

Table 16 Clinical Response by smoking status, Eligible Patients

	Gatifloxacin		Levofloxacin		Total		CI ^a
Clinical Response	Number of Patients (%)						
Applicant's Analysis							
	N = 167		N = 169		N = 336		S(-15.3%,11.0%)
	S=99	NS=68	S=96	NS=73	S=195	NS=141	
Cure	79 (80)	50 (74)	78 (81)	63 (86)	157	113	NS(-29.1%,2.4%)
Failure	5	13	5	7	10	20	
UTD	15	5	13	3	28	8	
Reviewer's Analysis #1^b							
	N = 167		N = 169		N = 336		S(-17.1%,11.4%)
	S=99	NS=68	S=96	NS=73	S=195	NS=141	
Cure	68 (69)	35 (52)	68 (71)	46 (63)	136	81	NS(-29.0%,5.3%)
Failure	16	28	15	24	31	52	
UTD	15	5	13	3	28	8	
Reviewer's Analysis #2^b							
	N = 152		N = 149		N = 301		S(-12.3%,16.3%)
	S=88	NS=64	S=82	NS=67	S=170	NS=131	
Cure	71 (81)	46 (72)	65 (79)	57 (85)	136	103	NS(-30.1%,3.1%)
Failure	4	13	5	7	9	20	
UTD	13	5	12	3	25	8	
Reviewer's Analysis #3^b							
	N = 152		N = 149		N = 301		S(-13.7%,16.7%)
	S=88	NS=64	S=82	NS=67	S=170	NS=131	
Cure	63 (72)	32 (50)	58 (71)	42 (63)	121	74	NS(-30.7%,4.9%)
Failure	12	27	12	22	24	49	
UTD	13	5	12	3	25	8	

^a 95% Confidence Interval for the difference in Cure Rates by smoking status (S= Current smokers; NS= Non-smokers)

^b For the description of the reviewer's analyses, refer to section 8.2.2.4.2 (Efficacy Results)

Reason Clinical Response Was Unable to Determine, Eligible Patients

Thirty-six Eligible Patients had a clinical response of Unable to Determine (Table 17). Half of those patients had inadequate follow-up and one third discontinued prematurely due to an adverse event prior to outcome assessment. The frequency was similar across treatment arms. Two patients had insufficient therapy to assess response, one patient on levofloxacin discontinued therapy before Day 3. Another patient lost study medication, prior to Day 5 of therapy.

Table 17 Reason Clinical Response is Unable to Determine, Clinically Eligible Patients

Reason	Number of Patients		
	Gatifloxacin N = 167	Levofloxacin N = 169	Total N = 336
Number of Responses Unable to Determine	20	16	36
Inadequate Follow-up	10	8	18
Adverse Event Prior to Assessment	7	5	12
Other Systemic Antibiotic Needed for Reason Other Than the Infection Under Study	3	1	4
Inadequate Therapy	-	2	2

Reviewer's comments: Reviewer agrees with applicant regarding the classification of these patients in the Unable To Determine group.

Bacteriologic Efficacy

Overall, gatifloxacin achieved eradication of 80% (135/168) of the pre-treatment pathogens isolated from Clinically Eligible Patients (Table 18). Levofloxacin eradicated 86% (130/151) of the pre-treatment pathogens. In most cases, pathogens were presumed eradicated. The eradication was similar in relation to the Clinically Evaluable patients.

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Table 18 Bacteriologic Eradication Rates by Pathogen, Clinically Eligible Patients

Pathogen	Number Eradicated/Number Isolated (%)		
	Gatifloxacin	Levofloxacin	Total
Total	135/168 (80)	130/151 (86)	265/319 (83)
<i>H. influenzae</i>	27/30 (90)	21/25 (84)	48/55 (87)
β-Lactamase +	11/13 (85)	9/13 (69)	20/26 (77)
β-Lactamase -	14/15 (93)	11/11 (100)	25/26 (96)
β-Lactamase Unknown	2/2 (100)	1/1 (100)	3/3 (100)
<i>M. catarrhalis</i>	35/42 (83)	24/30 (80)	59/72 (82)
β-Lactamase +	31/36 (86)	20/26 (77)	51/62 (82)
β-Lactamase -	3/5 (60)	4/4 (100)	7/9 (78)
β-Lactamase Unknown	1/1 (100)	-	1/1 (100)
<i>H. parainfluenzae</i>	13/18 (72)	21/23 (91)	34/41 (83)
β-Lactamase +	2/4 (50)	2/3 (67)	4/7 (57)
β-Lactamase -	10/13 (77)	19/20 (95)	29/33 (88)
β-Lactamase Unknown	1/1 (100)	-	1/1 (100)
<i>S. pneumoniae</i>	14/17 (82)	16/18 (89)	29/35 (88)
Penicillin Susceptible	9/9 (100)	9/9 (100)	18/18 (100)
Penicillin Intermediate	4/5 (80)	5/7 (71)	9/12 (75)
Penicillin Resistant	1/3 (33)	2/2 (100)	3/5 (60)
<i>S. aureus</i>	22/30 (73)	24/27 (89)	46/57 (81)
<i>K. pneumoniae</i>	1/1 (100)	2/3 (67)	3/4 (75)
<i>P. aeruginosa</i>	1/1 (100)	5/6 (83)	6/7 (86)
<i>E. cloacae</i>	2/4 (50)	1/1 (100)	3/5 (60)
Others ^a			
Gram-positive	13/16 (81)	12/13 (92)	25/29 (87)
Gram-negative	7/9 (78)	4/5 (80)	11/14 (79)

