follow-Up (For All Pathogens Combined and Key Pathogens) (Bacteriology ITT Population and Bacteriology PP Follow-Up Population)
Source: NDA 21376. Vol. 12/17. Table 27, p:95

		Gemifloxacin 320mg qd Bacteriology ITT N= 236		Bacteriology PP Follow-Up N=216	
Initial Pathogen	**Bacteriological Outcome**	**n**	**(%)**	**n**	**(%)**
All Pathogens	*(n)*	275	(100.0)	252	(100.0)
	Presumed Eradication	233	(84.7)	225	(89.3)
	Eradication	3	(1.1)	3	(1.2)
	Presumed Recurrence	13	(4.7)	13	(5.2)
	Recurrence	4	(1.5)	3	(1.2)
	Unable to determine	4	(1.5)	0	
	Missing	18	(6.5)	8	(3.2)
S. pneumoniae	*(n)*	101	(100.0)	91	(100.0)
	Presumed Eradication	88	(87.1)	85	(93.4)
	Presumed Recurrence	5	(5.0)	5	(5.5)
	Recurrence	1	(1.0)	0	
	Unable to determine	3	(3.0)	0	
	Missing	4	(4.0)	1	(1.1)
H. influenzae	*(n)*	50	(100.0)	46	(100.0)
	Presumed Eradication	44	(88.0)	43	(93.5)
	Presumed Recurrence	2	(4.0)	2	(4.3)
	Unable to determine	1	(2.0)	0	
	Missing	3	(6.0)	1	(2.2)
M. catarrhalis	*(n)*	15	(100.0)	15	(100.0)
	Presumed Eradication	15	(100.0)	15	(100.0)
**S. aureus*	*(n)*	12	(100.0)	9	(100.0)
	Presumed Eradication	8	(66.7)	6	(66.7)
	Eradication	1	(8.3)	1	(11.1)
	Presumed Recurrence	2	(16.7)	2	(22.2)
	Missing	1	(8.3)	0	
E. coli	*(n)*	12	(100.0)	12	(100.0)
	Presumed Eradication	11	(91.7)	11	(91.7)
	Presumed Recurrence	1	(8.3)	1	(8.3)

(n)=Total number of pathogens
n(%)=number (%) of pathogens with a particular outcome
*****Please see MO comment on page 83 regarding the MO's analysis of the S. aureus cases.

Four patients in the Bacteriology ITT F/U population had new pathogens identified; one had superinfection with *Comamonas acidovorans* and the other three patients had a new infection identified (*C. acidovorans, E. coli, and K. oxytoca*).

MO Comment: *The 4 organisms identified as new pathogens at F/U are not commonly associated with ABS. The clinical significance of their isolation is not clear and may reflect, a superinfection or colonization in the setting of antimicrobial therapy, or a problem with infection control measures or laboratory methods. Patients 206/502.34254/34169 are from Hungary, both had C. acidovorans isolated. Their samples were taken within 24 hours of each other which suggests the possibility of cross contamination.*

Secondary Efficacy parameters

Clinical Response at EOT

A successful clinical outcome for the ITT and Clinical PP populations at EOT was reported for 441/469 (94%), and 421/439 (95.9%) of patients respectively.

Bacteriological Response at EOT

The success rates in the Bacteriology ITT & Bacteriology PP populations were 94.5% (223/236) & 97.7% (214/219) respectively. Thirteen patients/236 (5.5%) failed in the Bacteriology ITT population, 7 of which had an outcome of "unable to determine". Five patients/219 (2.3%) failed in the Bacteriology PP population. Specific per pathogen outcomes for *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus, and E. coli* were comparable to the results noted in the Bacteriological Response populations at F/U, **Table-42**.

Therapeutic Response at EOT

The success rates in the Bacteriology ITT & Bacteriology PP populations were 91.5% (216/236) & 94.5% (207/219) respectively.

Clinical Response at F/U

The clinical success rates in the ITT & Clinical PP populations were 87.4% (410/469) & 90.1% (390/433) respectively. **Table-43** lists the clinical response by country for the Clinical PP population at F/U.

Table-43 Clinical Response At Follow-Up By Country
Clinical Per Protocol Follow-Up Population
Source NDA 21376. Vol. 15/17, Table 11.18, p:945

Country	Clinical Response	Treatment Group Gemi 5 days (N=433)	
Costa Rica	Success	2	(100.0%)
Hungary	Success	164	(89.6%)
	Failure	19	(10.4%)
Poland	Success	131	(94.9%)
	Failure	7	(5.1%)
USA	Success	93	(84.5%)

Failure	17 (15.5%)

Combined Clinical and Radiological Response at F/U

The success rate for the combined clinical and radiological response at F/U was 85.1% (399/469) patients in the ITT population and 87.8% (380/433) in the Clinical PP population.

Therapeutic Response at F/U

The success rate for the Therapeutic Response at F/U was 86.0% (203/236) in the Bacteriology ITT population and 90.3% (195/216) in the Bacteriology PP population. **Table-44** summarizes the primary and secondary efficacy endpoints:

Table-44 Primary & Secondary Efficacy Endpoint Outcomes

Population	ITT	Bact. ITT	Clinical PP	Bact. PP
Endpoint				
Primary				
Bact. Response at F/U		203/236 (86%)		195/216 (90.3%)
Secondary at EOT				
Bact. Response		223/236 (94.5%)		214/219 (97.7%)
Clinical Response	441/469 (94%)		421/439 (95.9%)	
Therapeutic Response		216/236 (91.5%)		207/219 (94.5%)
Secondary at F/U				
Clinical Response	410/469 (87.4%)		390/433 (90.1%)	
Combined Clin. & Rad Response	399/469 (85.1%)		380/433 (87.8%)	
Therapeutic Response		203/236 (86%)		195/216*(90.3%)

*Total number of subjects was 216

Other Efficacy Parameters:

Clinical & Bacteriological Response by pathogen susceptibility

There were 23 patients in the Bacteriology ITT who had 24 pathogens isolated (13 *S. pneumoniae*, 6 *H. influenzae*, 4 *S. aureus*, 1 *E. coli*) and were labeled as clinical failure at F/U. The MICs for These 24 pathogens had MICs that were sensitive to gemifloxacin at Screening. Three/23 patients consented for repeat sinus puncture. One patient had *S. pneumoniae* isolated at F/U, the MIC 0.015 was the same as the screening MIC. The second patient had *H. influenzae* that was eradicated, but had a new infection (*Comamonas acidovorans)* at F/U. The third patient had *S. aureus* that was eradicated, but had a new infection (*E. coli)* at F/U.

Table-45 Bacteriological Success Rate at Follow-Up by Screening Pathogen Susceptibility (MIC) to Gemifloxacin (Bacteriology ITT Follow-Up Population)
Source: NDA 21376, Vol. 12/17, Table-37, p:109

Pathogen Gemifloxacin MIC (ug/mL)	Gemifloxacin 320mg qd *n/N**	 N=236 (%)
S. pneumoniae		***n***= 101
0.002	1/1	(100.0)
0.008	4/4	(100.0)
0.015	42/49	(85.7)
0.03	40/45	(88.9)
0.06	1/2	(50.0)
All	88/101	(87.1)
H. influenzae		***n***= 50
≤0.001	1/1	(100.0)
0.002	23/26	(88.5)
0.004	14/16	(87.5)
0.008	4/5	(80.0)
Missing**	2/2	(100.0)
All	44/50	(88.0)
M. catarrhalis		***n***= 15
0.004	5/5	(100.0)
0.008	9/9	(100.0)
0.03	1/1	(100.0)
All	15/15	(100.0)
S. aureus		***n***= 12
0.008	0/2	(0.0)
0.015	6/7	(85.7)
0.03	1/2	(50.0)
8	1/1	(100.0)
All	8/12	(66.7)
E. coli		**n**= 12
0.004	1/1	(100.0)
0.008	4/4	(100.0)
0.015	5/6	(83.3)
0.25	1/1	(100.0)
All	11/12	(91.7)

*n/N=number of success / number of patients with a pathogen with the specified gemifloxacin MIC
**Missing=MICs not performed because isolates were not viable

MO Comment: *No conclusions can be drawn from Table-45 about bacteriological success rates at F/U, by Screening pathogen susceptibility due to the small number of isolates within the MIC subsets.*

Drug Resistant *Streptococcus pneumoniae*

Eight of 101 *S. pneumoniae* isolates were penicillin-resistant (MIC ≥2 µg/mL. All 8 patients with PRSP were clinical and bacteriological successes. The clinical and bacteriologic success in the penicillin sensitive isolates was 68/80 (85%). There were 20/101 *S. pneumoniae* isolates that were clarithromycin-resistant; 19/20 subjects were clinical and bacteriological successes. Five/101 isolates were intermediately ofloxacin resistant; 4/5 patients were clinical and bacteriological successes. **Table-46** lists *S. pneumoniae* isolates and the associated patient outcomes.

Table-46 Clinical and Bacteriological Success Rate At Follow-Up by Screening *S. pneumoniae* Susceptibility to Antimicrobial Agents (Bacteriology ITT Follow-Up Population)

Source NDA 21376. Vol. 12/17, Table 38, p:111

	Gemifloxacin 320mg qd			
	Clinical N= 236		Bacteriological N= 236	
S. pneumoniae	**n/N**	**%**	**n/N**	**%**
Susceptibility to Penicillin	101		101	
Susceptible (≤0.06 ug/mL)	68/80	(85.0)	68/80	(85.0)
Intermediate (0.12 ug/mL)	12/13	(92.3)	12/13	(92.3)
Resistant (≥2 ug/mL)	8/8	(100.0)	8/8	(100.0)
Susceptibility to Clarithromycin				
Susceptible (≤0.25 ug/mL)	68/80	(85.0)	68/80	(85.0)
Intermediate (0.5 ug/mL)	1/1	(100.0)	1/1	(100.0)
Resistant (≥1 ug/mL)	19/20	(95.0)	19/20	(95.0)
Susceptibility to Ofloxacin				
Susceptible (≤2 ug/mL)	84/96	(87.5)	84/96	(87.5)
Intermediate (4 ug/mL)	4/5	(80.0)	4/5	(80.0)

n/N=number of clinical or bacteriological successes/ number of susceptible, intermediate or resistant pathogens.
N=Number of MIC results

Beta-lactamase producing *Haemophiles influenzae*

One/50 *H. influenzae* isolate was resistant to ampicillin at screening; the patient was a clinical and bacteriologic success. Two isolates had unknown MICs because they were not tested. The two patients with these *H. influenzae* isolates with unknown ampicillin MICs were both scored as clinical and bacteriological success. Clinical and bacteriological success was achieved for 41/47 (87%) ampicillin sensitive isolates. Success rates (clinical and bacteriological) were similar to the susceptible clarithromycin isolates 40/46 (87%)and ofloxacin susceptible isolates 42/48groups (87%). There were no resistant clarithromycin or ofloxacin isolates.

Treatment Failures

EOT Failures:

The Applicant reported 13/236 (5.5%) of patients were Bacteriological ITT failures, and 5/219 (2.3%) in the Bacteriology PP populations at EOT. In the Bacteriological ITT, 7 patients were classified as "unable to determine," 4 had presumed bacteriological persistence, 1 had documented bacteriological persistence, and 1 patient had superinfection. These last two patients are briefly summarized below.

Patient #206.019.28345 had a persistent *P. aeruginosa* at EOT and was labeled as a clinical failure. The initial MIC had increased from 0.5 µg/mL to 1 µg/mL, a two fold increase (within the error of the test) by EOT. Patient #206.502.34254 had a *C. acidovorans* (gemifloxacin MIC 0.03 µg/mL) superinfection at EOT and was labeled as a clinical failure. Initially this patient had *H. influenzae* that was eradicated.

Follow-Up Failures:

There were 33/236 (14%) patient failures at F/U in the Bacteriology ITT, and 21/216 (9.7%) in the Bacteriology PP populations. Thirteen patients were EOT failures in the ITT population, 11 patients were presumed bacteriological recurrences, 3 patients had an outcome of "unable to determine", 3 patients were documented bacteriological recurrences, 2 patients were documented bacteriological new infections, and one patient was a documented bacteriological recurrence and a new infection. Most cases of failure due to recurrence or persistence are presumed because there were no F/U sinus aspirates performed. **Table-47** describes patients with documented bacteriological recurrence and new infections.

Table-47

Patient number	Initial isolate	MIC µg/mL at Screening (gemifloxacin)	Type of Failure	Isolate at F/U	MIC at F/U (gemifloxacin)
206.035.28514	*S. pneumoniae*	0.015	Recurrence	*S. pneumoniae*	0.015
206.501.28812	*Strep. Group A*	0.03	Recurrence	*Strep. Group A*	0.03
206.502.34166	*S. aureus*	0.03	New infection Persistence	*E. coli* *S. aureus*	0.015 0.25
206.502.34169	Enterobacter	0.015	New infection	*C. acidovorans*	0.008
206.502.34262	*K. pneumoniae* *Proteus mirabilis*	0.015 0.12	Recurrence	K. *pneumoniae*	0.015
206.601.28965	*Strep. Group C*	0.002	Recurrence	*Strep. Group C* *K. oxytoca*	0.001 0.03

MO Comment: Only one patient with *S. pneumoniae* failure had a repeat sinus re-puncture. As described in Table-47, the F/U MICs were not different from the initial screening MICs.

In Table-47 the *S. aureus* isolate had a higher MIC at F/U compared to the baseline isolate. Further analysis using PFGE, Phage typing, or PCR methodology to identify whether this was a new infection may be helpful.

CLINICAL REVIEW

D. Efficacy Conclusions

Summary of Efficacy Results for Study 206

Study-206 is primarily a bacteriological study evaluating the efficacy and safety of gemifloxacin 320 mg PO qd for 5 days. The study is an open-label, multicenter, non-comparative study conducted in the USA, Hungary, Poland, and Costa Rica. The 4 study populations were the ITT, Bacteriological ITT, Clinical PP, and the Bacteriological PP; the populations of interest for primary efficacy were the Bacteriology ITT and Bacteriology PP populations. The primary efficacy parameter defined in the protocol was the Bacteriological response at the F/U visit. **Table-48** lists the summary results for the primary efficacy parameter.

Table-48 Per patient bacteriological response at follow-up (Visit 4)
Source: NDA 21376. Vol. 12/17, p:5

Population		Gemifloxacin 320mg qd
Bacteriology ITT Follow-up	**n/N**	**(%)**
Success	203/236	(86.0)
95% Confidence Interval		(81.59, 90.44)
Bacteriology PP Follow-up	**n/N**	**(%)**
Success	195/216	(90.3)
95% Confidence Interval		(86.33, 94.23)

As noted in the Table, the overall per patient success rate in the Bacteriology ITT at F/U was 86% (203/236) and in the Bacteriology PP population was 90.3% (195/216). The combined per pathogen response at F/U in the Bacteriology ITT was 85.6% (236/275), and the response rate was 87.1% (88/101) for *S. pneumonia*e, 88.0% (44/50) for *H. influenza*e, 100.0% (15/15) for *M. catarrhali*s, 75.0% (9/12) for *S. aureus* and 91.7% (11/12) for *E. col*i. Results of the secondary efficacy parameters corroborate the efficacy results observed for the primary efficacy parameter.

MO Comment: *The MO reviewed all cases of S. aureus, and had concluded that the Applicant did not submit enough cases to support a claim as per Guidance document. The reader is referred to the analysis of the MO's discussion of the S. aureus cases on page 83.*

MO Comment: *The MO reviewed all cases of K. pneumoniae, and concluded that the cases that the Applicant submitted were not adequate to support inclusion of K. pneumoniae among the pathogens listed in the ABS indication.*

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Factive® (gemifloxacin) is a fluoronaphthyridone antimicrobial agent, a member of the quinolone class. Factive® was previously reviewed for the indication of ABS at a dose of 320 mg po qd for 7 days. This previously reviewed 7-day treatment regimen was one of the indications in NDA 21-158. NDA 21-158 received an action of not approvable on December 15, 2000. In NDA 21-158, gemifloxacin was found to have satisfactory evidence of efficacy in the treatment of ABS at the dose of 320 mg po qd for 7 days. However, the safety profile of gemifloxacin (frequent rash, insufficient information on the potential for cross-sensitization and the potential for more serious dermatologic adverse events including hypersensitivity reactions and the potential for hepatic toxicity, possibly as a result of hypersensitization) prevented a satisfactory benefit/risk profile from being attained for gemifloxacin for the indications in NDA 21-158 including the 7-day ABS regimen.

Gemifloxacin was well tolerated in Studies 186 and 206, in the limited number of patients (n=687) who received oral gemifloxacin 320 mg daily for 5 days. These patients are derived from one double-blind, active comparator study and one open-label, non-comparative study.

Overall, the most common adverse events reported during the On-Therapy and 30-day post therapy interval involved the gastrointestinal system (nausea 3.1% & diarrhea 2.9%), central nervous system (headache 2.2%, dizziness 1.6%, somnolence 1.5%), and the skin & appendages (rash 1.5%, urticaria 0.6%). Photosensitivity was not reported after using the 5-day gemifloxacin course. Patients' vital signs did not show clinically relevant changes of concern. The incidence of laboratory (hematology, liver function, and renal function) abnormalities was low.

No meaningful comparisons by race or age were possible, since the majority of patients were white (95% white in the 5-day treatment group), and more than 90% of patients were in the age category of > 18 to ≤ 65 years. The reader is referred to NDA 21-158 where age and race comparisons are available.

Seven patients were withdrawn due to a reported adverse event (AE) 7/890. The AEs leading to patient withdrawals in the 5-day treatment arm were: 2 patients had an elevated bilirubin level at Screening; 1 patient had a traumatic leg fracture; 1 patient developed rash; 1 patient developed fever that was secondary to pneumonia; 1 patient developed gastritis and nausea. Only 1 patient was withdrawn from the 7-day treatment arm. The patient had vertigo that was not related to study drug.

Serious AEs were uncommon (7/890): 1 patient reported a traumatic leg fracture; 1 patient had a maxillary sinus foreign body; 1 patient had fever secondary to an ongoing pneumonia; 1 patient

had a viral illness; 1 patient had depression and an attempted suicide; 1 patient had serum sickness, the event was judged by the investigator to be related to study drug; 1 patient had a miscarriage, the event was judged by the investigator to be related to study drug.