^a A patient may have more than one pathogen isolated pre-treatment.

Reviewer's comments: Reviewer agrees with the data presented in this table via the databases. Eradication rates were comparable for *H. influenzae*, *M. catarrhalis*, *H. parainfluenzae* and *S. pneumoniae*. Levofloxacin was more effective against *S. aureus*.

Reason Bacteriologic Response was Unable to Determine

Bacteriologic response could not be determined for 20 pre-treatment pathogens from 14 Eligible Patients treated with gatifloxacin, and from 12 pre-treatment pathogens from 10 Eligible Patients treated with levofloxacin because the patients from whom they were isolated could not have a clinical response determined (Table 19). In two cases, the pre-treatment pathogen was either gatifloxacin-resistant or levofloxacin-resistant.

Table 19 : Reasons Bacteriologic Response is Unable to Determine, Clinically Eligible Patients

Reason Unable to Determine	Number of Patients	
	Gatifloxacin	Levofloxacin
Unable to Determine Clinical Response	14	10
Receipt of Other Systemic Antibiotic	2	-
Pathogen Resistant	1	1
Total	17	11

Reviewer's comments: Reviewer agrees with applicant regarding the classification of these patients in the Unable To Determine group.

All Treated Patients

Clinical response

Clinical responses were lower in the All Treated Patients compared to the clinically evaluable patients (Table 20).

Table 20 Clinical Response, All Treated Patients

	Number of Patients (%)		
	Gatifloxacin N=179	Levofloxacin N=179	Total N=358
Cure	140 (78)	150 (84)	290 (81)
Failure/UTD	39 (22)	29 (16)	68 (19)

95% Confidence Interval for difference in cure rate: (-14.9%, 3.4%)

Reviewer's comments: This group comprised patients who did not have purulent sputum or had evidence of pneumonia on chest X-ray. The response rate for levofloxacin is higher in this group, with a CI that is still within acceptable limits.

New Infections

Fifteen (4%) patients developed new infections (Table 21). Among the gatifloxacin patients, there were a total of 10 new infections: five of the respiratory system, 3 of the genitourinary system, and 2 of the HEENT. One patient developed 2 new infections (dental abscess and vaginitis) and was treated with penicillin and tioconazole. No cultures were performed on the 9 gatifloxacin patients who had new infections. One patient on levofloxacin developed two infections, vaginitis and pharyngitis, and was treated with terconazole and amoxicillin.

Only one patient developed vaginitis as a new infection during gatifloxacin therapy, while 2 patients did on levofloxacin. An additional 6 patients receiving gatifloxacin and 2 receiving levofloxacin had vaginitis reported as an adverse event but were not listed as new infections.

Table 21 New Infections, All Treated Patients

Infection Type/Diagnosis	Number of Patients (%)					
	Gatifloxacin N = 179		Levofloxacin N = 179		Total N = 358	
<u>Number of Patients Reporting</u>	9	(5)	6	(3)	15	(4)
<u>Any New Infection^a</u>						
Respiratory System						
Influenza	1	(<1)	1	(<1)	2	(<1)
Sinusitis	2	(1)	2	(1)	4	(1)
Pharyngitis	1	(<1)	1	(<1)	2	(<1)
Upper Respiratory	1	(<1)	1	(<1)	2	(<1)
Genitourinary System						
Vaginitis	1	(<1)	2	(1)	3	(<1)
Urinary Tract Infection	2	(1)	-		2	(<1)
HEENT						
Abscess Dental	1	(<1)	-		1	(<1)
Otitis Media	1	(<1)	-		1	(<1)

^a Patients may have had more than one new infection.

Reviewer's comments: The number of new infections was low and comparable between the 2 groups, with no life-threatening infections noted.

8.2.2.4.3 Safety Evaluation

All Adverse Clinical Events

Adverse clinical events of all causes were more frequent in gatifloxacin than levofloxacin (Table 22). In both groups, approximately half were not considered drug-related according to the investigators. In general, there was no difference between treatment groups, except nausea and diarrhea, which were more frequent with gatifloxacin. The most frequent events overall were gastrointestinal (GI) intolerance and respiratory symptoms. Seven female patients receiving gatifloxacin developed vaginitis; five episodes were described as mild and two as moderate. Four of the vaginitis patients were treated with topical antifungal creams and two received fluconazole. All of their infections resolved. The seventh vaginitis patient had resolution of symptoms without treatment.

Four females receiving levofloxacin experienced vaginitis; two episodes were described as mild and two as moderate in intensity. One patient was treated with topical antifungal cream, one received fluconazole, and two did not have treatment. All cases of vaginitis resolved.

Drug-Related Adverse Clinical Events

The incidence of adverse clinical events assessed by the investigator to be related to gatifloxacin was 34% (60 patients) compared to 28% (50 patients) on levofloxacin (Table 23). GI intolerance and vaginitis were the most frequent drug-related events in both treatment groups. In both groups, the majority of events were mild or moderate. Gatifloxacin had more GI events rated severe than did levofloxacin. Drug-related nausea was more prevalent in the gatifloxacin group.

The incidence of adverse clinical events assessed by the investigator to be related to levofloxacin was similar to gatifloxacin. The most common were diarrhea, nausea, dizziness and vaginitis. Most levofloxacin-related adverse clinical events were mild or moderate in severity.

Deaths and Serious Adverse Events (SAE)

There were no deaths on study from the start of dosing until 30 days after the last dose. Eleven (3%) patients (4 in gatifloxacin group and 7 in levofloxacin group) experienced 17 serious adverse events, none of which was related to gatifloxacin or to levofloxacin according to the investigators. In general, this was a low incidence and both treatment groups were similar. Many of the SAEs were respiratory in nature, and were distributed as follows:

Gatifloxacin: there was one event each of testicular cancer, arm and back pain (musculoskeletal), hospitalization for severe AECB, and lung cancer.

Levofloxacin: there was one event each of left knee replacement due to long standing history of osteoarthritis, pneumonia, asthma, congestive heart failure, numbness, coughing, COPD, dyspnea, increase in sputum, back pain and two cases of bronchitis.

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Indication: Acute Exacerbations of Chronic Bronchitis

Table 22 Adverse Clinical Events of All Causes, All Treated Patients

Adverse Clinical Event ^a	Number (%) of Patients								
	Gatifloxacin N = 179				Levofloxacin N = 179				
	Drug-related	Not Drug-related		Unassessed	Total	Drug-related	Not Drug-related		Unassessed
Any Adverse Clinical Event	60 (34)	44 (25)	3 (2)	107 (60)	50 (28)	44 (25)	1 (<1)	95 (53)	
Nausea	19 (11)	4 (2)	-	23 (13)	10 (6)	3 (2)	-	13 (7)	
Abnormal Breath Sounds	2 (1)	19 (11)	-	21 (12)	-	17 (9)	-	17 (9)	
Diarrhea	12 (7)	7 (4)	-	19 (11)	12 (7)	1 (<1)	-	13 (7)	
Increased Coughing	3 (2)	13 (7)	-	16 (9)	-	16 (9)	1 (<1)	17 (9)	
Vaginitis ^b	7 (8)	-	-	7 (8)	4 (6)	-	-	4 (6)	
Increased Sputum	3 (2)	10 (6)	-	13 (7)	-	14 (8)	1 (<1)	15 (8)	
Chest Pain	1 (<1)	12 (7)	-	13 (7)	-	6 (3)	-	6 (3)	
Headache	4 (2)	7 (4)	-	11 (6)	5 (3)	11 (6)	-	16 (9)	
Dyspnea	-	11 (6)	-	11 (6)	-	9 (5)	-	9 (5)	
Dizziness	7 (4)	2 (1)	-	9 (5)	8 (5)	3 (2)	-	11 (6)	
Malaise	1 (<1)	6 (3)	2 (1)	9 (5)	2 (1)	6 (3)	-	8 (4)	
Rhinitis	-	8 (4)	-	8 (4)	-	11 (6)	-	11 (6)	
Vomiting	7 (4)	1 (<1)	-	8 (5)	3 (2)	2 (1)	-	5 (3)	
Pharyngitis	-	7 (4)	-	7 (4)	-	8 (4)	-	8 (4)	
Chills	1 (<1)	5 (3)	-	6 (3)	1 (<1)	2 (1)	-	3 (2)	
Fever	1 (<1)	5 (3)	-	6 (3)	-	2 (1)	-	2 (1)	
Abdominal Pain	5 (3)	-	-	5 (3)	4 (2)	2 (1)	-	6 (3)	
Insomnia	4 (2)	1 (<1)	-	5 (3)	2 (1)	-	-	2 (1)	
Dyspepsia	4 (2)	-	-	4 (2)	3 (2)	1 (<1)	-	4 (2)	
Pain	-	3 (2)	-	3 (2)	1 (<1)	7 (4)	-	8 (4)	
Asthenia	2 (1)	1 (<1)	-	3 (2)	4 (2)	1 (<1)	-	5 (3)	
Taste Perversion	3 (2)	-	-	3 (2)	3 (2)	1 (<1)	-	4 (2)	
Bronchitis	-	1 (<1)	-	1 (<1)	-	4 (2)	-	4 (2)	

a All Adverse clinical events occurring in $\geq 2\%$ of the total number of patients in either treatment group.

b Vaginitis was calculated on female patients only, not the entire study population.