There were no patient deaths reported. None of the patients experienced a “Temafloxacin Syndrome”. The use of gemifloxacin was not associated with hyperglycemia or hypoglycemia in association with the use of insulin or oral hypoglycemic agents. Within NDA 21-376, the QT interval was not evaluated. An evaluation of the effects of gemifloxacin on the QT interval was performed in NDA 21-158, found similar QT interval prolongation in gemifloxacin treated patients and comparators. More patients treated with gemifloxacin were observed to have prolonged QT intervals compared to comparators in the off-therapy period, the clinical correlate for this finding is not known.

The limited experience within NDA 21-376 is not sufficient to address the safety concerns related to gemifloxacin that are enumerated in the not approvable letter from the more substantive patient experience in NDA 21-158, Factive® (gemifloxacin).

Concern regarding gemifloxacin-associated rash, the potential for cross-sensitization, hepatic toxicity, and hypersensitivity persists. In addition, the Applicant should also further evaluate QT interval effects. These aforementioned outstanding safety assessments should be characterized in order to allow for an appropriate assessment of risk/benefit for the 5-day gemifloxacin regimen for the treatment of ABS.

B. Description of Patient Exposure

The majority of patients (>98%) received either 5 or 7 days of study medication. There were 687 patients who received 5 days of gemifloxacin. The maximum number of days any patient received gemifloxacin was 8 days. One patient in the 5-day arm received therapy for 7 days and one patient in the 7-day arm received therapy for 8 days. Data for two patients was missing. **Table-49** lists the extent of patient exposure in both studies.

Table-49 Cumulative Number of Patients Who Received Gemifloxacin 320mg qd by Duration of Therapy (Studies 186 and 206 Combined)
Source NDA 21376. ISS Table-8H31,p:21

	Gemifloxacin 320mg qd 5 days N = 687		Gemifloxacin 320mg qd 7 days N = 203	
Duration of Exposure	**n**	**(%)**	**n**	**(%)**
≥1 day *	687	(100.0)	203	(100.0)
≥2 days	681	(99.1)	201	(99.0)
≥3 days	681	(99.1)	201	(99.0)
≥4 days	678	(98.7)	201	(99.0)
≥5 days	675	(98.3)	201	(99.0)
≥6 days	2	(0.3)	200	(98.5)
≥7 days	1	(0.1)	200	(98.5)

* Unknown extent of exposure was counted as 1 day

MO Comment: *Study-186 was a randomized, double-blind, active control study. There were two groups: Group-A subjects received gemifloxacin 320 mg po qd for 5 days, and Group-B received gemifloxacin 320 mg po qd for 7 days. Study-206 was an open-label, non-comparative study. Gemifloxacin 320 mg po qd for 5 days was the study medication. The Applicant combined the data from Study-186 (the 5-day treatment arm) and Study-206 together for the Safety review, then compared the combined data to the 7-day gemifloxacin treatment arm in Study-186. Mixing the patient groups between the two studies has the potential of introducing bias because of different patient baseline characteristics. In order to address this issue the MO also reviewed the safety for each of the individual ABS studies in detail. Only the integrated summary of safety us presented within this document.*

Demographics: Combined data from Studies 186 & 206 showed comparable baseline characteristics between the 5-day treated group and the 7-day group, **Table-50**. The majority of patients enrolled were from Europe; almost one fifth of the patients were from North America. A total of 687 patients received the 5-day treatment and 203 patients received the 7-day treatment. The mean age was 39 years of age in both the 5 & 7-day groups. No patients less than 16 years of age were enrolled in either group.

Table-50 Demographic Characteristics (Combined Data from ABS Studies 186 & 206)
Source NDA 21376. ISS Table 8.H.4.1

Demographic Characteristics	Gemifloxacin 320mg qd 5-day N=687		Gemifloxacin 320mg qd 7-day N=203	
Age (yr) n (%)				
≥16 - <18	13	(1.9)	0	
≥18 - <65	635	(92.4)	194	(95.6)
≥65	39	(5.7)	9	(4.4)
Mean (SD)	38.8 (14.2)		39.7 (13.9)	
Range	16 - 81		18 - 80	
Gender n (%)				
Male	282	(41.0)	85	(41.9)
Female	405	(59.0)	118	(58.1)
Race n (%)				
White	650	(94.6)	199	(98.0)
Black	16	(2.3)	3	(1.5)
Oriental	1	(0.1)	0	
Other	20	(2.9)	1	(0.5)
Region n (%)				
North American countries	173	(25.2)	37	(18.2)
European countries	514	(74.8)	166	(81.8)

C. Methods and Specific Findings of Safety Review

NDA 21-376 includes two clinical Studies (Study-186 & Study-206) for the 5-day treatment of ABS. AEs were identified as those events that occur after the first dose of study medication, and up to 30-days after the last dose. The Applicant used the World Health Organization Adverse Reaction Terminology dictionary to code AEs.

To maintain data integrity, data reported from two clinical investigators (Dr. Carl DeAbate: enrolled 8 patients in Study-206; Dr. Pierre Passage: enrolled 11 patients in Study-186) were excluded after the trials were completed. The Agency issued a NIDPOE letter to Dr. DeAbate on April 13, 2001. An Internal GSK audit found the data collected by Dr. Passage unsuitable. **Tables-51/53,** and the analyses presented herein present a side-by-side comparison of the data with and without the two excluded investigators. Reanalysis of the data without the two investigators did not affect the study results or conclusions. The Applicant's safety results presented is inclusive of the two excluded investigators.

These 19 excluded patients (Drs. DeAbate & Passage's populations) decreased the safety population receiving the 5-day gemifloxacin course from 687 to 673 patients, and decreased the number of patients receiving the 7-day gemifloxacin from 203 to 198 patients. The Applicant was not able to identify substantial percentage changes in AEs after the data was excluded.

Table-51 Number (%) of Patients Reporting Adverse Experiences by Body System in Either Treatment Group During the Interval On Therapy Plus 30 Days Post Therapy (Studies 186 and 206 Combined, with and without Dr. DeAbate's and Dr. Passage's Data)

Source NDA 21376. ISS, p:8

	Treatment Group							
	Gemifloxacin 320mg qd 5-day				**Gemifloxacin 320mg qd 7-day**			
	Data included N=687		**Data excluded N = 673**		**Data included N=203**		**Data excluded N=198**	
Body system	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	200	(29.1)	**198**	(**29.4**)	82	(40.4)	**80**	(40.4)
Gastrointestinal	55	(8.0)	**54**	(8.0)	25	(12.3)	25	(**12.6**)
Central and peripheral nervous	32	(4.7)	32	**(4.8)**	11	(5.4)	11	(**5.6**)
Respiratory	31	(4.5)	**30**	(4.5)	6	(3.0)	6	(3.0)
Skin and appendages	26	(3.8)	26	**(3.9)**	25	(12.3)	25	(**12.6**)
Resistance mechanism	24	(3.5)	24	**(3.6)**	5	(2.5)	5	(2.5)
Body as a whole	19	(2.8)	19	(2.8)	16	(7.9)	16	(**8.1**)
Psychiatric	18	(2.6)	18	(**2.7**)	10	(4.9)	**9**	(**4.5**)
Metabolic and nutritional	14	(2.0)	14	(**2.1**)	6	(3.0)	6	(3.0)
General cardiovascular	13	(1.9)	13	(1.9)	1	(0.5)	1	(0.5)
Musculoskeletal	13	(1.9)	13	(1.9)	2	(1.0)	2	(1.0)

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Table-51 Number (%) of Patients Reporting Adverse Experiences by Body System in Either Treatment Group During the Interval On Therapy Plus 30 Days Post Therapy (Studies 186 and 206 Combined, with and without Dr. DeAbate's and Dr. Passage's Data)

Liver and biliary	12	(1.7)	**11**	(**1.6**)	2	(1.0)	2	(1.0)
Platelet, bleeding and clotting	6	(0.9)	6	(0.9)	0		0	
White cell and reticuloendothelial	6	(0.9)	6	(0.9)	0		0	
Autonomic nervous	5	(0.7)	5	(0.7)	1	(0.5)	1	(0.5)
Heart rate and rhythm	4	(0.6)	4	(0.6)	0		0	
Other special senses	4	(0.6)	4	(0.6)	1	(0.5)	1	(0.5)
Red blood cell	4	(0.6)	4	(0.6)	0		0	
Vision	4	(0.6)	4	(0.6)	1	(0.5)	1	(0.5)
Female reproductive	3	(0.4)	3	(0.4)	2	(1.0)	**1**	(**0.5**)
Hearing and vestibular	3	(0.4)	3	(0.4)	4	(2.0)	4	(2.0)
Urinary	3	(0.4)	3	(0.4)	0		0	
Application site	0		0		1	(0.5)	1	(0.5)

Boldface in data cells indicates numbers and percentages that changed with exclusion of data.

At least one AE was reported from 200/687 (29.1%) patients in the combined 5-day treatment group compared to 82/203 (40.4%) patients in the 7-day treatment group. The body systems mostly affected in the 5-day treatment group were the gastrointestinal tract 55/687 (8%), central and peripheral nervous system 32/687 (4.7%), respiratory 31/687 (4.5%), and the skin & appendages 26/687 (3.8%). In the 7-day treatment group, the same body systems were affected but the order was different. The most notable difference was the higher rate of AEs in the skin & appendages [25/203 (12.3%)] and gastrointestinal [25/203 (12.3%)] systems.

MO Comment: *The rate of skin rash developing in patients using gemifloxacin is related to the length of time the product is used. Patients who received gemifloxacin for 7-days had an increased rate of rash. The high rate of rash was also observed in NDA 21-158. Although, the 5-day treatment regimen had a lower rate of rash (1.8%), it is still higher than the historical rate observed in the comparators (0.9%) used in NDA 21-158. This is described in more detail in the safety results section for skin & appendages AEs. In clinical practice it would be very difficult to strictly limit the use of an antibiotic to a certain period of time of use. It is likely that health care providers will expose their patients to more than the 5-day treatment regimen or patients may be exposed to longer than the 5-day regimen. Ways to limit potential confusion that could arise because of prolonged use should be explored by the Applicant.*

In the combined 5-day treatment group, the most frequent AEs reported were nausea 3.1% , diarrhea 2.9%, and headache 2.2%. The three most common AEs in the 7-day treatment group were nausea 3.4%, diarrhea 3.4%, rash 3.4%. Other common AEs in this group were somnolence 3% and fatigue 3%. **Table-52** summarizes the most frequently occurring AEs in either treatment group.

Table-52 Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences in Either Treatment Group (Studies 186 and 206 Combined)

Source NDA 21376 ISS Table 8H52

	Treatment Group			
	Gemifloxacin 320mg qd 5-day		Gemifloxacin 320mg qd 7-day	
		N=687		N=203
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	200	(29.1)	82	(40.4)
Nausea	21	(3.1)	7	(3.4)
Diarrhea	20	(2.9)	7	(3.4)
Headache	15	(2.2)	3	(1.5)
Dizziness	11	(1.6)	2	(1.0)
Hypertension	10	(1.5)	0	
Otitis Media	10	(1.5)	1	(0.5)
Rash Maculo-Papular	10	(1.5)	4	(2.0)
Somnolence	10	(1.5)	6	(3.0)
Insomnia	7	(1.0)	0	
Vomiting	7	(1.0)	1	(0.5)
↑ Creatine Phosphokinase	6	(0.9)	4	(2.0)
Injury	5	(0.7)	5	(2.5)
Flatulence	4	(0.6)	5	(2.5)
Urticaria	4	(0.6)	5	(2.5)
Fatigue	3	(0.4)	6	(3.0)
Eczema	2	(0.3)	3	(1.5)
Paresthesia	0		3	(1.5)
Rash Erythematous	0		7	(3.4)

Study investigators reported gemifloxacin as suspected or having a probable relationship to an AE in 95/687 (13.8%) patients in the 5-day treatment group and 43/203 (21.2%) patients in the 7-day treatment group, **Table-53**. Nausea 17/687 (2.5%), diarrhea 14/687 (2.0%), and somnolence 9/687 (1.3%) were frequently reported as suspected or probable relationship to study medication in both groups.

Table-53 Number (%) of Patients With the Most Frequently Reported (1%) Adverse Experiences of Suspected/Probable Relationship to Study Medication in Either Treatment Group During the Interval On Therapy Plus 30-Days Post Therapy (Studies 186 and 206 Combined, with and without Dr. DeAbate's and Dr. Passage's Data)
Source NDA 21376. ISS, p:12

	Treatment Group			
	Gemifloxacin 320mg qd 5 days		Gemifloxacin 320mg qd 7 days	
	Data included N=687	Data excluded N=673	Data included N=203	Data excluded N=198
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**

Patients with at least one AE of suspected /probable relationship to study medication	95	(13.8)	94	(**14.0**)	43	(21.2)	**42**	(21.2)
Nausea	17	(2.5)	17	(2.5)	6	(3.0)	6	(3.0)
Diarrhea	14	(2.1)	14	(2.1)	7	(3.4)	7	(**3.5**)
Somnolence	9	(1.3)	9	(1.3)	3	(1.5)	3	(1.5)
Rash maculopapular	8	(1.2)	8	(1.2)	3	(1.5)	3	(1.5)
Urticaria	4	(0.6)	4	(0.6)	4	(2.0)	4	(2.0)
Flatulence	3	(0.4)	3	(0.4)	3	(1.5)	3	(1.5)
Fatigue	1	(0.1)	1	(0.1)	2	(1.0)	2	(1.0)
Rash erythematous	0		0		7	(3.4)	7	(**3.5**)
Eczema	0		0		2	(1.0)	2	(1.0)

Boldface in data cells indicates numbers and percentages that changed with exclusion of data.

Exclusion of these two investigator's data did not affect the time of when an AE appeared. Also, no effect was observed on rates of skin related AEs. None of the patients enrolled at the two excluded investigator sites had a serious AE or had to be withdrawn from the studies.

MO Comment: *The MO concurs that the data (with and without the two investigator exclusions) as described by the Applicant did not affect study results.*

The majority of reported severe AEs were mild or moderate in both groups, **Table-54**. Patients in the 5-day group reported a severe AE in 3.5% (25/687) vs. 3% (6/203) in the 7-day group. The leading causes of severe AEs in the 5-day group were headache and dry mouth 3/687 (0.4%) for each AE, followed by diarrhea 2/687 (0.3%). In the 7-day group the most commonly reported severe AE was fatigue 2/203 (1%). Somnolence and rash were the third common AEs in the 5 and 7-day treatment groups respectively. Most AEs occurred during the period of On-Therapy, with the exception of rash that was most frequently reported on day-4 in the 5-day treatment group and days-7 to day-8 in the 7-day treatment group.

Table-54 Number (%) of Patients with at Least One Adverse Experience, by Severity (Studies 186 and 206 Combined)
Source NDA 21376. ISS Table-8H53

	Treatment Group			
	Gemifloxacin 320mg qd 5 days N=687		Gemifloxacin 320mg qd 7 days N=203	
Severity	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	200	(29.1)	82	(40.4)
Mild	144	(21.0)	57	(28.1)
Moderate	86	(12.5)	34	(16.7)
Severe	24	(3.5)	6	(3.0)
Unknown	1	(0.1)	0	

Deaths: No deaths were reported in Study-186 or Study-206.

Serious AEs: Six patients in the 5-day treatment group reported a serious AE. Two patients had injury (included surgery and medical procedures), 1 patient had fever (the only withdrawal On-Therapy secondary to a serious AE), 1 had serum sickness, 1 had a miscarriage, and 1 patient was depressed and attempted suicide. Only 1 patient reported a serious AE (vertigo) in the 7-day treatment group.

Table-55 Patients and Narrative for Serious AEs (Combined Studies 186 & 206)

Patient #	Serious AE	Narrative
206.602.28922	*****Fever	21-year old female. Developed fever on 2nd day of therapy. She was hospitalized. A CXR showed a focal pneumonia. Study medication was D/C after receiving a total of 4 doses.
206.607.28954	Injury	51-year old female. She had a suspected foreign body in Lt. Maxillary sinus due to old stomatological treatment. Hospitalization was advised. Patient SA grew Serratia species. She completed 5-day regimen.
206.003.28549	Serum Sickness	42-year old female reported rash, fever, arthralgia, Rt. Lung infiltrate, and lymphadenopathy. Symptoms started 13 days after the last dose of gemifloxacin. She had (+) acute mycoplasma titers.
206.040.34401	Depression / Suicide Attempt	19-year old female. Suicidal 17 days after discontinuing study medication. She has a h/o endometriosis, allergic rhinitis, and prothrombin fragment mutation. Also headaches since 1996 intermittent. The patient developed nausea & vomiting on day 4 of On-Therapy, and rash 4 days after completing study drug. Patient was cited as a Failure at EOT. She initially grew *S. pneumoniae*.
186.315.31828	Influenza	65-year old female with DM. Required hospitalization for a viral illness. She was treated with doxycycline, roxithromycin, and cefuroxime one week after completing gemifloxacin course. She was cited as a Failure in the study.
186.143.31464	Leg Fracture	23-year old male. Traumatic fracture occurred 4 days after completing therapy for ABS. He was hospitalized and underwent surgery for correction of fracture. The patient was withdrawn from the study at EOT visit. He did not return for F/U.
186.155.31811	******Vertigo	65-year old male. He had a h/o chronic otitis media in Rt. Ear and vertigo. Vertigo was severe 5 days after last dose of gemifloxacin. He underwent a revision tympanoplasty procedure 6 weeks after experiencing vertigo with resolution of his symptoms. The patient was described as a Failure, since he did not return for F/U and outcome was not known.

*Patient was withdrawn from study during the On-Therapy phase.
**The patient with vertigo was the only serious AE in the 7-day treatment group.

MO Comment: *The MO reviewed all patients with a reported serious AE. Two patient AEs are potentially linked to study drug (The miscarriage and the serum sickness patients).*

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***MO Comment:**. There were no patients with a serious rash in either group reported. The MO notes that in the 5-day treatment group in Study-186, one patient #186.274.32384 was described with severe dermatitis and was withdrawn from the study. The rash was reported on the 2nd day of On-Therapy and progressed by day 4. Although the patient completed the 5-day gemifloxacin regimen she was withdrawn from the study at the EOT visit In the 7-day treatment group, there are 3 patients who had a severe skin rash, these rashes were not cited as serious AEs.*

Withdrawals: Out of a total of 890 patients in both studies, 7 patients were withdrawn due to an AE. One patient was in the 7-day treatment group, the other 6 patients were in the combined 5-day treatment group, **Table-55**. AEs leading to withdrawal in the 5-day treatment group were: injury, rash, fever, gastritis and nausea, increased bilirubin. The two patients with rash, gastritis and nausea where withdrawn due to a suspected/probable relationship to study drug. In the 7-day group, the one patient who was withdrawn had a long history of otologic problems and vertigo.