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Table 23 Drug-related Adverse Clinical Events, All Treated Patients

Adverse Clinical Event ^a	Number (%) of Patients Gatifloxacin N = 179					Levofloxacin N = 179				
	Mild	Moderate	Severe	Very Severe	Total	Mild	Moderate	Severe	Very Severe	Total
Any Drug-related Adverse Clinical Event	31 (17)	24 (13)	5 (3)	-	60 (34)	27 (15)	19 (11)	4 (2)	-	50 (28)
Nausea	13 (7)	5 (3)	1 (<1)	-	19 (11)	8 (4)	2 (1)	-	-	10 (6)
Vaginitis ^b	5 (6)	2 (2)	-	-	7 (8)	2 (3)	2 (3)	-	-	4 (6)
Diarrhea	6 (3)	5 (3)	1 (<1)	-	12 (7)	9 (5)	3 (2)	-	-	12 (7)
Dizziness	3 (2)	3 (2)	1 (<1)	-	7 (4)	4 (2)	4 (2)	-	-	8 (4)
Vomiting	3 (2)	2 (1)	2 (1)	-	7 (4)	-	3 (2)	-	-	3 (2)
Pain, Abdominal	2 (1)	3 (2)	-	-	5 (3)	1 (<1)	2 (1)	1 (<1)	-	4 (2)
Headache	1 (<1)	2 (1)	1 (<1)	-	4 (2)	2 (1)	2 (1)	1 (<1)	-	5 (3)

a All adverse clinical events occurring in $\geq 1\%$ of the total number of patients.

b Vaginitis was calculated on female patients only, not the entire study population.

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Adverse Events Leading to Discontinuation of Study Therapy

Of the 358 patients who received at least one dose of gatifloxacin, twenty one (6%) discontinued treatment due to adverse clinical events. The gatifloxacin and levofloxacin arms were comparable with respect to discontinuations due to adverse events (7% and 6%, respectively). In both groups, gastrointestinal and central nervous system events were the main reason leading to discontinuation. One event (arm pain) for one of the twelve gatifloxacin patients was considered by the investigator to be unrelated to study drug while the other patients' events were considered to be gatifloxacin-related (taste distortion, flatulence, headache, hand tremors, flushing, nausea, vomiting, dizziness, abdominal pain, dyspepsia, diarrhea, malaise, arthralgia, asthenia, pruritus). In the levofloxacin arm four patients' events were unrelated to study drug (dyspepsia, taste perversion, eructation, chest pain, chills) and the other five patients' events were considered by the investigators to be levofloxacin-related (headache, dizziness, nausea, vomiting, diarrhea, nervousness, confusion, dyspnea, wheezing, respiratory distress, bronchitis, COPD, abdominal pain, malaise, palpitations, congestive heart failure, taste distortion, flatulence).

Reviewer's comments: Most adverse events in the gatifloxacin group were non-serious in nature. Nausea was more frequent with gatifloxacin, and so was vomiting. The incidence of dizziness was comparable. Class-related events, namely phototoxicity, tendinitis, and seizures, were not encountered. One case of premature atrial and ventricular beats was noted. From this study, it appears that gatifloxacin has a favorable clinical adverse event profile.

Laboratory Test Results

Patients with Normal Pre-treatment Values

Very few patients with normal baseline values developed abnormal laboratory test results during or post-treatment. There were no appreciable differences between the treatment arms. When abnormalities were present, they were minimal and mild. The most frequent lab tests affected were hemoglobin and electrolytes in both treatment groups. There were 2 out of 4 tested patients on gatifloxacin with increased glucose values (132 and 127 mg/dL). Grade 1 BUN/urea abnormalities were noted in 13 (8%) of 162 tested patients; Grade 2 bilirubin abnormalities were noted in 7 of 165 tested patients (4%) on gatifloxacin; Grade 1 AST abnormalities were noted in 10 of 148 tested patients (7%) on gatifloxacin; Grade 1 ALT abnormalities were noted in 9 of 154 tested patients (6%) on gatifloxacin.

Development of a Grade 3 or Grade 4 laboratory test elevation occurred in two levofloxacin patients and in none of the gatifloxacin patients.

Patients with Abnormal Pre-treatment Values

Patients who had abnormal (Grade 1, 2 or 3) pre-treatment laboratory values occasionally experienced worsening to a higher grade during or post-treatment. Levofloxacin patients

worsened to a Grade 2 more often than gatifloxacin patients did. However, worsening to a Grade 3 or Grade 4 result was rare. This occurred in only one patient on gatifloxacin for two different tests. Two liver function parameters, AST and ALT, worsened to Grade 3 on Day +9 in a patient later discovered to have testicular cancer.

Reviewer's comments: Gatifloxacin appears to have a favorable adverse event profile in terms of laboratory parameters. However, the number of patients who had a pre-treatment Fasting Blood Sugar done was small, 25 in gatifloxacin group and 14 in levofloxacin group. Moreover, only 4 patients on gatifloxacin and 5 on levofloxacin had a Fasting Blood Sugar done during treatment. Two of those 4 patients on gatifloxacin (one of whom had a history of gestational diabetes) had mild elevations in their blood sugar. A larger number of patients is needed for a better assessment of a potential relationship between gatifloxacin and hyperglycemia. Abnormalities in liver function tests were not severe. Among patients with normal pre-treatment values, 3 patients on gatifloxacin and 2 patients on levofloxacin had an elevation of both AST and ALT; one of the gatifloxacin patients also had an elevated bilirubin. For this patient, the values were the following: AST 103 (nl 15-37), ALT 91 (nl 30-65), Total Bilirubin 1.3 (nl <1).

8.2.2.5 Conclusions

The applicant's conclusion was that "the results of this study indicate that gatifloxacin 400 mg daily is safe and effective given for seven or ten days for the treatment of acute exacerbations of chronic bronchitis. The drug demonstrated a favorable safety profile and clinical and bacteriologic efficacy in a highly representative cohort of patients with this disease compared to levofloxacin. Efficacy was documented in microbiologically evaluable patients, with complete eradication of *H. influenzae* and *S. pneumoniae*. Eradication of the other respiratory pathogens, *M. catarrhalis*, *H. parainfluenzae*, and *S. aureus*, also documented efficacy".

*Reviewer's comments: Data in this study were well presented in tables and appendices in hard copy and electronic format, which allowed easy derivation for further analysis. Individual patient data were well documented on Case Report Forms, as shown by a thorough review of 10% of those. The study was well designed, but separating cured patients from those who were only improved would have been a better approach. Cure rates were slightly higher for levofloxacin, and the lower limits for the 95% Confidence Intervals were close to or exceeded the designated limit. Data regarding microbiologic efficacy were supportive of effectiveness against the major pathogens involved in AEBCB, namely *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, but also against *S. aureus* and *H. parainfluenzae*. The safety profile seemed favorable but should be examined more thoroughly through the review of the data from the integrated safety summary.*

8.2.3 Trial #3

Applicant's Study AI420-020: A Randomized, Double-Blind, Multicenter Comparative Study of Gatifloxacin Versus Cefuroxime Axetil in the Treatment of Acute Exacerbations of Chronic Bronchitis

8.2.3.1 Rationale/Objective

An open-label Phase II study with gatifloxacin 400 mg PO QD in the treatment of AECB (AI420-004) was already conducted in the United States. There was a good response rate and the majority of adverse events were considered mild.

The objectives of this study (AI420-020) were to demonstrate clinical efficacy and safety of gatifloxacin in AECB relative to a standard regimen of cefuroxime axetil, and to demonstrate microbiological eradication rates and responses for the most common pathogens causing AECB.

8.2.3.2 Design

This was a randomized, double-blind, multicenter study designed to assess the safety and efficacy of gatifloxacin at a dose of 400 mg PO QD for 7-10 days versus a standard regimen of cefuroxime axetil, 250 mg PO BID for 7-10 days in the treatment of adult patients with AECB. Fifty-five study sites in the U.S., Argentina, Brazil, Mexico, Puerto Rico, South Africa and Canada were recruited; 31 sites enrolled patients. Patients were stratified at the time of randomization based on their smoking status. A patient was considered a current smoker if he or she was a smoker at the time of enrollment or had stopped smoking within the two months before enrollment. The planned enrollment was 316 patients.

Sample size was initially determined using a cure rate of 84% for cefuroxime axetil in an evaluable patient population with AECB. Assuming equivalence in response rates between the two treatment groups and 90% power to rule out a maximum difference of 15%, 126 evaluable patients per arm were needed (158 patients per arm assuming an 80% evaluability rate for a total of 316 patients).

After 183 investigator clinical responses were present in the study database, the pooled (blinded) response rate was determined to be 88%. The evaluability rate was 77%. The revised calculation indicated 100 evaluable patients per arm were needed (260 total patients). The original sample size was maintained after this reassessment was completed.

In North America (U.S. and Canada) the randomization system used the Pocock minimization algorithm, which adjusted the randomization probabilities in order to minimize any imbalance of treatment arms within each site, within each smoking group and for the overall study. At sites located in other countries (Argentina, Mexico, Puerto

Rico and South Africa), patients were enrolled into this study using a permuted block within smoking strata randomization.

Reviewer's comments: This trial attempts to establish equivalence of gatifloxacin to an approved drug for the indication of AECB. The study design uses an active control drug and a random assignment of patients to the investigational drug and the active control drug groups in a double-blind fashion. This is the preferred design according to the IDSA/FDA "Guidelines For The Evaluation Of Anti-Infective Drug Products".