Table-55 All AEs leading to withdrawal (Combined Study 186 & 206)

Pt number	Age/Sex	Organ Involved	Intensity	Relation to study drug	Serious AE	Hospital
186.143.31464	23M	Fracture leg	Moderate	Unrelated	Yes	Yes
186.274.32384	42F	Rash	Moderate	Suspected	No	
186.155.31811	65M	*Vertigo	Moderate	Unrelated	Yes	Yes
206.501.34288	48M	**↑ Bili	Moderate	Unrelated	No	
206.501.34338	45M	**↑ Bili	Mild	Unrelated	No	
206.602.28922	21M	Fever	Severe	Unrelated	Yes	Yes
206.607.28889	34F	Gastritis Nausea	Moderate	Probably	No	

* This patient is in the 7-day treatment group, all the other listed patients are in the 5-day treatment group.
** Pre-study laboratory screening results

Pregnancies: There were no pregnancies reported for Study-186. Two pregnancies were reported for Study-206, one pregnancy ended in miscarriage, the other one was still ongoing at the time when the report was submitted. Both patients reported pregnancy after the study drug course was completed. The two patients were exposed to the gemifloxacin 5-day regimen in the first trimester of pregnancy.

Patient #206.601.28875 was 25 years old. Her LMP was reported from January 24-28. She received gemifloxacin from February 4-8. At 14 weeks gestation the patient had a dilatation and curettage after fetal demise. Serum HCG test done at screening was negative. Gemifloxacin exposure probably occurred at the time of ovulation/fertilization and not during organogenesis.

***MO Comment:** The Applicant has taken reasonable action to screen females of child-bearing potential, in this instance, the serum pregnancy test was negative at screening. The probable cause of fetal demise was judged by the investigator as "suspected relation to study drug."*

Patient #206.035.28512 was 20 years old. The patient received gemifloxacin from January 20-24, 2000. Fifteen days after her last dose of medication she tested HCG positive. Her pregnancy was ongoing at the time of reporting. The investigator judged the pregnancy "not related to treatment with study medication."

MO Comment: *The patient had a negative serum HCG reported on screening January 19. She reported amenorrhea on January 20. A repeat HCG at the F/U was positive. The negative result for HCG test at screening is of concern, since the test should have picked up the pregnancy by then, although it is conceivable that it could have been too early. The patients LMP is not recorded. A sonogram could provide an estimate for the date of conception; however, the MO could not verify that a sonogram was done for the patient. The patient reported amenorrhea during the On-Therapy visit (January 24) after she had completed therapy.*

Skin & Appendages: The incidence of skin related AEs in the 5-day treatment group was 26/687 (3.8%) and 25/203 (12.3%) in the 7-day treatment group, **Table-56**. Rash is often first reported on day 7 or 8 after gemifloxacin is stopped in the 7-day treatment group, and on days 4 & 5 in the 5-day treatment group. In the 5-day treatment group, there was no severe rash AE reported. In the 7-day treatment group 2/203 (1%) patients had a severe AE rash reported. None of these events were cited as serious AEs. Photosensitivity was not reported in any of the patients in either group.

Table-56 Number (%) of Patients Reporting AEs in the Skin and Appendages (Combined Studies 186 and 206)

Source: NDA 21-376 ISS Table 8.H.5.6. p:35)

	Treatment Group			
	Gemifloxacin 320mg qd 5 Days		Gemifloxacin 320mg qd 7 Days	
		N=687		N=203
Body System	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	200	(29.1)	82	(40.4)
Skin and Appendages	26	(3.8)	25	(12.3)
Rash Maculo-Papular	10	(1.5)	4	(2.0)
Pruritis	6	(0.9)	1	(0.5)
Urticaria	4	(0.6)	5	(2.5)
Dermatitis	2	(0.3)	1	(0.5)
Eczema	2	(0.3)	3	(1.5)
Rash	2	(0.3)	1	(0.5)
Skin Hypertrophy	2	(0.3)	0	
Acne	1	(0.1)	2	(1.0)
Genital Pruritis	1	(0.1)	1	(0.5)
Rash Pustular	1	(0.1)	0	
Skin Discoloration	1	(0.1)	1	(0.5)
Ani Pruritis	0		1	(0.5)

Dry Skin	0	1	(0.5)
Rash Erythematous	0	7	(3.4)

AEs related to skin and appendages were associated with female gender and age. In the 5-day combined treatment arm there were 26/687 (3.8%) patients who reported a skin & appendage AE. And in the 7-day arm there were 25/203 (12.3%) patients. In both arms rash was far more common in females than males.

MO Comment: *If you consider the subset of patients with rash and urticaria only (gemifloxacin related rash), the rate in the 5-day treatment arm is 17/687 (2.5%), and 17/203 (8.3%) in the 7-day treatment arm. This rate of 8.3% is similar to the observed rate of rash in NDA 21-158 (~9%) while the rate observed in NDA 21-158 for comparators was 0.9%. Therefore, although the reported rate of rash/urticaria in the 5-day treatment arm is less than the 7-day treatment arm, it is still higher than the rate of comparators observed for NDA 21-158.*

MO Analysis: *Using the electronic datasets the MO observed: 42 patients from Study-186 reported a skin & appendage AE. Fourteen patients were in the 5-day treatment arm, and 28 were in the 7-day treatment arm. Most patients with skin and appendage AEs were in the age group 30-46. Of the 42 patients 29 (69%) were females. In Study-206 there were 20 AEs related to the skin and appendages. These events occurred in 15 female (75%) and 5 male patients. Fifty percent of these AEs occurred in subjects between the ages of 20-27 years of age.*

MO Comment: *The Applicant recently completed a Skin Study-344 that was performed as a result of the increased frequency of skin related AEs associated with gemifloxacin exposure. The Agency's clinical review is currently in progress for Study-344. Based upon a study synopsis presented within a briefing package, the MO has included some preliminary data from Skin Study-344 in this review under Section-D of the ISS. The MO stresses that the information provided is preliminary and has not undergone rigorous review by this MO.*

Laboratory Results: Laboratory data reflects the combined total of patients in both studies (687 patients in the 5-day treatment group and 203 patients in the 7-day treatment group. The applicant defined the abnormalities to fall into one of three groups that were defined in the following manner:

- Out of Laboratory Normal Range (F1): This flag denotes a value above or below the normal range supplied by the specified laboratory.
- Change from Baseline (F2): This flag denotes a value that increased or decreased from baseline by more than a specified amount defined by the sponsor. The associated range is referred to as the F2 range.
- Extended Normal Range (F3): This flag denotes a value that falls outside an extended normal range defined by the sponsor. This range is independent of direction of change or other values, and is outside the normal range. The associated range is referred to as the F3 range.
- Combined Flagging Criteria (F2F3): This flag denotes a value that changed

(increased or decreased) from baseline by more than a specified amount and also falls outside an extended normal range; it denotes values that are both F2 and F3 flagged.

The F2 range for a particular laboratory test is calculated in one of two ways:

- Proportional: The upper and lower limits are defined by multiplying the baseline laboratory value by a specified factor. For example, in the Phase IIIb studies, the lower F2 limit for hematocrit is equal to 85% of baseline.
- Normal Range Span: The normal range span (NRS) is the difference between the upper and lower limits of the normal range. The upper limit of the F2 range is calculated by adding a factor of the NRS to the baseline value. The lower limit is calculated by subtracting the same factor of the NRS from the baseline value. For example, the lower F2 limit for albumin is baseline minus 50% of the NRS.

The F3 range for a particular laboratory measurement is calculated in one of two ways:

- Absolute: Pre-specified limits. For example, F3 platelet values are below a lower limit of $100x10^9$ /L and above an upper limit of $500x10^9$ /L.
- Normal Range Limit: The upper limit is the normal range high (NRH) multiplied by a factor; the lower limit is the normal range low (NRL) multiplied by a factor. For example, the upper F3 limit for CPK is 250% of the NRH

Hematology: Abnormalities were infrequent with less than 1.0% of patients experiencing a change in parameters from Screening to EOT that was outside the Applicant defined limit. Few patients ≤2% had an F3 at Screening or at EOT in either group. The most common abnormality noted at EOT was a high platelet count 3/661 (range: 574-629 $X10^9$/L) in the 5-day treatment group and 2/193 (range: 515-525 $X10^9$/L) in the 7-day treatment group. One patient in the 5-day treatment group developed low platelets (33 X 10^9 /L), and leukopenia (WBC 2.2 $X10^9$/L), both resolved 13 days after study medication.

MO Comment: *The MO agrees with the applicant's narrative with regard to hematological parameters with some exceptions: One patient #206.603.28858 developed severe thrombocytopenia and leukopenia that resolved after 13 days of stopping medication. The investigator listed this as an unrelated event to study medication exposure. The MO does not agree with the Applicants assessment in the absence of another plausible explanation for the noted hematological abnormalities observed.*

Liver Function Tests: . Abnormal liver function tests were in general low in frequency. Few patients (not more than 0.5%) experienced a change in liver function parameters from Screening to EOT that was outside the Applicant's defined range. Most abnormalities were mild except in patient #206.012.28364. In the 5-day group an increased SGOT was reported in 3/687 (0.4%), SGPT in 5/687 (0.7%). In the 7-day treatment group there were no reported SGOT increases, and SGPT was increased in 2/203 (1%), **Table-57.**

Table-57 Patients with Liver Function Values of Potential Clinical Concern (F2F3-Flagged) with Associated AEs and Relevant Medical Conditions (Studies 186 and 206 Combined)

Source NDA 21376. ISS Table-8H10.8, p:59

Patient Number Laboratory Test	Visit* SCR	 EOT	Reference Range**	Associated AEs and Relevant Medical Conditions †
Gemifloxacin 320mg qd 5 days				
186.145.31490 AST (SGOT)	59	107	0-42U/L	57-year male, no h/o medical problems aside from sprains. On no prior medications. AE on day-11 of moderate SGOT increased, ongoing, unlikely relationship to study Medication. Severe CPK (1824 IU/L) increased, ongoing, suspected relationship to study medication. CPK at SCR=118 IU/L
186.155.31717 ALT (SGPT)	72	110	0-48 U/L	AE on day-10 of moderate SGPT increased, ongoing, probable relationship to study medication
186.155.31720 ALT (SGPT)	60	135	0-48 U/L	AE on day-10 of moderate SGPT increased, ongoing, probable relationship to study medication
206.012.28364 ALT (SGPT) AST (SGOT)	253 138	351 181	0-48 U/L 0-42 U/L	AE of mild hepatic function abnormal at baseline, resolved 2 days later; AE worsened to moderate on day-22, ongoing, unrelated to study medication
206.501.34320 Total bilirubin	26	45	0–22 umol/L	AE of moderate bilirubinemia day-9, resolved 9 days later, unlikely relationship to study medication
Gemifloxacin 320mg qd 7 days				
186.135.31827 Total bilirubin	13	36	0–22 umol/L	None
186.153.31444 ALT (SGPT)	60	130	0-48 U/L	AE on day-11 of moderate SGPT increased, ongoing, suspected relationship to study medication

* SCR = screening; EOT = end of therapy; ALT (SGPT) = alanine aminotransferase; AST (SGOT) = aspartate aminotransferase; CPK = creatine phosphokinase

** Units are shown only in the Reference Range column

MO Comment: *Most of these patients have mild elevations of ALT/AST at baseline, which may be due to preexisting liver disease with fluctuations. The MO could only speculate that the etiology may be viral, alcohol, drug related, or other etiology.*

Renal Function: There were 53/644 patients in the 5-day treatment group and 14/190 in the 7-day treatment group who had a change in serum creatinine at EOT. None of these patients had a value that exceeded the limit F2F3 suggesting that the magnitude of change may not equate with

a relationship to study drug. Two patients developed hyponatremia at EOT with no associated clinical manifestations.

MO Comment: *Patient #186.254.31347 (5-day treatment), a 71-year old female with a h/o HTN and increased cholesterol had a Serum Na=103 mmol/L at EOT. Her medications included atorvastatin and aspirin. The patient was otherwise well, although there were other biochemical abnormalities noted on her chemistry panel. She was cited as a Success in terms of her response to gemifloxacin. The MO agrees that this patient's result was most likely secondary to a laboratory error. The other patient #206.501.28815 reported a decline in sodium from 142 mmol/L at Screening to 126 mmol/L at EOT.*

Metabolic: Reports for calcium and glucose levels did not show abnormalities that were consistent with a treatment related effect. There were no hypoglycemic events noted at Screening or at EOT. None of the patients in either study experienced a "temafloxacin syndrome" (defined as an elevated bilirubin, serum creatinine, and decreased hemoglobin levels). Two patients in the 5-day treatment arm had elevated CPK at EOT. Patient #186.145.31490 had a CPK of 1824 IU/L (Screening CPK=118 IU/L, Normal=0-235 IU/L) of suspected relationship to study medication, the patient also had other AEs (increased liver enzymes). No significant prior medical history, and he is not receiving any medications. The second patient #206.004.28591 was a 22-year old male with no prior significant medical history, had a CPK of 2105 IU/L (Screening CPK=86), also observed to have an elevated diastolic blood pressure (142/116 mmHg) at F/U. Two patients in the 7-day treatment group had elevations in CPK. Patient #186.281.31553 was a 19-year old male with no significant prior medical history, had a CPK of 728 IU/L (Screening CPK=217 IU/L), no other AEs were observed in this patient. Patient #186.272.32358 was a 22-year old male, had a CPK of 940 IU/L (Screening CPK=458). The elevated CPK was suspected to be secondary to gemifloxacin exposure. This patient withdrew from the study due to non-compliance, he completed 5/7 doses of gemifloxacin. The patient also reported diarrhea, fatigue, vomiting, and flatulence. No corrective therapy was required, with resolution of his signs and symptoms.

MO Comment: *The observed CPK elevations in 2/4 patients were suspected to have a relation to study drug. The range of elevation of CPK was 728-2105 U/L. CPK elevations were observed in 1.3% of subjects exposed to gemifloxacin and 1.5% in comparators in NDA 21-158. The results described here are consistent with what has already been described in NDA 21-158. Also, on comparison of results from NDA 21-158 ABS studies, the MO noted that CPK elevation was reported in 8/540 (1.5%) patients on gemifloxacin 7-day regimen vs. 19/536 (3.5%) patients from all comparators.*

Arthralgia's were reported in 3/687 (0.4%) 5-day group and 1/203 (0.5%) patient in the 7-day group. No patients in either group reported a tendon-related disorder, phototoxicity, or pancreatitis.

Vital Signs: The mean values for vital signs (blood pressure, pulse rate, and respiratory rate) were observed to be similar in the 5- and 7-day treatment groups at Screening, EOT, and F/U. The applicant reported 6/687 patients in the 5-day treatment group with blood pressure values of possible concern at EOT. Five patients had an elevated systolic blood pressure and 6 patients had

an elevated diastolic blood pressure. These 6 patients were all from Study-206. In the 7-day treatment group there were no vital signs of concern in the patients at On-therapy, EOT, or F/U. The observed vital signs abnormalities were reported to have no relationship to study drug.

MO Comment: *The MOs review of patients (#206.013.28531, #206.301.29067, #206.004.28591, #206.042.28402, #206.301.29066, #206.608.34065) supports the Applicant's statement that vital sign abnormalities did not appear to have a relationship to study drug.*

Electrocardiograms: EKG's were not performed in Studies 186 & 206. There were no reports of syncope, convulsions, death, or cardiac arrest in either study.

MO Comment: *Paired EKGs were performed and interpreted in NDA 21-158. A detailed Safety review for EKGs / QT interval was provided in NDA 21-158 by the clinical Safety Reviewer Dr. John Powers.*

Phototoxicity: Photosensitivity and photosensitivity allergic reactions were not reported in patients who received gemifloxacin in Studies 186 & 206.

Drug Interactions: Gemifloxacin was not reported to inhibit or induce any of the important P450 enzymes in NDA 21-158. Also, the P450 enzyme system in the liver is minimally involved in the metabolism of gemifloxacin. Excretion of gemifloxacin is partly renal 40%. Therefore it was not predicted that gemifloxacin would have significant drug interactions. The applicant compared the frequency of AEs in patients receiving gemifloxacin and concomitant medications from the two combined studies. The results of this comparison were:

- Omeprazole: Nine patients received concomitant omeprazole, 3/9 patients reported an AE, none of which was a clinically meaningful interaction.
- Maalox & Sucralfate: No patients in either group received sucralfate. One patient received Maalox and had an AE reported (dizziness, epistaxis, cervical lymph node enlargement, and photophobia).
- Digoxin: One patient received digoxin, no AEs were reported.
- Theophylline: Three patients received theophylline. One patient reported serum sickness, related to study drug.
- Warfarin: There were no patients who received warfarin.
- Hormones/Contraceptives: 127 patients in the 5-day treatment group received hormone replacement or oral contraceptive therapy; 47/127 patients reported an AE. While 47 patients in the 7-day group received hormone replacement or oral contraceptive therapy. 22/47 patients from the 7-day group reported an AE. No specific patterns of AEs were observed in either group.
- Oral Hypoglycemic Agents/ Insulin: Fifteen patients in total received an oral hypoglycemic agent or insulin. Three patients reported an AE: bilirubinemia, hypertension, thrombocytopenia, and cough. No clinically meaningful interaction was observed.
- Probenecid: This agent was not used by any of the patients in the two studies.
- Paracetamol: 119/687 (17%) patients in the 5-day treatment group received paracetamol, 61 of these patients reported an AE. While 43/203 (21%) patients in the 7-day treatment group received paracetamol, 30/43 patients reported an AE. Paracetamol was used for headache in most cases. No clinically meaningful interaction was noted.

- Salbutamol: 17 patients in both groups used salbutamol. Eleven patients reported an AE mainly, dizziness, flatulence, and nausea. One patient had rash. These AE's were expected.
- Aspirin: In total there were 55 patients who received aspirin. 25 patients reported an AE mainly, nausea, arthralgia, diarrhea, and somnolence. These AE's were expected AE's (Arthralgia: was an indication for aspirin use).
- NSAIDs: 103 patients in both groups used NSAIDs. 51 patients reported an AE mainly, nausea, diarrhea, and headache. These AE's were expected (Headache: was an indication for NSAID use).
- Drugs that Prolong QT Interval: A total of 18 patients received drugs that could prolong the QT intervals. These drugs included other quinolones and cisapride. Eight patients reported an AE. The observed AE's included: bronchitis, diarrhea, dizziness, dyspepsia, dyspnea, headache, flatulence, somnolence, pharyngitis, taste perversion, rhinitis, and hepatic function abnormality. No clinically meaningful interaction was noted.

MO Comment: *These two studies did not include performing EKG's, therefore it is not known whether any AEs had a relation to QT interval prolongation.*

- Class IA / Class III Antidysrhythmic agents that prolong QT Interval: Four patients received amiodarone, propafenone, and/or sotalol. Two patients reported an AE. One patient had a traumatic injury reported, the other patient reported cough. No clinically meaningful interaction was noted.

D. Adequacy of Safety Testing

Due to the increased incidence of rash that was observed in the clinical studies for gemifloxacin, the Applicant conducted Study-344. The study was designed to evaluate skin related AEs that develop as a result of exposure to gemifloxacin.

The Applicant provided the following brief preliminary report on the study results for Study-344 in a background package for a meeting with the Agency on February 27th, 2002. Note that the results of Study-344 will soon be officially submitted for the Agency's review.

Study-344 Preliminary Brief Report: Young adult females who provided informed consent were randomized (4:1) to gemifloxacin 320 mg qd or ciprofloxacin 500 mg bid for 10 days. Subjects receiving gemifloxacin developed rash at a rate of 31.7% (260/819) and patients who received ciprofloxacin developed rash at a rate of 4.3% (7/164). In the second stage of the study, (one of the patient groups) patients who developed rash after gemifloxacin exposure were randomized (3:1) to receive ciprofloxacin or placebo. Patients who initially received gemifloxacin & developed a rash then received ciprofloxacin, were reported to have a rash in 10.4% (15/144). This may suggest that gemifloxacin may cause cross-sensitization to ciprofloxacin.

MO Comment: *The observed rate of rash in the enriched population in Study-344 is 7 times that of the comparator. None of the patients who received gemifloxacin developed a life-threatening event. Nevertheless, the full potential of serious skin AEs that could result when a large population is exposed to the drug is a concern that has not been resolved.*

E. Summary of Critical Safety Findings and Limitations of Data

The combined safety data for gemifloxacin in Studies 186 & 206 for the treatment of ABS have not identified new concerns for NDA 21-376. The vast majority of the clinical safety data for gemifloxacin was reported in NDA 21-158, which received a not approvable letter on December 15, 2000. In NDA 21-158, the high incidence of rash with the potential consequence of serious dermatologic AEs, and potential liver toxicity were cited among the deficiencies in the not approvable letter.

Studies 186 & 206 evaluated the safety and efficacy of gemifloxacin 320 mg po qd for 5 days. The incidence of rash in these two 5-day studies was less frequently observed in the 5-day treatment arm 1.5%, compared to 5.4% in the 7-day treatment arm. However, the incidence of rash in the 5-day treatment group is still higher than the historical incidence of rash in comparators (0.9%) from the ABS clinical studies in NDA 21-158.

MO Comment:. *The two 5-day sinusitis studies raise several difficult questions pertaining to the mass use of gemifloxacin.*

- *What are the means available to strictly limit the use of the drug to a 5-day period, without exposing patients to longer duration of therapy?*
- *In the event a patient develops a rash, does this mean that the whole quinolone class would be contraindicated to use?*
- *How do you resolve the issue of physician confusion when a physician decides to use another antibiotic and the patient develops a rash; Is the rash from gemifloxacin or from the new antibiotic (gemifloxacin rash commonly develops after the agent is stopped)?*
- *Would the Applicant limit the use of the drug in the young female population? (Young females were identified to have a high incidence for developing rash when exposed to gemifloxacin)*

These issues are important to consider because of the inherent differences between exposures in clinical trials where patients are carefully selected and studied vs. a population exposure that may amplify events that appeared as signals in the trials. Case in point is the rash that may lead to a Steven Johnson's Syndrome, or the mildly elevated liver function tests that could herald liver failure.

Liver function test abnormalities were observed to be mild; however, the potential for developing serious liver toxicity in patients who receive more than the recommended dose of gemifloxacin 320 mg po qd for 5 days warrants the consideration of studies to evaluate liver events.

VIII. Dosing, Regimen, and Administration Issues

The dosing regimen proposed gemifloxacin 320 mg po qd for 5-days for the treatment of ABS. This had been changed from the original proposed dosing of a 7-day course in the original NDA. There were no adverse events attributed to drug interactions associated with the use of gemifloxacin in Studies 186 & 206.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Combined data from the two clinical Studies 186 & 206 show a preponderance of females in both the 5 and 7-day treatment groups. The gender distribution in the 5-day treatment group was 59% females and 58% females in the 7-day group.

***MO Comment**: The observed preponderance of females in both studies may reflect that females with sinusitis are more likely to seek medical care and enroll in a clinical study of ABS than males with sinusitis*

Differences in AEs related to gender are listed in **Table-58**. As noted in the table, AEs were more frequently reported in females in both treatment groups. Also the rate of AEs was higher as a group as the duration of treatment increased from 5 to 7 days. Skin AEs were observed in 11% (12/118) of females in the 7-day group compared to 3% (13/405) of females in the 5-day group. Similarly, skin-related AEs were observed in 7% (6/85) of males in the 7-day group compared to 1% (3/282) of males in the 5-day group.

Table-58 (Studies 186 & 206 Combined). Most Frequently Occurring (≥1%) AEs On-Therapy Plus 30 Days Post-Therapy by Gender

AE	Gemi 5-day N=405		N=282		Gemi 7-day N=118		N=85	
	Females		Males		Females		Males	
Patients with at least one AE	31.1%	(126)	26.2%	(74)	41.5%	(49)	38.8%	(33)
Nausea	4.2%	(17)	1.4%	(4)	5.1%	(6)	1.2%	(1)
Urticaria	1%	(4)	0		2.5%	(3)	2.4%	(2)
Eczema	0.2%	(1)	0.4%	(1)	2.5%	(3)	0	
Rash	2%	(8)	0.7%	(2)	5.1%	(6)	4.8%	(4)
Fatigue	0.7%	(3)	0		1.7%	(2)	4.7%	(4)
CPK elevation	0		0.7%	(2)	0		4.7%	(4)
Diarrhea	2.2%	(9)	3.9%	(11)	3.4%	(4)	3.5%	(3)
Headache	2.5%	(10)	1.8%	(5)	1.7%	(2)	1.2%	(1)
Somnolence	1.5%	(6)	1.4%	(4)	3.4%	(4)	2.4%	(2)

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The majority of patients in Studies 186 & 206 were white (95% in 5-day treatment group and 98% in the 7-day treatment group. Patient groups were mainly recruited from Europe and North America. The centers in North America were mainly in Canada and the USA. Centers in the USA enrolled 18%, and centers from Canada enrolled 25% of patients from both groups.

The mean age of patients in the two groups was 39 years. Most patients >90% were in the age group 18-65. There were 13 patients in the 5-day treatment group who were in the age group 16-18. Patients younger than 16 years of age were not enrolled in the study. The number of patients who were ≥65 years was 39 patients in the 5-day treatment group and 9 patients in the 7-day treatment group.

There were 16 black patients, 1 oriental patient, and 20 patients listed as “other” race in the 5-day treatment group. In the 7-day treatment group there were 3 black patients and one patient was listed as “other” race.

Analysis of the three age groups in the 5-day treatment arm (≥16-18; ≥18 - <65; ≥65) revealed that there were was 1 AE in the ≥16-18 age group (no meaningful comparison due to small number, n=13, AE=1). The number of patients in the ≥18-<65 age group who developed an AE was 187/635 (29.4%) compared to 12/39 patients in the ≥65 years age group.

In the 7-day treatment arm, AEs were reported by 76/194 (39.2%) patients in the age group ≥18-<65 and 6/9 (66.7%) patients in the age group ≥65. Therefore the applicant was unable to provide meaningful analyses in relation to age-related differences and the overall incidence of

AEs due to the small numbers of patients in the ≥65 group and absence of patients in the ≥16-<18 group.

Most of the patients in the two studies were white and therefore no meaningful conclusions for any differences between races could be made. The reader is referred to NDA 21-158 for detailed information on race and age adverse event differences.

C. Evaluation of Pediatric Program

The applicant applied for a pediatric waiver on deferral for NDA 21-376. A cross reference is made to a letter dated March 31, 2000 in which GSK requested a full waiver and/or deferral for conducting pediatric studies in NDA 21-158. The rationale provided by the Applicant for the deferral was:

- Paranasal sinuses are poorly developed in children ≤1 year of age.
- GSK proposed that an indication for pediatric sinusitis be supported by bridging with otitis media studies. The otitis media studies could be conducted after developing a pediatric formulation.

F. Comments on Data Available or Needed in Other Populations

Patients with Impaired Liver Function at Baseline: The Applicant defined the presence of liver disease at baseline in two ways: Either the baseline medical evaluation suggests ongoing liver disease or a liver and biliary system AE is coded at baseline. The number of patients who were enrolled at baseline with impaired liver function was small. There were a total of 27 patients in both studies (22 patients in the 5-day group & 5 patients in the 7-day group). Elevations in liver function tests were generally mild and in the 2-3x higher than normal range. Twelve patients reported an AE during the On-Therapy plus the 30-day post-therapy interval. None of the reported AEs were serious or lead to withdrawal of patients from the study. At EOT, 2 patients (#206.012.28364, #186.155.31669) in the 5-day treatment group had a liver enzyme abnormality that was ≥4x normal.

MO Comment: *Patient #206.012.28364 is a patient that was recruited at an excluded site (Dr. DeAbate's) therefore I am unable to verify the accuracy of the information provided in the submission. The other patient is a 21-year-old man with elevated AST/ALT that did not change at EOT from Screening.*

In both groups 12/27 patients reported an AE; 9/22 (41%) patients in the 5-day treatment group, and 3/5 (60%) patients in the 7-day treatment group, **Table-59**. The proportions were higher than observed among the study population but lower than the rate observed in NDA 21-158 in patients who had baseline liver impairment (67/107 patients 63%).

MO Comment: *Numbers of AE are too small to justify any conclusions in patients with baseline liver impairment.*

Table-59 Number of Patients with Adverse Experiences in Patients with Baseline Liver Disease (Studies 186 and 206 Combined)
Source NDA 21376. ISS Table-8H14.3, p:96

	Gemifloxacin 320mg 5-day N = 22	Gemifloxacin 320mg 7-day N = 5
Preferred Term	**n**	**n**
Patients with baseline liver disease with at least one adverse experience	9	3
Thrombocythemia	3	0
Anemia	2	0
Hepatic function abnormal	2	0
Bilirubinemia	1	0
Bronchitis	1	0
Diarrhea	1	0
Epistaxis	1	0
Frequent micturition	1	0
Hypertension	1	0
Increased creatine phosphokinase	1	0
Leukopenia	1	0
Nausea	1	0
Skeletal pain	1	0
Hypesthesia	0	1
Infection viral	0	1
Tinnitus	0	1

Patients with Impaired Renal Function at Baseline:
(Patients with a CrCL > 80 mL/min were listed as normal kidney function)

Mild: CrCL >60 to ≤ 80 mL/min- There were 57/890 patients in both groups (42 patients in the 5-day, and 15 patients in the 7-day treatment group) who had evidence of mild renal dysfunction at baseline. Twenty-six patients reported an AE {17/42 (40%) in the 5-day group and 9/15 (60%) in the 7-day group}. The applicant reports that these proportions are higher than what is observed in the study population, but comparable to what was described in NDA 21-158 {262/580 (45%) in patients with mild renal dysfunction at baseline developed an AE}.

Five AEs were reported in more than one patient in the 5-day treatment group. These were somnolence, diarrhea, headache, nausea and maculopapular rash. In the 7-day treatment group, somnolence and nausea were the two AEs reported in more than one patient. Twenty-three AEs were judged by the investigator to be of suspected or probable relationship to study medication. No patients in either group were withdrawn from the study. There were no AEs that were described as serious in this group of patients.

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Moderate: CrCL >30 to ≤60 mL/min- Few patients had moderate renal dysfunction and these were limited to the 5-day treatment group 13/687 patients. Two patients reported AEs. One patient had diarrhea and flatulence, judged to have had a relation to the study drug. The other patient had hypertension, which was deemed not to be related to gemifloxacin administration. No patients were drawn from the study. There were no AEs that were described as serious in this group of patients.

Severe: CrCL <30 mL/min- One patient (186.135.31494) in the 5-day treatment group had a CrCL. Of 29mL/min. This patient reported mild pruritus developing on Day-2, which was not felt by the investigator to have a relationship to the study drug.

***MO Comment**: The patient who was described as having a CrCL of 29 mL/min, is a 31-yr-old woman with no significant medical history. She had a normal Hematocrit, and had a normal BUN at screening. A repeat creatinine level at EOT was in the normal range. Therefore, the baseline creatinine value is most likely a laboratory error. Also, the rash and itching developed on day 2 of therapy and lasted for 9 days. The MO can reasonably predict that the rash was related to the study medication, judging from the epidemiology of the exposure and what is already known of the propensity of gemifloxacin to cause rash especially in young women (Study-344).*

X. Conclusions and Recommendations

A. Conclusions

Factive® (gemifloxacin mesylate) is a quinolone-related fluoronaphthyridone antimicrobial agent. Factive was previously reviewed for the indication of ABS at a dose of 320 mg po qd for 7 days. This previously reviewed 7-day treatment regimen was one of the indications in NDA 21-158. NDA 21-158 received an action of not approvable on December 15, 2000. In NDA 21-158, gemifloxacin was found to have satisfactory evidence of efficacy in the treatment of ABS at the dose of 320 mg po qd for 7 days. However, the safety profile of gemifloxacin (specifically its potential for serious skin and liver toxicity) prevented a satisfactory benefit risk profile from being attained for gemifloxacin for the indications in NDA 21-158.

In NDA 21-376, the Application that is the subject of this review, the Applicant is seeking an indication for the use of gemifloxacin for the treatment of ABS using a 5-day treatment regimen for gemifloxacin in patients 18 years of age and older. The proposed dose of gemifloxacin is 320 mg po qd for 5 days. The efficacy data in NDA 21-376 (Studies 186 & 206) for the 5-day gemifloxacin regimen provides satisfactory evidence of the efficacy of gemifloxacin 320 mg po qd for 5 days in the treatment of ABS due to *S. pneumoniae*, *H. influenzae*, and *M. cattarhalis*. GSK is seeking approval for the treatment of acute bacterial sinusitis using a 5-day course, **Tables 60** & **61**.

Table-60 Study-186: Double-blind, double-dummy, randomized, multicenter, parallel group. Sites in Europe and Canada.

	5-day gemifloxacin 320 mg qd	7-day gemifloxacin 320 mg qd	Treatment Difference (95% CI)
Enrolled	N=220	N=203	
Received Medication (ITT)	N=218	N=203	
Withdrawn	N=9 (4.1%)	N=8 (3.9%)	
***Clinical PP at F/U**	N=181	N=175	
Clinical success	N=158 (87.3%)	N=152 (86.9%)	**0.44% (-6.54, 7.41)**
Bacteriology ITT	N=20	N=22	
Bacteriology PP at F/U	N=18	N=21	

*Primary population of interest was the Clinical PP population at F/U

Table-61 Study-206: Open-label, multicenter, non-comparative study. Sites in USA, Canada, Costa Rica, and Europe. Total enrolled = 469 patients (8 patients were excluded from site 012 due to DSI investigation). Mean age 37.7 years; 93.3% White; 1° population: *ITT Bacteriology at Follow-Up.

	5-day gemifloxacin 320 mg qd	Treatment Difference (95% CI)
Enrolled	N=469	
Received Medication (ITT)	N=469	
Withdrawn	N=17 (3.6%)	
***Bacteriology ITT**	N=236	
Success at F/U	N=203 (86.0%)	(81.59, 90.44)
Bacteriology PP at F/U	N=216	
Success at F/U	N=195 (90.3%)	(86.33, 94.23)
Pathogen Eradication Bacteriology ITT at F/U		
All pathogens	N=236/275 (85.8%)	
S. pneumoniae	N=88/101 (87.1%)	
H. influenzae	N=44/50 (88.0%)	
M. catarrhalis	N=15/15 (100%)	
***S. aureus*	N=9/12 (75%)	

*Primary population of interest was the Bacteriology population at F/U

**The MO review of *S. aureus* cases does not support a labeling indication due to insufficient number of acceptable organisms (Reviewed under Study-206, primary efficacy results, p:84)

The safety data from the two 5-day sinusitis studies in NDA 21-376 is somewhat limited in scope (one non-comparative study and one study comparing gemifloxacin 5 days vs. gemifloxacin 7 days). NDA 21-376 also cross-references NDA 21-158, which provides a more substantial safety database for gemifloxacin. The potential for cross-sensitization to other quinolones, the potential for hypersensitivity and more serious dermatologic reactions and hepatic toxicity. While the rates of rash were lower with a 5-day gemifloxacin treatment regimen, the data from NDA 21-376 are not sufficient to address the concerns raised regarding the aforementioned safety issues for gemifloxacin. Concerns still remain regarding the high rates of rash observed with gemifloxacin, cross-sensitization to other quinolone antimicrobials, and the potential for hepatic toxicity, despite the shortened duration of therapy of 5-days in NDA 21-376.

It is the recommendation of the reviewing MO that NDA 21-376 receive an action of **not approvable**, because the risks associated with gemifloxacin therapy outweigh its benefits. The notable safety issues that have led to an unsatisfactory risk benefit profile include the following:

- The high rate of gemifloxacin-associated rash.
- The potential for cross-sensitization to other fluoroquinolones.

- The likelihood that the high rate of gemifloxacin-associated rash will result in patients being labeled as "quinolone allergic" resulting in the restriction of the quinolone class of antibiotics as a therapeutic option for individuals exposed to gemifloxacin.
- For the proposed indication of ABS, there isn't an unmet medical necessity that warrants the risks of gemifloxacin therapy.
- The potential for hepatic toxicity based upon the liver abnormalities exhibited when a 640 mg dose of gemifloxacin was administered.
- In addition there are concerns that attempts to limit the duration of Factive® therapy may be met with limited success. Therefore realistically the likelihood that patients will receive durations of therapy beyond 5 or 7 days should be considered.

B. Recommendations

The MO is recommending an action of not approvable for NDA 21-376 as noted in the preceding section "Recommendation on Approvability." Therefore no specific recommendations for postmarketing studies are provided. However, if the Applicant should in the future be able to demonstrate a satisfactory risk/benefit profile for gemifloxacin such that it were to receive an approval, consideration to the following type of study should be given: A large safety study to further investigate the adverse events associated with gemifloxacin in an actual use situation. The study should include information on the duration of gemifloxacin therapy, indication of use, patient demographics, patient drug allergy history, along with a detailed description of the adverse event.