8.2.3.3 Protocol

8.2.3.3.1 Population

For inclusion, patients with a history of chronic bronchitis (i.e., productive cough on most days for at least three consecutive months in two consecutive years) and a diagnosis of AECB had to meet all of the following criteria:

Eighteen years of age or older;

Clinical diagnosis of acute exacerbation of chronic bronchitis, defined as:

- The presence of purulent sputum confirmed by Gram stain examination [>25 polymorphonuclear leukocytes (PMN) and <10 squamous epithelial cells (epi) per low power field (LPF)]
- The presence of at least two of the following signs and symptoms:
 - increased cough and/or dyspnea;
 - increased sputum volume;
 - increased sputum purulence.

For women of childbearing potential:

- Documented negative serum/urine pregnancy test (minimum sensitivity 25 IU/L of β -human chorionic gonadotropin [β -HCG]) within 48 hours prior to the start of study therapy, and
- Commitment to use an effective method of contraception from the start of study treatment until completion of post-treatment procedures.

Written informed consent (from patients or their guardians) before any study procedures were performed.

Patients were excluded if they met any of the following criteria:

Pregnant or lactating

History of significant hypersensitivity reaction to either fluoroquinolone compounds or cephalosporins

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Received a systemic antibiotic therapy within seven days prior to enrollment, or were likely to require other systemic antibiotic(s) concomitantly

Diagnosis of pneumonia confirmed by the presence of pulmonary infiltrates on a chest x-ray

Previously diagnosed disease(s) of immune function (e.g., AIDS or history of clinical manifestations of HIV infection, neutrophil count $< 1000/\text{mm}^3$)

Previously diagnosed condition that would tend to mimic or complicate the course and evaluation of the infectious process

Known renal insufficiency (i.e., serum creatinine ≥ 1.5 mg/dL or requiring renal dialysis);

Current clinically significant hepatic disease (i.e., aspartate amino transferase (AST) and/or alanine amino transferase (ALT) and/or total bilirubin ≥ 3 times the upper limit of normal);

Malabsorption syndromes or other gastrointestinal disturbances that would affect drug absorption;

Previous treatment in any gatifloxacin study.

Reviewer's comments: Inclusion and exclusion criteria were appropriate and clearly identified prior to initiation of the study. The criterion of < 10 epithelial cells/LPF was later relaxed by the applicant via the analysis plan to include patients who were shown at the central laboratory reading of the sputum Gram stain to have > 10 epithelial cells/LPF. The applicant's explanation was that "epithelial cells, when associated with > 25 PMNs, only indicate that the purulent bronchial secretions have been contaminated by mouth flora. It does not detract from the clinical findings and confirms that the patient has purulent sputum". The applicant also cited a precedent where disregard of this criterion was acceptable to FDA, and provided FDA with a list of those patients who were enrolled despite having > 10 epithelial cells/LPF. The exclusion of patients with AIDS, renal insufficiency and hepatic disease makes it difficult to predict safety and efficacy in these population groups.

Exacerbation type at entry was determined according to the following criteria established by Anthonisen, et al.

Type I - increased dyspnea, increased sputum volume and increased sputum purulence;

Type II - any two of the three symptoms of Type I;

Type III - any one of the three symptoms of Type I.

Patients received gatifloxacin 400 mg PO once a day or cefuroxime axetil 250 mg PO twice a day with placebo without regard to meals.

Patients were to be excluded if they had received antibiotic therapy within 7 days before enrollment. Other antimicrobial agents, such as antivirals and antifungals, were permitted pre-treatment. Adjunctive measures, such as oral or topical decongestants, antihistamines, and intranasal steroids, were permitted during and post-treatment as

needed by the patient. In addition, concomitant or post-treatment non-drug therapies, such as postural drainage or oxygen were allowed. Investigators were permitted to discontinue study drug and remove patients from the study for the following reasons:

An adverse event;

Persistence or worsening of signs and symptoms of the acute infection after three days of study drug therapy;

An intercurrent illness;

Patient's decision not to participate any further;

Investigator's decision that discontinuation was in the patient's best interest;

A female patient with a positive pregnancy test during study drug therapy (immediate discontinuation);

Decision of the sponsor to terminate the study (at some or all sites).

Patients with one or more study drug-resistant pre-treatment pathogens were removed from the study if the investigator felt it was in their best interest. Patients whose condition had not improved or had worsened after three days of study drug therapy (early treatment failures) were to be removed from the study and to have the clinical and laboratory procedures specified for the post-treatment visit performed before starting alternative antibiotic therapy.

Clinical and bacteriologic responses to gatifloxacin therapy were assessed at Day +7 to Day +14 post-treatment visit, or earlier for those who discontinued therapy prematurely. Clinical response to gatifloxacin therapy was based upon the signs and symptoms of the acute infection; the bacteriologic response for each pre-treatment pathogen was based on culture results or, if there was no source to culture, the clinical assessment at the Test of Cure (TOC) visit. Relapse was evaluated at the Day +21 to Day +28 extended follow-up assessment.