B. Labeling

Given that this NDA is intrinsically linked to NDA 21-158, only the portions of the label addressing the ABS indication will be addressed in this review.

<u>The Applicant's proposed labeling for ABS is:</u>

"**Acute bacterial sinusitis** caused by *S. pneumoniae* (including clarithromycin-resistant strains); *H. influenzae; M. catarrhalis; K. pneumoniae, S. aureus*."

"DOSAGE AND ADMINISTRATION
Factive can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of Factive is 320 mg daily, according to the following table."

Indication	Dose	Duration
Acute bacterial sinusitis	One 320 mg tablet daily	5 days

The MO is recommending the following changes to the proposed labeling section of the submission:

- MO revised label:

"**Acute bacterial sinusitis** caused by *S. pneumoniae*; *H. influenzae; M. catarrhalis.*"

"DOSAGE AND ADMINISTRATION
Factive can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of Factive is 320 mg daily for 5 days."

- A label claim for *S. pneumoniae, H. influenzae,* and *M. catarrhalis* is supported by the data reviewed in the submission. The label claim for *S. aureus* and *K. pneumoniae* is not supported by the data in the submission. *K. pneumoniae* is not a recognized cause ABS.
- The Agency has not previously awarded a claim for Macrolide-resistant *S. pneumoniae* (MRSP). Such a claim would be the ideal subject of discussion at a scientific advisory meeting.
- The Applicant should provide a detailed skin & appendages adverse events section, to include results of Study-344 when available.
- The Applicant should address, whether gemifloxacin use would be limited in certain populations (e.g., young females) due to the high incidence of rash.

XI. Appendix

A. Other Relevant Materials

Study-186: Table-11.04 Clinical Response at F/U By Center (Clinical PP Population)
Study-206: Table-11.17a Clinical Response at F/U by Center, (ITT Population)

B. Individual More Detailed Study Reviews (If performed)

_____

Sary O. Beidas, M.D.
Reviewing Medical Officer/HFD 590
DSPIDP

Concurrences Only: _____
Renata Albrecht, MD
HFD-590/Acting Division Director

HFD-590/Divisional File, IND 21-376
HFD-590/MedTL/Cox
HFD-590/Chem/Nschmuff
HFD-520/Chem/SMilton
HFD-590/Micro/Pdionne
HFD-590/Micro/SBala
HFD-590/Pharm/SHundley
HFD-590/Stat/KHiggins
HFD-590/MO/SBeidas
HFD-590/TM/Mbourg
HFD-590/Biopharm/Bdavit
HFD-590/Biopharm/PColangelo

Clinical Response At Follow-Up By Center (Clinical PP Population at F/U)
Source: NDA 21-376. **Study-186** Vol. 10/17. Table 11.04. p: 463-466

			Treatment Group			
			Gemi 5 days		Gemi 7 days	
Center		Clinical Response	(N=181)		(N=175)	
110	(LAFONTAINE)	Success	1	(100.0%)	2	(100.0%)
111	(VAN ESCH)	Failure	2	(100.0%)	0	
112	(EECKELEERS)	Success	1	(100.0%)	0	
114	(CORNELLI)	Success	1	(100.0%)	0	
115	(DUPREZ)	Success	1	(50.0%)	1	(100.0%)
		Failure	1	(50.0%)	0	
117	(VAN LIEFFERINGE)	Success	2	(100.0%)	2	(100.0%)
118	(VILEYN)	Success	2	(100.0%)	0	
119	(MEHUYS)	Success	1	(100.0%)	0	
120	(CHARLIER)	Success	1	(100.0%)	0	
122	(DE VALCK)	Success	1	(100.0%)	0	
123	(LELIAERT)	Success	1	(50.0%)	0	
		Failure	1	(50.0%)	0	
124	(VERELST)	Success	0		2	(66.7%)
		Failure	2	(100.0%)	1	(33.3%)
125	(HEYVAERT)	Success	1	(50.0%)	0	
		Failure	1	(50.0%)	0	
135	(BARAN)	Success	13	(81.3%)	16	(94.1%)
		Failure	3	(18.8%)	1	(5.9%)
136	(BLEIF)	Success	1	(50.0%)	2	(100.0%)
		Failure	1	(50.0%)	0	
138	(BOEHME)	Success	2	(100.0%)	2	(100.0%)
139	(DE BARY)	Success	1	(100.0%)	2	(100.0%)
140	(DETERS)	Success	1	(100.0%)	2	(100.0%)
142	(ISSING)	Success	2	(100.0%)	2	(100.0%)
143	(KITZKE)	Success	2	(100.0%)	3	(100.0%)
144	(KRETSCHMANN)	Success	1	(100.0%)	0	
145	(MAIER-BOSSE)	Success	1	(100.0%)	0	
149	(REINHARDT-FEYERABEND)	Success	2	(100.0%)	2	(100.0%)
150	(ROHR)	Success	0		1	(100.0%)
152	(TANGERDING)	Success	14	(100.0%)	15	(100.0%)
153	(WALTER)	Success	4	(100.0%)	1	(33.3%)
		Failure	0		2	(66.7%)
154	(WEBER)	Success	0		3	(100.0%)
		Failure	1	(100.0%)	0	
155	(WEICH-JUNG)	Success	14	(100.0%)	13	(100.0%)
158	(ZASTROW)	Success	0		1	(100.0%)
186	(FIORELLA)	Success	5	(100.0%)	5	(100.0%)
200	(O'DOHERTY)	Success	2	(100.0%)	2	(100.0%)
202	(SWEENEY)	Success	1	(100.0%)	0	
245	(COSTONGS)	Success	2	(100.0%)	1	(100.0%)
246	(PASSAGE)	Success	3	(100.0%)	4	(100.0%)
247	(CROUGHS)	Success	3	(100.0%)	2	(100.0%)
248	(SCHAPERS-DE BRUIN)	Success	1	(50.0%)	1	(50.0%)
		Failure	1	(50.0%)	1	(50.0%)
249	(VAN DER WERF)	Success	0		1	(100.0%)
250	(FERGUSON)	Success	1	(50.0%)	2	(66.7%)
		Failure	1	(50.0%)	1	(33.3%)
251	(DE BACKER)	Success	1	(100.0%)	0	
		Failure	0		1	(100.0%)
252	(VERMETTEN)	Success	6	(85.7%)	4	(66.7%)
		Failure	1	(14.3%)	2	(33.3%)
253	(VAN MIERLO)	Success	5	(100.0%)	3	(100.0%)

CLINICAL REVIEW

Center		Clinical Response	Gemi 5 days		Gemi 7 days	
254	(BUITENHUIS)	Success	3	(75.0%)	2	(50.0%)
		Failure	1	(25.0%)	2	(50.0%)
255	(BEEKMAN)	Success	1	(100.0%)	2	(100.0%)
256	(SCHUT)	Success	0		2	(100.0%)
270	(DESROSIERS)	Success	1	(100.0%)	1	(100.0%)
271	(BERGER)	Success	2	(100.0%)	2	100.0%)
272	(LASKO)	Success	4	(80.0%)	2	(100.0%)
		Failure	1	(20.0%)	0	
273	(MARTEL)	Success	3	(60.0%)	3	(60.0%)
		Failure	2	(40.0%)	2	(40.0%)
274	(SHU)	Success	6	(75.0%)	7	(70.0%)
		Failure	2	(25.0%)	3	(30.0%)
275	(ST. PIERRE)	Success	7	(100.0%)	7	(87.5%)
		Failure	0		1	(12.5%)
276	(TELLIER)	Success	5	(100.0%)	3	(60.0%)
		Failure	0		2	(40.0%)
281	(KASINSKAS)	Success	6	(100.0%)	8	(100.0%)
282	(MARTINKENAS)	Success	7	(100.0%)	6	(100.0%)
291	(RASSMUSSEN)	Success	4	(66.7%)	5	(83.3%)
		Failure	2	(33.3%)	1	(16.7%)
292	(KYROENPALO)	Success	1	(100.0%)	1	(50.0%)
		Failure	0		1	(50.0%)
301	(LUHT)	Success	4	(100.0%)	3	(75.0%)
		Failure	0		1	(25.0%)
308	(PASSALI)	Success	3	(100.0%)	1	(50.0%)
		Failure	0		1	(50.0%)

Clinical Response At Follow-Up By Center (Intent-To-Treat Population)
Source: NDA 21-376 **Study-206** Vol. 15/17. Table 11.17a. p:938-940

			Gemi 5 days	
Center		**Clinical Response**	**(N=469)**	
001	(ABDALLAH)	Success	2	(66.7%)
		Failure	1	(33.3%)
002	(ABERNATHY)	Success	1	(100.0%)
003	(ADELGLASS)	Success	6	(85.7%)
		Failure	1	(14.3%)
004	(ALBARRACIN)	Success	16	(100.0%)
007	(BORDENAVE)	Success	8	(100.0%)
010	(CHRISTENSEN)	Success	4	(66.7%)
		Failure	2	(33.3%)
012	(DEABATE)	Success	5	(62.5%)
		Failure	3	(37.5%)
013	(DEGENNARO)	Success	2	(100.0%)
014	(FIDELHOLTZ)	Success	4	(66.7%)
		Failure	2	(33.3%)
018	(GILL)	Success	1	(100.0%)
019	(GLINKOWSKI)	Success	6	(66.7%)
		Failure	3	(33.3%)
022	(HANSHAW)	Success	2	(100.0%)
023	(HENDRICK)	Success	2	(66.7%)
		Failure	1	(33.3%)
024	(HEUER)	Success	5	(83.3%)
		Failure	1	(16.7%)
025	(HILTY)	Success	2	(66.7%)
		Failure	1	(33.3%)
026	(HOLLOWAY)	Success	2	(66.7%)
		Failure	1	(33.3%)
027	(HUNT)	Success	1	(100.0%)
035	(MILLIGAN)	Success	3	(50.0%)
035	(MILLIGAN)	Failure	3	(50.0%)
036	(RIFFER)	Success	4	(80.0%)
		Failure	1	(20.0%)
039	(SCHEAR)	Success	8	(100.0%)
040	(SCHNEIDER)	Success	1	(50.0%)
		Failure	1	(50.0%)
041	(SHERMAN)	Failure	1	(100.0%)
042	(SINGH)	Success	11	(84.6%)
		Failure	2	(15.4%)
046	(TURNER)	Success	3	(100.0%)
050	(HANDLEY)	Success	1	(100.0%)
051	(ZITER)	Success	7	(100.0%)
053	(ANON)	Success	1	(100.0%)
301	(ARCE)	Success	2	(100.0%)
501	(HORVAI)	Success	71	(91.0%)
		Failure	7	(9.0%)
502	(SZABO)	Success	15	(68.2%)
		Failure	7	(31.8%)
503	(GORGEY)	Success	39	(92.9%)
		Failure	3	(7.1%)
504	(HENDE)	Success	44	(86.3%)
		Failure	7	(13.7%)
601	(DYCZEK)	Success	9	(90.0%)
		Failure	1	(10.0%)
602	(BARDADIN)	Success	6	(75.0%)
		Failure	2	(25.0%)
603	(GIEREK)	Success	19	(95.0%)
		Failure	1	(5.0%)
604	(NAMYSLOWSKI)	Success	25	(92.6%)
		Failure	2	(7.4%)

605	(OLSZEWSKI)	Success	26	(100.0%)
606	(CHODYNICKI)	Success	10	(100.0%)
607	(MIKULEWICZ)	Success	17	(85.0%)
		Failure	3	(15.0%)
608	(GOLABEK)	Success	19	(90.5%)
		Failure	2	(9.5%)

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/s/

Sary Beidas
4/12/02 12:23:25 PM
MEDICAL OFFICER

Edward Cox
4/12/02 04:18:41 PM
MEDICAL OFFICER

Renata Albrecht
5/3/02 05:29:03 PM
MEDICAL OFFICER

Appendix C

Cutaneous Reactions Associated With the Use of Gemifloxacin (Post-Marketing)

Division of Drug Risk Evaluation (DDRE) Consultation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: July 26, 2006

PID # D060543

TO: Renata Albrecht, M.D., Director
Division of Special Pathogens and Transplant Products (DSPTP)

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)

FROM: Evelyn R. Farinas, R.Ph., M.G.A.
Safety Evaluator, DDRE

Melissa Truffa, R.Ph.
Safety Evaluator Team Leader

Syed Rizwanuddin Ahmad, M.D., M.P.H.
Medical Epidemiologist

Allen Brinker, M.D., M.S.
Epidemiologist Team Leader

PRODUCT: Gemifloxacin (Factive®) NDA 21-158

SUBJECT: Cutaneous Reactions Associated With the Use of Gemifloxacin

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

1. EXECUTIVE SUMMARY

Factive® (gemifloxacin) was approved on April 4, 2003 as a 5-day regimen for the treatment of acute bacterial exacerbation of chronic bronchitis and as a 7-day regimen for the treatment of community-acquired pneumonia of mild to moderate severity. In clinical trials it was noted that the incidence of rash was higher in patients receiving gemifloxacin, and rash was commonly observed in patients < 40 years of ages, especially in females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment durations (>7days). On both December 5, 2000 (NDA 21-158) and April 12, 2002 (NDA 21-376) the Agency issued a not approvable letter for a 7-day acute bacterial sinusitis (ABS) regimen and a 5-day ABS regimen, respectively, because data provided do not indicate a favorable risk versus benefit profile to support the approval of gemifloxacin for ABS[1].

The sponsor submitted a new efficacy supplement to NDA 21-158 (S-006) on November 18, 2005 for a proposed 5-day ABS regimen. The Division of Special Pathogens and Transplant Products (DSPTP) refused to file (RTF) this efficacy supplement because data submitted to date do not constitute substantial new evidence necessary to support a re-evaluation of the risk benefit profile regarding the proposed 5-day regimen for the treatment of ABS[2]. The sponsor appealed the RTF decision and the supplement is currently under review by DSPTP. DSPTP will discuss the 5-day ABS regimen at a September 12, 2006 Advisory Committee meeting and requested an overview of post-marketing cutaneous adverse event reports associated with the use of gemifloxacin in FDA's Adverse Event Reporting System (AERS) as background material for this meeting.

As of May 31, 2006 (approximately 3 years post-approval) there were 799 reports in AERS for gemifloxacin; 83% (or 667) of all reports for gemifloxacin listed a cutaneous adverse event. Six (6) percent or 41 of these cutaneous adverse event reports had a serious outcome and where stated, approximately 73% (430/592) of the cutaneous adverse events were reported in women. Drug use data estimate that 363,000 prescriptions for gemifloxacin were dispensed by retail pharmacies between January 1, 2004 and May 31, 2006[3]. The majority were dispensed to women (211,000 or 58%).

Where both age and gender are stated (n=247 for women), the postmarketing reports listed 42% (104/247) of women ≤40 year of age reporting a cutaneous adverse event associated with the use of gemifloxacin. Of all prescriptions dispensed to females during this time period (January 1, 2004 through May 31, 2006), approximately 21% were age 40 years or less. In a subset of reports (categorized as a severe cutaneous event, photosensitivity reaction, allergic reaction, or rash) approximately 41% (range, 33-49%) of women ≤ 40 years of age experienced one of these cutaneous adverse events (see

[1] NDA 21-158/006: 04Apr06 Factive ABS RTF Minutes from Meeting between DSPTP and Oscient
[2] NDA 21-158/006: 19Jan06 Factive ABS RTF letter
[3] Total number of prescriptions includes new and refill, and retail pharmacies include chain, independent, food stores and mass merchandisers in the US only.

Table 1). For men, adverse event report counts for the ≤ 40 years of age group were 45% (42/93). Of all prescriptions dispensed to males during this time period (January 1, 2004 through May 31, 2006), approximately 23% were age 40 years or less.

In addition to age and gender, we analyzed time to onset of rash with gemifloxacin therapy. In a subset review of 291 postmarketing reports coded with the MedDRA preferred term Rash (see Table 4) the median time to event onset was 4 days (range, 3-5 days); 77 of 291 reports reviewed had a time to onset of rash of ≤ 5 days. Further, upon review of 10 reports of specific severe skin events of interest (Stevens Johnson Syndrome (SJS), Erythema Multiforme EM), Skin Exfoliation (SE) and Dermatitis Exfoliative (DE), see Table 2) the time to event onset in 4 of these cases was ≤ 5 days as well as a review of 37 cases with a serious outcome, the time to event onset in 8 of these cases was ≤ 5 days.

Thirty-seven patients (derived from individual review of the cases and removal of duplicate reports) experienced a **serious** adverse event (per regulatory definition). Out of these 37 patients, 3 died, 19 were hospitalized, 2 required intervention, 1 was considered life-threatening and 12 were determined to be medically important by the reporter. The three fatalities were not attributable to gemifloxacin use as death was associated with cardiomegaly, hemophagocytic syndrome and dental surgery. Of the 19 cases that required hospitalization, the majority experienced gemifloxacin-associated adverse events and required treatment such as steroids, antihistamines, oxygen, and intravenous fluids. Many of these serious cases under the "required intervention" and "other medically important" categories described a hypersensitivity component to the adverse reaction including urticaria, swelling of face, anaphylaxis, allergic vasculitis, etc. that required intervention with epinephrine, steroids, and antihistamines. Interestingly, of these 37 serious outcome cases, 9 (25%) reported previous fluoroquinolone use and 13 (35%) reported a history of drug allergy. Of the 10 **severe** skin reports (EM, SJS, SE and DE), the available information in the reports was either lacking or incomplete to adjudicate the three EM and four SJS reports as definitive cases of EM and/or SJS. The remaining three cases described the adverse events as skin peeling or exfoliating.

We also calculated crude reporting rates for categorically serious skin reactions (as per regulatory definition) reported in association with gemifloxacin and selected comparators. (Categorically serious refers to reports that indicate an outcome of death, life-threatening, hospitalization, intervention required, resulted in disability or considered medically significant by reporter.) Reporting rate calculations are typically based on case counts divided by dispensed prescriptions. Standard reporting rate comparisons require 1) similar drug products [e.g., time on market, route of delivery, spectrum of indication(s)] and 2) assumption that reporting practices are similar for similar drug products over the observed reporting period. Furthermore, standard reporting rate comparisons require an accurate estimate of drug exposure or utilization within the population. Due to the voluntary, spontaneous nature of MedWatch reports submitted to AERS, reporting rates cannot be interpreted as true incidence rates within the population.