Patient assessments were scheduled to occur as follows (Table 1):

Pre-treatment (within 48 hours before dosing);

During treatment (Day 3 to Day 5);

End of treatment (Day +1 to Day +3) – [telephone contact; office/clinic visit if clinically indicated];

Post-treatment (Day +7 to Day +14);

Final follow-up (Day +21 to Day +28) – [telephone contact; office/clinic visit if clinically indicated].

Table 1 Study Procedures

Procedure	Pre-treatment (Within 2 days prior to dosing)	During Treatment (Days 3 to 5)	End of Treatment a (Days +1 to +3)	Post- treatment (Days + 7 to +14)	Extended Follow- up ^a (Days + 21 to +28)
Screening	X	-	-	-	-
Chest x-ray	X	X ^b	-	X ^b	-
Medical History	X	-	-	-	-
Physical Exam	X	-	-	X	-
Vital Signs	X	X	-	X	-
Clinical Evaluation	X	X	X	X	X ^c
Pulmonary Function Tests	X	-	-	X	-
Laboratory Tests	X	X	-	X	-
Sputum Smear	X	X	-	X	X ^c
Sputum Assessment	X	X	-	X	X ^c
Sputum Culture	X	X	-	X	X ^c
Assess Adverse Events	-	X	X	X	X
Assess Medication Use	-	X	X	X	-
Pregnancy Test	X	-	-	X	-

a Telephone contact. If patient not clinically improved, office visit to be scheduled for further evaluation.

b If clinically indicated.

c Office visit to be scheduled for further evaluation if increased sputum production persisted. Culture to be done if purulent sputum specimen obtained.

For non-U.S. sites, all laboratory procedures, including appropriate cultures, were performed by local laboratories. Gram stain sputum smears were prepared by the site or at a local laboratory to determine sputum purulence and, therefore, patient eligibility.

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For U.S. sites, all laboratory procedures, including appropriate cultures, were performed by a central laboratory. Investigators performed initial Gram stain procedures on site to expedite determination of sputum purulence and, therefore, patient eligibility. The central laboratory performed an independent Gram stain. If the site reading did not match the central laboratory, the Medical Monitor used the overread done by the central laboratory for determining patient eligibility.

All pre-treatment sputum specimens were plated semi-quantitatively for aerobic growth, and all potential pathogens isolated were tested for study drug susceptibility. Hematology, serum chemistry, and urinalysis tests included: White blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, amylase, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, microscopic urinalysis. A urine pregnancy test was performed on all women of childbearing potential. Positive urine pregnancy tests were confirmed with a serum-based pregnancy test.

Patients were observed at least once during treatment (between Day 3 and Day 5, inclusive), and as frequently as deemed necessary by the investigator. If a sputum specimen was produced during this visit, purulence was assessed and, if purulent, the specimen was plated for culture and antibiotic susceptibility. A chest x-ray was taken if clinically indicated.

In the three-day period immediately following the end of therapy (i.e., Day +1 to Day +3, inclusive), patients were contacted by telephone and queried about the clinical signs and symptoms of infection, the occurrence of adverse events, and compliance with the dosing regimen. If a patient's signs and symptoms had not returned to baseline, or if clear clinical improvement had not occurred, the patient was scheduled for an immediate office visit.

Between Day +7 and Day +14, patients were evaluated in the office/clinic for clinical and bacteriologic response to study drug therapy and the occurrence of adverse clinical events. If a patient was still producing sputum, a specimen was obtained for assessment of purulence, quantitative culture and susceptibility testing. If a laboratory test result became abnormal or worsened from an abnormal pre-treatment level, the test was repeated at appropriate intervals until the value either returned to the pre-treatment level or stabilized.

Patients were contacted by telephone approximately two weeks later (Day +21 to Day +28) to assess relapse of the acute infection. Patients were queried as to the presence and severity of clinical signs and symptoms of infection, ingestion of any antibiotics since the last office/clinic visit, and occurrence of adverse clinical events.

If increased sputum production persisted, or recurred after initial improvement, an office/clinic visit was scheduled for further evaluation. This included collection of a sputum sample for assessment of appearance and evaluation of a Gram-stained smear; if the specimen was purulent, bacteriologic culture and susceptibility testing of any isolated pathogens were performed.

Reviewer's comments: Patient monitoring was adequate in terms of frequency of visits and phone check-ups. Laboratory tests were also adequate for proper detection of toxicity. Study drug levels were not measured to verify compliance, which was only done through a patient maintained diary.

8.2.3.3.2 Endpoints

Clinical and bacteriologic responses were determined from data at the TOC visit scheduled between Day +7 and Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit from Day +5 to Day +18, inclusive, was acceptable. Treatment failures could be assessed at any time prior to Day +18, but patients had to receive a minimum of three days of therapy.