Crude (not adjudicated) counts for categorically serious reports were used in this analysis because the large number of reports precluded analysis of individual reports at this time. Categorically serious reports of cutaneous adverse events have been reported more frequently in association with gemifloxacin than with either cefditoren or telithromycin. The reporting rate for gemifloxacin (105 per million prescriptions) was 7.5 times that of cefditoren (14 per million prescriptions) and 5 times that of telithromycin (20 per million prescriptions). This difference was notable and concerning. An individual review of serious skin reports with these three drugs (gemifloxacin, cefditoren, and telithromycin) is planned to assess if the differences observed in analysis of crude counts will be maintained after adjudication of cases.

Clinical trial data found a higher incidence of rash in patients receiving gemifloxacin than in those receiving comparator antibiotics, and a 2003 Advisory Committee presentation on gemifloxacin [4] identified female gender, age <40, planned duration of treatment >7 days, and hormone replacement therapy in women >40 years of age as risk factors for rash development. Postmarketing data from AERS showed the propensity of gemifloxacin to be associated with cutaneous adverse events predominately in females. AERS data for gemifloxacin also indicated that the proportions of cutaneous adverse event reports were greater in the ≤ 40 of age group for both females and males in comparison to the amount of drug use in that same age bracket. Clinical trial data of cutaneous safety[4] showed that 2/3 of rash in gemifloxacin patients began after day 7 of therapy. However, in our postmarketing analyses, time-to-event was shorter with AERS reports of cutaneous events coded as rash having a median time-to-event onset at 4 days. One-quarter and 1/3 of the serious skin adverse event reports listed previous fluoroquinolone use or history of drug allergy, respectively. Further, many of the serious outcome cases reported an allergic/hypersensitivity component to the cutaneous events with numerous cases reporting significant morbidity. Although information included in the three cases of EM and the four cases of SJS was insufficient to assign such diagnoses, the lack of a definitive EM or SJS case does not imply that severe skin adverse reactions have not or cannot occur in association with gemifloxacin use. Spontaneous adverse event reporting databases such as AERS have multiple limitations. Under reporting, as well as incomplete reporting, coupled with the low postmarketing drug utilization for gemifloxacin may underlie the current lack of definitive EM or SJS cases reported to the AERS database. Comparisons of gemifloxacin with other recently approved oral antibiotics used to treat minor infections showed that for serious skin reactions, the safety of gemifloxacin is of concern. In addition, the crude reporting rate of serious skin reactions was notably higher for gemifloxacin than the comparator drugs. Individual case review of all serious skin reactions associated with gemifloxacin and comparator drugs (cefditoren and telithromycin) is planned to calculate case-adjudicated reporting rates.

Given the concerning nature of these post-marketing data analyses which add to the already known definitive clinical trials data delineating drug-related cutaneous adverse reactions, we recommend that the magnitude of the drug benefit for the indication under review by DSPTP (acute bacterial sinusitis) be clearly defined so that the magnitude of the drug risk can be appropriately examined and weighed in context.

[4] Tierney, Maureen. FDA Safety Presentation Regarding Factive® (gemifloxacin). (http://www.fda.gov/ohrms/dockets/ac/03/slides/3931s1.htm)

2. BACKGROUND

This document was drafted to provide information to the September 12, 2006 Advisory Committee members on gemifloxacin post marketing experience. The information in this document is limited as it presents a summary of gemifloxacin reports in the Adverse Events Reporting System (AERS) listing this product as suspect drug but does not include data from post-marketing studies nor literature reports. The focus of the document is further restricted to a summary of AERS reports where gemifloxacin use was associated with a cutaneous adverse event.

3. METHODOLOGY

3.1 AERS Searches

3.1.1 AERS was searched on June 28, 2006, to identify reports indicating one or more cutaneous adverse event in association with gemifloxacin and received by the Agency through May 31, 2005. The specific MedDRA terms used in the search are listed below.

MedDRA terms: Skin and subcutaneous tissue disorders (System Organ Class [SOC])
Rash (Preferred Term [PT])
Rash Maculo-Papular (Preferred Term [PT])
Rash Erythematous (PT)
Rash Pustular (PT)
Urticaria (PT)
Pruritus (PT)
Erythema Multiforme (PT) [EM]
Stevens Johnson Syndrome (PT) [SJS]
Toxic Epidermal Necrolysis (PT)
Skin Exfoliation (PT) [SE]
Dermatitis Exfoliative (PT) [DE]

Except where specified, data in the results section was derived from line listings which may include duplicates, and not from individual review of the reports.

3.1.2 AERS was searched for reports of gemifloxacin listing a serious outcome (per regulatory definition) using the same MedDRA terms and data lock date as in 3.1.1. These reports were reviewed individually and are summarized in Table 4/section 4.1

3.1.3 AERS was searched for reports of gemifloxacin listing the most frequently reported PT term (i.e. Rash) which represents 44% of all the cutaneous adverse event reports. These reports were reviewed individually and are summarized in Table 4/section 4.1.

3.1.4 A similar search to 3.1.1 using the same MedDRA terms and data-lock date was conducted for four additional fluoroquinolones, ciprofloxacin, levofloxacin, moxifloxacin and gatifloxacin. The resulting data, derived from line listings, are presented in Appendix One.

3.1.5 A search limited to domestic reports only, using the same MedDRA terms and data-lock date, included the following five antimicrobial products: moxifloxacin, gatifloxacin, gemifloxacin, cefditoren and telithromycin. The resulting data, derived from line listings, are presented in Appendix One.

3.2. Case Definitions

All cutaneous events: Includes all AERS gemifloxacin reports captured using the overall MedDRA SOC classification Skin and Subcutaneous Tissue Disorders.

Serious events: Includes reports captured under the SOC Skin and Subcutaneous Tissue Disorders where the reporter determined that the event met the regulatory definition of serious outcome (death, hospitalization, life-threatening, congenital abnormality, disability, required intervention or other considered medically significant).

Severe skin events: Includes reports of specific cutaneous adverse events of interest, such as Stevens Johnson Syndrome or erythema multiforme, captured under the SOC Skin and Subcutaneous Tissue Disorders which are deemed clinically severe but which may not meet the regulatory definition of a serious outcome. This category includes reports coded under these specific MedDRA PTs: Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Dermatitis Exfoliative and Skin Exfoliation. This definition applies to Table 1. However, in Table 2 where the information is captured through individual review of the reports, this definition is expanded to include also reports where reporters listed Stevens Johnson Syndrome as an adverse event, but the reports were not coded as such.

Photosensitivity events: Includes reports captured under the SOC Skin and Subcutaneous Tissue Disorders that list an adverse event indicative of a photosensitivity reaction, coded under the following PTs: Photosensitivity and Skin Hyperpigmentation. Reports listing any of the terms included under the severe skin events category are not included in this grouping. This definition is applied in Table 1.

Allergic Events: Includes reports uncovered under the SOC Skin and Subcutaneous Tissue Disorder listing cutaneous adverse events that may be indicative of an allergic type reaction. This category includes reports coded under the following MedDRA PTs: Urticaria, Urticaria generalised, Pruritus, Swelling Face, Oedema peripheral, Angioneurotic edema, Swelling, Oedema, Dermatitis allergic, Face oedema and Pruritus generalised. Reports that also list any of the terms used to retrieve severe events or photosensitivity events are not included in this category. This definition is applied in Table 1.

Rash: Includes reports captured under the SOC Skin and Subcutaneous Tissue Disorders that indicate patients experienced a type of rash, and that were coded using the following MedDRA PTs: Rash, Rash Generalised, Rash Erythematous, Rash Maculo-papular, Rash Pruritic, Rash Macular and Rash Morbiliform. Reports that also list any of the terms used to retrieve severe skin events, photosensitivity events or allergic events are not included in this category. This definition is applied in Table 1.

Erythema Multiforme: Skin reaction characterized by erythematous plaques, blisters and target or bull's eye lesions. The mucous membranes of the mouth and eyes may also be involved. Cutaneous lesions favor the extremities (often the palms) and symmetric. Target lesions are diagnostic and are recognized by a central, dark purple area or a blister surrounded by a pale, edematous, round zone, surrounded in turn by a peripheral rim of erythema.[1]

Stevens Johnsons Syndrome: Skin reaction similar to EM, but where the skin disease is more widespread, with blisters and painful erosions in the mouth and eyes. The patients look and feel ill with fever, prostration, and difficulty eating. Histologically subepidermal separation is found in the blistering center of the target lesion. When early lesions are biopsied, immunofluorescence reveals immunoglobulin and complement in the walls of the small dermal blood vessels. Inflammation and bulla form in response to vascular damage and leaking.[1]

3.3 Drug use data

Proprietary databases licensed by the FDA were used to obtain drug utilization data for gemifloxacin. Data for this analysis include prescriptions dispensed for Factive® (gemifloxacin) from January 1, 2004 through May 31, 2006. Outpatient use was measured by audits from Verispan, LLC, Vector One®: National (VONA), and Physician Drug and Diagnosis Audit (PDDA).

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims, representing over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from

approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

VERISPAN, LLC

Vector One®: Physician Drug and Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey that monitors disease states and the physician intended prescribing habits on a national-level. The survey is designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The audit is composed of approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

4. RESULTS

AERS Data and Drug Use showed the following:

- 83% of all AERS reports for gemifloxacin reported a cutaneous adverse event; 6 % (41/667) of the cutaneous adverse events indicated a serious outcome.
- Where stated, 73% (430/592) of the cutaneous events were reported in females; drug use (based on estimated prescriptions) indicated that 58% of total use was in females.
- Where age and gender were stated, 42% (104/247) of females aged 40 or less experienced a skin adverse event; of all prescriptions dispensed to females during this time period (January 1, 2004 through May 31, 2006),, approximately 21% were age 40 years or less.
- Among the reports reviewed individually (n=338, 291 PT Rash, 37 serious, 10 severe), the three most frequently mentioned indications were bronchitis, pneumonia and sinusitis. Sinusitis is not a currently approved indication.

In addition, based on individual review of the 338 reports, AERS data showed the following:

- Thirty-seven patients experienced a serious adverse event per regulatory definition (note that the number of AERS reports with a serious outcome per regulatory definition differs among Tables 1, 2 and 3. Table 1[n=41] includes all reports with serious outcome, which include domestic, foreign and duplicate reports. Table 3

[n=37] includes AERS reports with serious outcomes that have been individually reviewed and duplicate reports removed. Table 7 [n=38] includes only US reports with serious outcomes and where duplicates have not been removed). Among the 37 patients, three died, 19 were hospitalized, 2 required intervention, adverse event was considered life-threatening in 1, and medically important in 12. The three fatalities were not attributable to gemifloxacin use where death was associated with cardiomegaly, hemophagocytic syndrome and dental surgery. Of the 19 cases that required hospitalization, the majority experienced gemifloxacin-associated adverse events and required treatment such as steroids, antihistamines, oxygen, and intravenous fluids. The majority of hospitalizations (71%) were due to the reported cutaneous events.

- Of the potential 10 severe event reports (EM, SJS, SE and DE), the available information presented in the three EM and four SJS reports did not correspond with our case definitions; the remaining three described the events as skin peeling or exfoliating.
- Among reports coded under the PT Rash, which represented the most frequently reported event (n=291 or 44% of all cutaneous event reports), 56% indicated rash occurred in females, and where stated (n=188) 38% of the patients were 40 years of age or younger. Where stated (n=149) the rash manifested in three days or less after starting therapy in 37% of the patients. Therapy with steroids and antihistamine was required to treat the rash in 12 %.

4.1 AERS data

Analysis of AERS data is presented in tabular form. Table 1 is an overview of AERS data derived from line listing, with emphasis on specific categories of interest and where each category is mutually exclusive. Tables 2, 3 and 4 summarize the characteristics of specific severe cutaneous events, of serious outcome reports, and of reports listed under the PT rash, respectively. Data presented in Tables 2 through 5 were derived from individual review of the reports.

Table 1 – Gemifloxacin AERS reports indicating cutaneous events (foreign and domestic) through May 31, 2006[1,2] derived from line listings

Total # of AERS reports (all events, all outcomes) through May 31, 2005: 799					
	All cutaneous events[3]	**Severe events[4]**	**Photosensitivity events[5]**	**Allergic events[6]**	**Rash[7]**
# of AERS reports	667 (100%)	7/(1%)	8 (1 %)	86 (13%)	550 (82%)
General overview					
Total # of reports/# serious[8]	667/41	7/3	8/2	86/21	550/12
Country US/foreign	665/2	7/0	8/0	84/2	550/0
# Females/# Males	430/162	6/0	8/0	59/20	350/133
Average age: females/ males	46/44	47/NA	43/NA	42/41	47/44
# listing age ≤40: females/males	104/42	2/NA	2/NA	20/7	79/34
# serious outcome: females/males	31/5	3/NA	2/NA	17/4	9/1
# serious outcome ≤ 40 years	14	1	0	10	3
Sex:	N=592	N=6	N=8	N=79	N=483
Females	430	6	8	59	350
Males	162	0	0	20	133
Age (males, females, gender NS)	N=348	N=6	N=5	N=55	N=274
Average	45	47	43	41	46

Table 1 – Gemifloxacin AERS reports indicating cutaneous events (foreign and domestic) through May 31, 2006[1,2] derived from line listings					
Total # of AERS reports (all events, all outcomes) through May 31, 2005: 799					
	All cutaneous events[3]	**Severe events[4]**	**Photosensitivity events[5]**	**Allergic events[6]**	**Rash[7]**
Median	44	51	41	41	45
Range	14-84	20-67	25-66	18-80	14-84
# ≤40 years	147	2	2	47	115
Average age females	46	47	43	42	47
Average age males	44	NA	NA	41	41
Age and Sex distribution					
Females	N=247	N=6	N=5	N=41	N=192
0-40	104	2	2	20	79
>40	143	4	3	21	113
% ≤40 where age is listed	42%	33%	40%	49%	41%
Males	N=93	N=0	N=0	N=14	N=73
0-40	42	-	-	7	35
>40	51	-	-	7	38
% ≤ 40 where age is listed	45%	-	-	50%	47%
Serious outcome[4] [N, % of total in category]	[41, 6%]	[3, 43%]	[2, 25%]	[21, 24%]	[14, 2.5%]
# Death	4	0	0	2	0
# Hospitalization	19	3	0	8	7
# Life-threatening	1	0	0	1	0
# Disability	2	0	2	0	0
# Required intervention	2	0	0	2	0
# Other (medically important)	13	0	0	8	5
# of females with serious outcome	31	3	2	17	9
# of males with serious outcome	5	0	0	4	1
# with age ≤ 40 and serious outcome	14	1	0	10	3

[1] Total number of AERS reports for all events from initial approval date (2003) through May 2005

[2] Data derived from line listings, not from individual review of the reports. However, each of the four specific categories (severe, photosensitivity, allergic events and rash) is mutually exclusive.

[3] Data retrieved under the MedDRA System Organ Class (SOC) grouping Skin and Subcutaneous Tissue Disorders, which includes reports listing one or more cutaneous adverse events.

[4] Data retrieved using the following MEDDRA PT terms that may indicate severe skin conditions: Erythema multiforme, Stevens Johnson Syndrome, Toxic epidermal necrolysis, Skin exfoliation, Dermatitis exfoliative

[5] Data retrieved using the following MEDDRA PT terms that may be indicative of a photosensitivity reaction: Photosensitivity, Skin hyperpigmentation. Reports listing any of the terms included under severe skin conditions are not included in this category.

[6] Data retrieved using the following MEDDRA PT terms that may be indicative of an allergic reaction: Urticaria, Urticaria generalised, Pruritus, Swelling Face, Oedema peripheral, Angioneurotic edema, Swelling, Oedema, Dermatitis allergic, Face oedema and Pruritus generalised. Reports that also listed any of the terms used to retrieve severe events or photosensitivity events are not included in this category.

[7] Data retrieved using MEDDRA PT terms that indicate rash: Rash, Rash generalised, Rash erythematous, Rash Maculo-papular, Rash pruritic, Rash macular and Rash morbiliform. Reports that also listed any of the terms used to retrieve severe events, photosensitivity or allergic type events are not included in this category.

[8] Serious outcome by regulatory definition, which includes death, life-threatening, hospitalization, congenital anomaly, required intervention, other medically important event

Abbreviations: AERS= Adverse Events Reporting System; EM= Erythema multiforme; NOS= Not otherwise specified; SJS= Stevens Johnson Syndrome; TEN=Toxic Epidermal Necrolysis

Table 2 – Characteristics of AERS reports listing <u>specific severe</u> events of interest – Stevens Johnson Syndrome, Erythema Multiforme, Dermatitis Exfoliative and Skin Exfoliation – in association with the use of gemifloxacin through May 31, 2006[1,2]					
	Cumulative	**Stevens Johnson Syndrome**	**Erythema Multiforme**	**Skin Exfoliation**	**Dermatitis Exfoliative**
# of reports	10	4	3	2	1
Assessment		**Not true SJS**	**Not true EM**		
Country	US 10	US 4	US 3	US 2	US 1

Table 2 – Characteristics of AERS reports listing specific severe events of interest – Stevens Johnson Syndrome, Erythema Multiforme, Dermatitis Exfoliative and Skin Exfoliation – in association with the use of gemifloxacin through May 31, 2006[1,2]					
	Cumulative	**Stevens Johnson Syndrome**	**Erythema Multiforme**	**Skin Exfoliation**	**Dermatitis Exfoliative**
Sex Females/Males	N=8 7/1	N=2 2/0	N=3 2/1	N=2 2/0	N=1 1/0
Age[3] Average Range # ≤ 40	N=8 44 18-67 3	N=2 43 18-67 1	N=3 43 20-62 1	N=2 40 32-47 1	N=1 - 55 0
Indication[4]	N=8 Sinus 5 Strep throat 1 Bronchitis 3 Pneumonia 1 Right otitis 1 UTI 1	N=2 Sinus inf. 1 Strep throat 1	N=3 Sinusitis 2 Bronchitis 2	N=2 Sinusitis 1 Bronchitis 1 Pneumonia 1	N=1 Sinusitis Right otitis UTI
Length of therapy Average Range	N=6 6 days 2-8 days	N=0 - -	N=3 7 days 5-7 days	N=2 5 days 2-7 days	N=1 - 8 days
Time to onset Average Range # ≤ 5 days	N=8 7 days 2-15 day 4	N=2 3 days 2-4 days 2	N=3 7 days 5-9 days 1	N=2 5 days 2-8 days 1	N=1 - 15 days -
Outcome Hospitalization	N=5 5	N=3 3	- -	N=2 2	-
Cause for Hosp.	N=4 AEs 4	N=3 AEs 3	- -	N=2 AEs 2	-
Required treatment Type of treatment	N=9 ST, AH, EPI	N=3 1 EPI 1 ST 1 ST + AH	N=3 2 ST 1 ST+AH	N=2 1 ST+AH 1 Epi + ST + AH	N=1 ST+AH
Previous use of FQ	N=3	N=1 (no rx)	N=2 (no rx)	-	-
Hx of drug reaction	N=1	-	-	N=1	-

[1] Data derived from individual review of the reports. Duplicates merged.
[2] Table 2 includes reports captured under the individual MedDRA PT terms Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Dermatitis Exfoliative and Skin Exfoliation. Table 2 also includes serious outcome reports not coded under these specific PT terms but where the reporters described the cutaneous event as Stevens Johnson Syndrome.
[3] Total figures (i.e., N) includes reports where age was stated or implied, ex. "mid 30's", "under 40", etc.. Calculations for average were derived only from reports that provided discrete age information.
[4] Note that one report may list more than one indication
Abbreviations: AH= antihistamines; AEs=Adverse events;EPI=Epinephrine; Hosp=Hospitalization; Inf=Infection; Rx=Reaction; ST=Steroids

Observations for Severe Events from Table 2 (n=10):

- Although 7 reporters indicated that patients experienced SJS/EM or SJS type of event, none of the descriptions match our case definitions nor do they provide sufficient information to verify the diagnoses.
- In this subset more events were reported in women than in men; and in reports where both age and sex were identified (8), 38% occurred in women 40 years of age or younger.

- Where stated, 66% of reports indicate an off-label use for gemifloxacin
- Four reports indicated onset of events within 5 days or less after starting gemifloxacin therapy.

Table 3 – Characteristic of serious[1] outcome AERS reports listing a cutaneous adverse event in association with gemifloxacin use through May 31, 2005						
	All serious outcomes	**Deaths[2]**	**Hospitalization**	**Life-threatening**	**Required intervention**	**Other (Medically important)**
# of reports	**37**	**3**	**19**	**1**	**2**	**12**
Country	US 35 Foreign 2	US 3	US 17 Foreign 2	US 1	US 2	US 12
Sex: Females Males ≤ 40 years	N=35 29 6 16	N=3 1 2 1	N=18 15 3 10	N=1 1 0 1	N=2 2 0 0	N=11 10 1 5
Age Average Median Range ≤ 40 years	N=37 44 42 20-80 15	N=3 44 44 33-66 1	N=19 43 36 17-80 10	N=1 67 67 NA 0	N=1 47 47 NA 0	N=12 44 42 20-59 5
Age and Sex distribution Females 0-40 >40 Males 0-40 >40	N=35 N=29 12 17 N=6 4 2	N=3 N=1 0 1 N=2 1 1	N=18 N=15 8 7 N=3 2 1	N=1 N=1 0 1 N=0 - -	N=1 N=1 0 1 N=0 - -	N=11 N=10 4 6 N=1 1 0
Most frequently reported skin event	Rash 28	Rash 2	Rash 13	Hives 1	Rash 2	Rash 11
Indication[4] Sinusitis Bronchitis Pneumonia Strep throat Otitis media Exacerbation COPD URI UTI	N=33 17 9 7 2 1 1 1 1	N=3 1 1 - - - - 1 -	N=17 9 3 7 1 1 - - -	N=1 - 1 - - - - - -	N=2 2 - - - - - - -	N=10 6 4 0 1 - 1 - 1
Duration of therapy Average Range	N=32 6 1-10 days	N=3 5 4-6	N=17 6 1-10	N=0 - -	N=2 4 1-7	N=11 5 1-7 days
Time to onset Average Range # ≤ 5 days	N=32 7 1-17 days 8	N=2 5 4-6 days 1	N=18 7 1-15 3	N=0 - - -	N=2 9 1-17 days 1	N=10 7 1-15 3
Cause of death or hospitalization	N=20	N=3 Cardiomyopathy HPS 1 Dental surgery 1	N=17 Skin events 12 Pneumonia 2 Thrombocy. 1 Jaundice 1	NA	NA	NA
Previous use of FQ	N=9	NS	N=4	NS	NS	N=3
Hx of drug allergy	N=13	N=1	N=5	NS	N=1	N=6

[1] Serious by regulatory definition: Death, Life-threatening, Hospitalization, Congenital abnormality, Disability, Required intervention and Other (medically important)

[2] Subset categories of Death, Life-threatening, Hospitalization, Required intervention and Other are mutually exclusive.

[4] The number of indications is greater than the number of reports because there were several reports listing more than one indication.

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; HPS= Hemophagocytic syndrome; NS= Not stated; URI= Upper respiratory infection; UTI=Urinary tract infection

Observations for serious outcome reports from Table 3 (n=37):

- **Deaths (n=3):** None of the 3 fatalities can be attributed to the use of gemifloxacin. In two, autopsies stated deaths were attributable to severe hemophagocytic syndrome in a 33-year old male and to cardiomyopathy secondary to hypertensive heart disease in a 44-year old male. In the third report, the 66-year old female died after dental surgery four months after having used gemifloxacin. This report did not provide a cause of death, nor if there was a relation to the use of any medication. The cutaneous adverse events experienced by these patients were rash in the 33-year old male, excoriation in the 44-year old male and severe hives in the 66-year old female. Time to onset was clearly described for only one patient, the 66-year old female, where the severe hives appeared on the fifth day of gemifloxacin therapy.
- **Hospitalizations (n=19):** Cutaneous events manifested on average on the seventh day of therapy; three reports indicated that events developed in 5 days or less. Thirteen patients required therapy for the adverse events, twelve of which required steroids; other medications administered were antihistamines, epinephrine, oxygen, Pepcid® (famotidine) and/or IV fluids. Admissions were due to adverse events in twelve, pneumonia in two, shortness of breath in one, acute jaundice and pancreatitis in one, and thrombocytopenia in one, with an additional two not reporting the cause for hospitalization. Five of the nineteen reports meet our criteria for "severe events", describing the events as SJS in three patients and skin exfoliation in two. However, none of the reports of SJS provided sufficient information to determine that these were true SJS cases. In the two remaining severe reports, patients experienced peeling of the skin one month after starting gemifloxacin in one, and painful desquamation in multiple areas of the skin in the other. Note that all five are also included in Table 2.
- **Life-threatening (n=1):** This consumer report does not provide specific criteria as to why the severe hives in this patient are considered a life-threatening event. The reporter stated that his 67-year old mother experienced chronic severe hives, taste changes and pain within weeks of using gemifloxacin, and that due to the adverse events "the possibility of death exists". Relevant information such as duration of therapy, specific time to onset, concomitant drugs, indication, therapy to treat adverse events, and exclusion criteria were not provided.
- **Required intervention (n=2):** Two reports stated that female patients experienced rash, hives, pruritus or face swelling within seven days or less of starting gemifloxacin therapy for a sinus condition, but neither report described the specific therapy administered to treat the adverse events. The 47-year old experienced rash on arms and a swollen face within 24 hours of taking gemifloxacin, for which she went to the Emergency Room. The 29-year old experienced "itchy skin" within a few days after starting gemifloxacin therapy, and "on day 7 awoke with severe rash/hives covering entire body from head to toe that continued to get worse".
- **Other (medically important events, n=12)):** All of the 12 reports stated that adult patients experienced rash or urticaria within two weeks of starting therapy, where in three patients adverse events started within 24 hours of initiation of treatment and in six cases therapy with antihistamines, steroids and/or epinephrine was administered to relieve the adverse events. In six of the 11 patients with rash, patients indicated rash was generalized involving multiple areas of the body; rash was associated with anaphylaxis in a 20-year old female and with allergic vasculitis in a 56-year old

female. Five patients had a history of allergies to multiple medications, such as penicillin and sulfa drugs.

Table 4 – Characteristics of AERS reports captured under the MedDRA PT RASH in association with the use of gemifloxacin through May 5, 2006

	Total	Males	Females	Gender not stated
# of cases	291	73	162	56
Country	US	US	US	US
Age[1] (% of total) Average Median Range # where age ≤ 40	N=188 (65%) 44.5 years 43.5 years 14-81 73	N=48 (66%) 43.7 years 42.5 years 18-79 19	N=131 (81%) 44.2 years 42.5 years 14-81 53	N=9 (16%) 53 years 54 years 35-70 years 1
Indication (% of total)	N=83 (29%) Bronchitis 34 (7 AECB) Pneumonia 21 (5 CAP) Sinusitis 17 Respiratory infection 5 Infection NOS 3 UTI 2 Strep tonsillitis 1	N=31 (42%) Bronchitis 11 (2 ACEB) Pneumonia 8 (3 CAP) Sinusitis 8 Respiratory infection 1 Infection NOS 2 UTI 1	N=50 (31%) Bronchitis 22 (5 AECB) Pneumonia 13 (2 CAP) Sinusitis 8 Respiratory infection 4 Infection NOS 1 UTI 1 Strep tonsillitis 1	N=2 (4%) Bronchitis 1 - Sinusitis 1
Outcome (% of total)	N=23 (8%) 2 death 7 hospitalization 14 other	N=5 (7%) 1 Death - 4 Other	N=15 (9%) 1 death 6 Hospitalization 8 Other	N=3 (5%) - 1 Hosp 2 Other
Time to onset[2] Average Median Range # reports ≤ 5 days # reports post DC	N=149 4.8 days 4 days 1-11 days 77 37	N=44 5 days 5 days 1-9 days 24 1	N=89 4.8 days 5 days 1-11 days 40 36	N=16 3.5 days 3 days 2-6 days 13 -
Required tx /type of tx	N=34 Antihistamines 9 AH + steroids 4 Steroids 18 Epinephrine 2 Topical medication 1	N=6 Antihistamine 2 - Steroids 3 - Topical medication 1	N=26 Antihistamines 6 AH + steroids 4 Steroids 15 Epinephrine 1	N=2 Antihistamines 1 - - Epinephrine 1

[1] Total figures (i.e., N) includes reports where age was stated or implied, ex. "mid 30's", "under 40", etc.. Calculations for median and average were derived only from reports that provided specific information.

[2] Time to onset in days after initiation of therapy. Total figures (i.e., N) include reports where the time to onset was alluded to, such as "post discontinuation". Calculations for median and average were derived only from reports that provided specific information.

Abbreviations: AECB= Acute bacterial exacerbation of chronic bronchitis; AERS= Adverse Events Reporting System; AH= antihistamines; CAP= Community acquired pneumonia; DC= discontinuation; NOS= Not otherwise specified; Tx= therapy; UTI- Urinary tract infection

Observations for Reports coded under PT Rash from Table 4 (n= 291):

- 36% of all AERS reports for gemifloxacin were coded under the PT term Rash.
- More females than males experienced rash (162 versus 73); where both age and sex were identified, 40% of females with rash were 40 years of age or younger (53/131)
- A time to onset for development of rash was equal to 5 days or less in 77 patients.
- 34 reports indicated that patients required therapy with steroids, antihistamines and/or epinephrine to ameliorate the rash.

4.2 Drug Use Information

Table 5. Projected number of total prescriptions for oral products only dispensed by retail pharmacies in the US for selected antibiotics (through May 2006)

(NUMBERS ARE IN THOUSANDS: ADD THREE ZEROS [000].)

	1997 TRxs (000)	1998 TRxs (000)	1999 TRxs (000)	2000 TRxs (000)	2001 TRxs (000)	2002 TRxs (000)	2003 TRxs (000)	2004 TRxs (000)	2005 TRxs (000)	YTD/MAY/2006 TRxs (000)
TOTAL MARKET	1,388	3,657	7,593	13,287	18,717	20,239	23,761	27,741	34,283	15,847
cefditoren pivoxil	--	--	--	--	1	30	37	292	204	34
gatifloxacin oral, solid, liquid	--	--	--	1,892	3,532	2,811	2,160	1,668	1,161	289
gemifloxacin oral, solid, liquid	--	--	--	--	--	--	--	20	193	150
levofloxacin all	1,388	3,517	6,687	9,495	11,090	11,599	12,758	12,836	14,366	6,212
oral, solid, liquid	1,388	3,516	6,682	9,490	10,999	11,288	12,402	12,640	14,234	6,165
Injectable	0	2	5	5	5	3	4	2	2	1
moxifloxacin oral, solid, liquid	--	--	0	885	1,917	2,584	3,024	2,929	3,044	1,628
injectable	--	--	--	--	--	0	0	0	0	0
Telithromycin oral, solid, liquid	--	--	--	--	--	--	--	843	3,240	1,257

Citation: Verispan Vector One®: National, 1996-2006, data extracted July-2006

* -- = no data

[1] Total= New and Refill prescriptions

Table 6 – Projected Number of Total Prescriptions Dispensed by Retail Pharmacies (Chain, Independent, Food Stores, Mass Merchandisers) in the US for selected antibiotics- Numbers are in thousands: add three zeros

	2002		2003		2004		2005		YTD MAY/06	
	TRxs (000)	Share %	TRxs (000)	Share %	TRxs (000)	Share %	TRxs (000)	Share %	TRxs (000)	Share %
TOTAL MARKET	20,240	100.00%	23,761	100.00%	27,741	100.00%	34,283	######	15,847	100.00%
cefditoren pivoxil	30	0.15%	37	0.16%	292	1.05%	204	0.60%	34	0.22%
Female	19	62.99%	22	60.79%	176	60.44%	121	59.39%	20	59.79%
0-40	6	33.65%	8	34.50%	60	34.27%	38	31.56%	6	28.25%
41+	13	65.69%	15	65.13%	115	65.35%	83	68.23%	15	71.58%
Male	11	36.71%	14	38.97%	113	38.82%	81	39.80%	14	39.80%
0-40	4	39.17%	5	35.94%	40	35.06%	26	32.45%	4	29.29%
41+	7	60.19%	9	63.58%	73	64.45%	55	67.18%	10	70.18%
gatifloxacin oral, solid, liquid	2,811	99.99%	2,161	78.39%	1,668	51.66%	1,161	39.37%	289	26.40%
Female	1,771	63.01%	1,357	62.79%	1,041	62.39%	715	61.61%	178	61.59%

0-40	509	28.75%	369	27.18%	259	24.92%	165	23.08%	41	23.03%
41+	1,257	70.95%	984	72.56%	779	74.84%	549	76.78%	137	76.86%
Male	1,034	36.79%	797	36.89%	615	36.85%	437	37.68%	110	38.14%
0-40	277	26.82%	202	25.31%	141	22.88%	91	20.76%	23	21.00%
41+	753	72.79%	592	74.29%	472	76.77%	346	79.00%	87	78.87%
gemifloxacin oral, solid, liquid	--	--	--	--	20	100.00%	193	######	150	100.00%
Female	--	--	--	--	12	58.01%	112	58.26%	87	57.97%
0-40	--	--	--	--	3	24.09%	23	20.35%	18	20.84%
41+	--	--	--	--	9	75.80%	89	79.55%	69	79.07%
Male	--	--	--	--	9	41.82%	79	41.25%	63	41.89%
0-40	--	--	--	--	2	25.29%	18	22.10%	14	22.53%
41+	--	--	--	--	6	74.53%	62	77.77%	49	77.39%
levofloxacin oral, solid, liquid	11,288	97.32%	12,402	97.21%	12,640	98.47%	14,234	99.08%	6,165	99.24%
Female	6,862	60.79%	7,560	60.96%	7,637	60.42%	8,536	59.97%	3,698	59.97%
0-40	1,693	24.67%	1,843	24.38%	1,731	22.66%	1,808	21.18%	756	20.44%
41+	5,148	75.03%	5,693	75.30%	5,883	77.04%	6,714	78.65%	2,937	79.43%
Male	4,399	38.97%	4,799	38.70%	4,891	38.70%	5,580	39.20%	2,449	39.72%
0-40	891	20.26%	968	20.17%	914	18.69%	982	17.59%	422	17.23%
41+	3,489	79.33%	3,811	79.40%	3,957	80.90%	4,583	82.13%	2,022	82.57%
UNSPEC.	18	0.41%	21	0.43%	20	0.41%	15	0.28%	5	0.20%
moxifloxacin oral, solid, liquid	2,584	100.00%	3,024	82.93%	2,929	57.34%	3,044	51.89%	1,628	52.77%
Female	1,615	62.50%	1,884	62.32%	1,806	61.66%	1,853	60.87%	994	61.05%
0-40	451	27.92%	502	26.65%	438	24.23%	424	22.90%	222	22.37%
41+	1,161	71.90%	1,379	73.17%	1,365	75.57%	1,427	76.99%	769	77.39%
Male	964	37.31%	1,132	37.44%	1,102	37.61%	1,156	37.99%	628	38.57%
0-40	270	27.98%	300	26.50%	261	23.67%	254	22.00%	137	21.74%
41+	692	71.77%	829	73.27%	838	76.07%	900	77.83%	490	78.02%
telithromcyin oral, solid, liquid	--	--	--	--	843	100.00%	3,240	######	1,257	100.00%
Female	--	--	--	--	541	64.16%	2,043	63.06%	789	62.72%
0-40	--	--	--	--	175	32.34%	664	32.48%	255	32.31%
41+	--	--	--	--	365	67.51%	1,378	67.43%	533	67.56%
Male	--	--	--	--	296	35.16%	1,179	36.38%	466	37.03%
0-40	--	--	--	--	100	33.84%	406	34.42%	161	34.57%
41+	--	--	--	--	195	65.91%	771	65.42%	304	65.24%

Citation: Verispan Vector One®: National, 2002-2006, data extracted July-2006
Source Files: 0607antibio_sex_age.qry, 0607antibio_sex_age.xls
Drug Use Specialist: Carol Pamer
* -- = no data

[1] Total= New and Refill prescriptions

5. EPIDEMIOLOGICAL ANALYSES

In this section we calculated crude reporting rates for categorically serious skin reactions reported in association with gemifloxacin and selected comparators.

Spontaneous reporting systems are the most common method used in pharmacovigilance to generate and detect signals on new or rare adverse events associated with drug therapy.[2] According to a World Health Organization publication, a signal has been defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information".[3]

Spontaneous reporting systems are designed for the detection of rare and unexpected events associated with drug therapy. However, even in the setting of rare and unexpected events the fraction of incident cases that are actually reported is unknown, but estimates of 1% to 10% are commonly cited.[4] Spontaneous reporting systems are not designed to identify an increased risk for a common condition that occurs as a side effect of therapy. In addition to a bias against report of common clinical events (i.e., myocardial infarction among an aged population), spontaneously-reported information is subject to other biases, including the length of time a product has been on the market (Weber effect), secular reporting trends, sponsors' reporting practices, size of sponsors' detail force, target population, healthcare providers' awareness of the association, the quality of the data, and publicity effects.[4-9] Reporting rates (presented in Table 7 below) are based on division of crude (not adjudicated) counts of categorically serious, cutaneous reports for the drugs of interest divided by some measure of drug utilization. These reporting rates have been calculated with the first two and a half years' of drug dispensation data for telithromycin and gemifloxacin; first three years of data for moxifloxacin and gatifloxacin; and first 4 years for cefditoren (only 1,000 prescriptions were dispensed in 2001).

Reporting rate calculations/comparisons have been used in addition to other data to support previous regulatory actions by the agency. Reporting rate calculations are typically based on case counts divided by dispensed prescriptions. Standard reporting rate comparisons require 1) similar drug products [e.g., time on market, route of delivery, spectrum of indication(s)] and 2) assumption that reporting practices are similar for similar drug products over the observed reporting period. Furthermore, standard reporting rate comparisons require an accurate estimate of drug exposure or utilization within the population. Due to the voluntary, spontaneous nature of adverse event reports, reporting rates cannot be interpreted as true incidence rates within the population. Crude (not adjudicated) counts for categorically ***serious*** report counts are used in this analysis because the large number of reports precludes a hands-on analysis at this time. [Categorically ***serious*** report refers to reports that indicate an outcome of death,

hospitalization, intervention required, resulted in disability, or considered medically significant by reporter.]

Estimated domestic drug dispensed, report counts, and crude reporting rates of serious cutaneous reactions are shown in the following table:

Table 7- Domestic utilization, crude (not adjudicated) categorically serious report counts with a cutaneous adverse event, and reporting rates for selected antimicrobial products.[1] [Categorically serious report refers to reports that indicate an outcome of death, hospitalization, intervention required, or resulted in disability.]

Products	**Moxifloxacin Avelox®**	**Gatifloxacin Tequin®**	**Cefditoren Spectracef®**	**Gemifloxacin Factive®**	**Telithromycin Ketek®**
Approval date	12/10/1999	12/17/1999	8/29/2001	4/4/2003	4/01/2004
Estimated dispensed Rx[2] for selected drugs[1] (in 1000s)	5,386	8,237	360	363	5,340
Total reports	226	141	5	38	109
Reporting rate - per million Rx[2]	42	17	14	105	20

1= first two and a half years for telithromycin and gemifloxacin; first three years for moxifloxacin and gatifloxacin; And first 4 years for cefditoren (only 1,000 prescriptions were dispensed in 2001)
2= Rx= prescription

Categorically serious reports of cutaneous adverse events have been reported more frequently in association with gemifloxacin use than either cefditoren or telithromycin. The reporting rate for gemifloxacin is 7.5 times (or 105 per million prescriptions) that of cefditoren (14 per million prescriptions) and 5 times that of telithromycin (20 per million prescriptions). This difference is notable and concerning.

Crude (not adjudicated) counts of categorically serious reports are used in this analysis because the large number of reports precludes an analysis of individual reports. Categorically serious reports of cutaneous adverse events have been reported more frequently for gemifloxacin than cefditoren or telithromycin. The reporting rate for gemifloxacin (105 per million prescriptions) is 7.5 times that of cefditoren (14 per million prescriptions) and 5 times that of telithromycin (20 per million prescriptions). This difference is notable and concerning. Given the substantially higher risk for serious skin reactions in association with gemifloxacin use, a hands-on-review of serious skin reports from these three drugs (gemifloxacin, cefditoren, and telithromycin) is planned to assess if the differences observed in analysis of crude counts will be maintained after adjudication of cases.

6. CONCLUSIONS/RECOMMENDATIONS

Clinical trial data found a higher incidence of rash in patients receiving gemifloxacin than in those receiving comparator antibiotics and a 2003 Advisory Committee presentation on gemifloxacin identified female gender, age <40, planned duration of treatment >7 days, and hormone replacement therapy in women >40 years of age as risk factors for rash development. Postmarketing data from AERS showed the propensity of gemifloxacin to be associated with cutaneous adverse events predominately in females. AERS data for gemifloxacin also indicated that the proportions of cutaneous adverse event reports were greater in the ≤ 40 of age group for both females and males in comparison to the amount of drug use in that same age bracket. Clinical trial data showed that 2/3 of rash in gemifloxacin patients began after day 7 of therapy. However, in our postmarketing analyses, time-to-event was shorter with AERS reports of cutaneous events coded as rash having a median time-to-event onset at 4 days. One-quarter and 1/3 of the serious skin adverse event reports listed previous fluoroquinolone use or history of drug allergy, respectively. Further, many of the serious outcome cases reported an allergic/hypersensitivity component to the cutaneous events with numerous cases reporting significant morbidity. Although information included in the three cases of EM and the four cases of SJS was insufficient to assign such diagnoses, the lack of a definitive EM or SJS case does not imply that severe skin adverse reactions have not or cannot occur in association with gemifloxacin use. Spontaneous adverse event reporting databases such as AERS have multiple limitations. Under reporting, as well as incomplete reporting, coupled with the low post marketing drug utilization for gemifloxacin may underlie the current lack of definitive EM or SJS cases reported to the AERS database. Comparison of gemifloxacin with other recently approved oral antibiotics used to treat minor infections showed that for serious skin reactions, the safety of gemifloxacin is of concern. In addition, crude reporting rate of serious skin reactions was notably higher for gemifloxacin than the comparator drugs.

Thus, much of the findings from AERS postmarketing reports of gemifloxacin regarding cutaneous adverse reactions were consistent with what we already know from the clinical trials data. As outlined in this review however, additional important clinical insight was provided by the AERS case series. The continued concerns raised with the AERS case series as well as the differential crude reporting rates in disfavor of gemifloxacin in comparison to other recently approved antibiotics for similar indications are not reassuring indicators of gemifloxacin's cutaneous safety profile. We plan to perform a follow-up individual case review of all serious skin reactions associated with gemifloxacin, cefditoren, and telithromycin to assess if the differences observed in the analysis of crude counts will be maintained after adjudication of cases. Given the concerning nature of these postmarketing data analyses which add to the already known definitive clinical trials data delineating drug-related cutaneous adverse reactions, we recommend that the magnitude of the drug benefit for the indication under review by the DSPTP (i.e. acute bacterial sinusitis) be clearly defined so that the magnitude of the drug risk can be appropriately examined/weighed in context.

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cc: Avigan/Johann-Liang/Truffa/Brinker/Dal Pan/Albrecht/Tierney/Sacks/Gitterman/ Chen/Birdsong/Marques

APPENDIX (Tables 7, 8, 9)

Table 7 – Comparison of cutaneous AERS reports (foreign and domestic) among selected fluoroquinolones through June 28, 2006[1]

Product	Ciprofloxacin	Levofloxacin	Moxifloxacin	Gatifloxacin	Gemifloxacin
Initial approval date	1987	1996	1999	1999	2003
Cumulative # of AERS reports/all events and all outcomes	11, 010	7,392	4, 113	3, 902	801
Cumulative # of AERS reports listing a cutaneous adverse event[2]	3428 (31%)	1588 (21%)	1045 (25%)	583 (15%)	667 (83%)
Sex, cutaneous adverse events					
Females	1845 (53.8%)	832 (52.3%)	611 (58.4%)	339 (58.1%)	430 (64.4%)
Males	1428 (41.6%)	676 (42.5%)	337 (32.2%)	205 (35.1%)	162 (24.2%)
Not stated	155 (4.5%)	80 (5%)	97 (9.2%)	39 (6.6%)	75 (11.2%)
Age and Sex distribution, cutaneous adverse events					
Females 0-20	98 (2.9%)	29 (1.8%)	14 (1.3%)	7 (1.2%)	11 (1.6%)
21-40	370 (10.7%0	140 (8.8%)	133 (12.7%)	61 (10.5%)	95 (14.2%)
41-60	489 (14.3%)	279 (17.6%)	203 (19.4%)	99 (17%)	99 (14.8%)
>60	752 (21.9%)	330 (20.7%)	131 (12.53%)	142 (24.3%)	46 (6.9%)
Age Not stated	136 (3.9%)	54 (3.4%)	130 (12.4%)	30 (5.1%)	179 (26.8%)
Males 0-20	51 (1.5%)	10 (0.6%)	9 (0.9%)	12 (2.1%)	5 (0.7%)
21-40	245 (7.1%)	85 (5.3%)	65 (6.2%)	24 (4.1%)	38 (5.7%)
41-60	422 (12.3%)	190 (12%)	113 (10.8%)	62 (10.6%)	40 (6%)
>60	597 (17.4%)	351 (22%)	105 (10.0%)	93 (16%)	12 (1.8%)
Age not stated	113 (3.3%)	40 (2.5%)	45 (4.3%)	14 (2.4%)	67 (10%)
Gender not stated 0-20	2 (0.06%)	0	0	0	0
21-40	2 (0.06%)	3 (0.2%)	1 (0.09%)	0	1 (0.1%)
41-60	7 (0.2%)	1 (0.1%)	3 (0.3%)	2 (0.3%)	6 (0.9%)
>60	11 (0.3%)	7 (0.4%)	2 (0.2%)	1 (0.2%)	1 (0.1%)
Age not stated	133 (3.9%)	68 (4.2%)	89 (8.5%)	35 (6%)	67 (10%)
Age , serious outcome[3] cutaneous adverse events					
Females 0-20	70	21	11	6	3
21-40	208	117	105	44	11
41-60	316	227	168	64	8
>60	517	212	110	100	6
Age Not stated	64	39	59	10	3
Males 0-20	24	6	8	8	0
21-40	137	69	55	19	5
41-60	276	150	104	52	3
>60	409	301	94	75	0
Age not stated	57	29	17	8	0
Gender not stated 0-20	1	0	0	0	0
21-40	0	1	1	0	0
41-60	4	6	3	1	1
>60	10	42	1	1	0
Age not stated	38		30	11	0
Outcome cutaneous adverse events (% of total cutaneous events)					
# of serious outcome reports	2133 (62.2%)	1283 (80.7%)	767 (73.3%)	400 (67%)	40 (6 %)
# Death reports	290 (8.4%)	172 (10.8%)	44 (4.2%)	12 (2%)	4 (0.6%)
# Hospitalization reports	1180 (34%)	598 (38%)	309 (30%)	199 (34%)	20 (2.9%)
# Life-threatening reports	248 (7%)	178 (11%)	110 (11%)	53 (9%)	1 (0.1%)
# Disability reports	120 (4%)	116 (7%)	23 (2%)	26 (4%)	3 (0.4%)
# of AERS reports listing Rash	120 (3.5%)	167 (10.5%)	162 (15.5%)	77 (13.2%)	291 (43.6%)

Table 7 – Comparison of cutaneous AERS reports (foreign and domestic) among selected fluoroquinolones through June 28, 2006[1]

Product	Ciprofloxacin	Levofloxacin	Moxifloxacin	Gatifloxacin	Gemifloxacin
(% of total cutaneous events)					
# of AERS reports listing EM (% of total cutaneous events)	57 (1.6%)	18 (1.1%)	7 (0.7%)	0	3 (0.4%)
# of AERS reports listing SJS (% of total cutaneous events)	170 (4.9%)	97 (6.1%)	36 (3.4%)	21 (3.6%)	2 (0.3%)
# of AERS reports listing TEN (% of total cutaneous events)	187 (5.5%)	78 (4.9%)	18 (1.7%)	5 (0.9%)	0
# of AERS reports listing Urticaria (% of total cutaneous events)	467 (13.6%)	160 (10.1%)	160 (15.3%)	64 (11%)	39 (5.8%)
# of AERS reports listing Pruritus (% of total cutaneous events)	701 (20.4%)	200 (12.6%)	161 (15.4%	86 (14.8%)	15 (2.2%)

[1] Data derived from line listings, not from individual review of the reports, which may include duplicates.
[2] Data retrieved under the MedDRA System Organ Class (SOC) grouping Skin and Subcutaneous Tissue Disorders, which includes reports listing one or more cutaneous adverse events
[3] Serious outcome by regulatory definition, which includes death, life-threatening, hospitalization, congenital anomaly, required intervention, other medically important event
Abbreviations: AERS= Adverse Events Reporting System; EM= Erythema multiforme; SJS= Stevens Johnson Syndrome; TEN=Toxic Epidermal Necrolysis

Table 8 – Comparison of US AERS reports listing a cutaneous adverse event occurring in association with selected antimicrobial products (serious outcome in parenthesis) through May 31, 2006[1]

Product	Moxifloxacin Avelox®	Gatifloxacin Tequin®	Cefditoren Spectracef®	Gemifloxacin Factive®	Telithromycin Ketek®
Initial approval date	12/10/1999	12/17/1999	8/29/2001	4/4/2003	4/01/2004
# of US AERS reports/all events	2672 (1629)	3035 (2011)	365 (61)	797 (72)	1351 (525)
# of US report/cutaneous adverse events only [% of total # of reports]	714 [27%]	469 [16%]	66 [18%]	665 [83 %]	242 [18%]
Sex (cutaneous AEs) Females	433	274	44	429	152
Males	196	157	19	161	61
Not stated	85	38	3	75	29
Age (cutaneous AEs) 0-40 year	156	74	10	148	42
>41 years	323	318	13	204	104
Not stated	235	77	43	313	96
# of reports listing rash	135 (71)	63 (47)	32 (1)	291 (11)	49 (16)
# of reports listing maculo-papular rash	8 (6)	8 (5)	0	29 (1)	2 (1)
# of reports listing erythematous rash	14 (12)	14 (9)	0	37 (4)	2 (2)
# of reports listing pustular rash	1 (0)	2 (0)	0	0	0
# of reports listing urticaria	129 (83)	56 (37)	12 (1)	37 (7)	33 (6)
# of reports listing pruritus	133 (98)	75 (41)	6 (0)	15 (11)	31 (15)
# of reports listing erythema multiforme	1 (1)	0	1(0)	3 (0)	0
# of reports listing Stevens Johnson Syndrome	20 (20)	12 (12)	0	2 (1)	3 (3)
# of reports listing toxic epidermal	11 (11)	4 (4)	0	0	0

Table 8 – Comparison of US AERS reports listing a cutaneous adverse event occurring in association with selected antimicrobial products (serious outcome in parenthesis) through May 31, 2006[1]					
Product	**Moxifloxacin Avelox®**	**Gatifloxacin Tequin®**	**Cefditoren Spectracef®**	**Gemifloxacin Factive®**	**Telithromycin Ketek®**
necrolysis					

[1] Data derived from line listings, may contain duplicates. Data collected through May 31, 2006, to parallel drug use data.

Table 9- Approved Indications for selected antimicrobial products							
	Ciprofloxacin	**Levofloxacin**	**Moxifloxacin**	**Gatifloxacin**	**Gemifloxacin**	**Cefditoren**	**Telithromycin**
ABS		x	x				x
AECB		x	x	x	x	x	x
AS	x			x			
CAP		x	x	x	x	x	x
NP	x	x					
IA	x	x					
LRI	x						
PT						x	
AP		x					
AURI				x			
CBP	x	x					
CUTI		x		x			
CUTIP	x						
UTI	x						
UUTI		x		x			
PN				x			
UUCG				x			
CIAI	x		x				
BJI	x						
CSSSI		x	x				
SSSI	x						
USSSI		x	x	x		x	

Abbreviations:
ABS= Acute bacterial sinusitis
AECB= Acute bacterial exacerbation of chronic bronchitis
AP= Acute pyelonephritis
AS=Acute sinusitis
AURI= Acute, uncomplicated rectal infection in women
BJI=Bone and joint infections
CAP= Community acquired pneumonia
CIAI= Complicated intra-abdominal infections
CBP= Chronic bacterial prostatitis
CSSSI= Complicated skin and skin structure infections
CUTI= Complicated urinary tract infections
CUTIP= Complicated urinary tract infections and pyelonephritis
IA= inhalational anthrax
LRI= Lower respiratory infections
NP= Nosocomial pneumonia
PN= Pyelonephritis
PT=Pharyngitis/Tonsillitis

SSSI=Skin and skin structure infections
USSSI= Uncomplicated skin and skin structure infections
UUCG= Uncomplicated urethral and cervical gonorrhea
UUTI=Uncomplicated urinary tract infections
UTI= Urinary tract infections

The attached documents are CLEARED for the following purposes ONLY. This coversheet must accompany all final documents that have been CLEARED.

Audience:	FDA Anti-Infective Drugs Advisory Committee Members and Oscient Pharmaceuticals on approximately July 28, 2006. Public (including FDA website) on September 12, 2006
Purpose:	FDA Advisory Committee Meeting
Dates of Disclosure:	July 28 and September 12, 2006
Data Vendors Used:	Verispan

Clearance Requestor's Signature: DDRE (Farinas and Ahmad)

Date: July 28, 2006

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Rosemary Johann-Liang
7/26/2006 06:03:32 PM
MEDICAL OFFICER

Appendix D

Non-inferiority Studies in Acute Bacterial Sinusitis

Appendix D

Non-inferiority studies are predicated on two basic principles. The first is that the comparator to which the new agent is being compared is safe and effective, i.e., the comparator is superior to placebo. The second is that the magnitude of this effect is known: the margin of non-inferiority is less than the margin of effectiveness. This latter criterion is intuitively obvious: a non-inferiority study with a 15% margin would tell little about the efficacy of a drug with a 5% difference relative to placebo.

The issues regarding non-inferiority trials, including ABS trials, have been discussed at a number of public meetings. These include:

- an Anti-Infective Drugs Advisory Committee meeting on non-inferiority trials in **February 2002** (http://www.fda.gov/ohrms/dockets/ac/02/agenda/3837a1.htm),
- an open public workshop with FDA-IDSA-PhRMA in **November 2002** (http://cdernet/ob/Useful_Information/Review_Related/PhRMA_2002/PhRMA_Program.htm) ,
- a PhRMA-FDA statistical workshop in **November 2002** (http://www.fda.gov/cder/present/idsaphrma/),
- an open meeting of the Anti-Infective Drugs Advisory Committee meeting specifically addressing clinical trial design for acute bacterial sinusitis in **October 2003** (http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3997T2.htm), and
- an open public FDA/IDSA/ISAP workshop in **April 2004** (http://www.fda.gov/cder/drug/antimicrobial/FDA_IDSA_ISAP_Presentations.htm).

The October 2003 meeting specifically dealt with acute bacterial sinusitis and is directly relevant to this application. At the 2003 meeting, participants head FDA presentations on review of data from literature publications of placebo-controlled trials in ABS.

The consensus recommendation of the advisory committee in 2003 was that sponsors should conduct clinical trials in ABS as superiority trials in order to obtain substantial evidence of effectiveness from clinical trials in this disease.

Appendix E

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