Reviewer's comments: The TOC window of +7 to +14 days was expanded to +5 to +18 days. This was done to allow for any difficulties in the patient scheduling an office visit. This change was made with the understanding that the lower value of the TOC window would still be greater than 5 half-lives of gatifloxacin, and it was done prior to datalock and unblinding of the study. This expansion did not affect the interpretation of the study results.

Investigators assigned a clinical response to each patient and a bacteriologic response to each pre-treatment pathogen.

Clinical Response

Each patient was assigned a clinical response of Cured, Failure, or Unable to Determine (UTD).

CURED:

All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) have improved or returned to the patient's baseline level with the original therapy alone without need for further antimicrobials; and

No new signs or symptoms of acute infection were present.

(Note: Baseline is defined as the patient's assessment of their typical/usual condition when free of acute infection)

FAILURE:

Signs and symptoms related to the acute infection (cough, dyspnea, sputum production, or sputum purulence) did not improve after 3 days of study therapy; or

New clinical signs and symptoms of acute infection were present; or

If present at study entry, fever persisted (i.e., temperature >38.0°C); or

The patient was removed from the study and placed on alternate antibiotic therapy because of persistent, worsened or new signs and symptoms of acute infection after at least three days of study therapy; or

Clinical/radiological evidence of pneumonia; or

Another antibiotic is required for treatment of this acute episode despite the resolution of signs and symptoms.

UNABLE TO DETERMINE:

No post-treatment evaluation of signs and symptoms was done (i.e., no TOC visit); or

The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the TOC visit.

Bacteriologic Response

Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted or Unable to Determine:

ERADICATED:

The original pathogen was absent from the culture of a good quality sputum specimen (i.e., >25 PMN per LPF) obtained at the TOC visit.

PRESUMED ERADICATED:

No post-treatment culture was performed and the clinical response was Cured;

The patient was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was Cured.

PERSISTED:

The original pathogen was present in the culture of a good quality sputum specimen (i.e., >25 PMN per LPF) obtained at the TOC visit.

PRESUMED PERSISTED:

No post-treatment culture was performed and the clinical response was failure;

The patient was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was Failure.

UNABLE TO DETERMINE:

No post-treatment evaluation was done (i.e., no TOC visit); or

The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the TOC visit; or

The patient did not receive a minimum of three days of therapy; or

The patient's pre-treatment pathogen was resistant to either study treatment; or

The clinical response of the patient in question was designated Unable to Determine.

Relapse

Patients who had a clinical response of Cured at the time of the TOC visit were evaluated for relapse at the extended follow-up assessment (Day +21 to Day +28). Relapse was defined as:

Worsening, or recurrence after initial improvement/resolution, of the signs and symptoms related to the acute infection (cough, dyspnea, sputum production, sputum purulence); or

Appearance of new clinical signs and symptoms of acute respiratory infection without documentation of a new pathogen; or

Persistence, worsening or emergence of new signs and symptoms of acute bronchial infection requiring alternate antibiotic therapy.

Isolation of a new pathogen from a purulent sputum specimen in the presence of signs and symptoms of AECB.

Pathogens isolated from relapsed patients were speciated and tested for susceptibility to gatifloxacin, cefuroxime axetil and other antibiotics as appropriate.

New Infections

A new infection was defined as the occurrence, at any time during or after gatifloxacin therapy, of one of the following:

Isolation of any pathogen from a new site of infection, with associated clinical signs and symptoms;

The presence of clinical signs and symptoms indicative of a new infection for which a culture would not usually be obtained (e.g., skin infection).

Pathogens isolated from patients with new infections were speciated and tested for susceptibility to gatifloxacin, cefuroxime axetil and other antibiotics as appropriate.

Safety Variables and deaths were collected between the first day of study drug treatment and 30 days after the last day of study drug treatment, inclusive.

Adverse Clinical Events

Investigators reported all adverse clinical events to the Sponsor, along with their judgment of the causality. For the purpose of analysis, events that were certainly, probably or possibly drug-related were grouped and categorized as "drug-related". Investigators also assessed the severity (mild, moderate, severe, or very severe) of each adverse clinical event.

Abnormal Laboratory Results

Any worsening in laboratory parameters during or post-treatment was categorized according to a severity grading scale derived from the National Cancer Institute's Common Toxicity Criteria (CTC) or the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) classification of laboratory abnormalities. Four grades of abnormality were defined (Grades 1-4), and the range of laboratory values associated with each grade was established for each test. Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the abnormal values returned to pre-treatment levels or were deemed by the investigator to be unrelated to the study medication.

Reviewer's comments: Clinical, microbiologic and laboratory endpoints were adequately and accurately defined prior to study initiation.

8.2.3.3.3 Statistical Considerations

Data Set Descriptions

There were four study populations of interest:

All Treated Patients: All patients who received at least one dose of study medication.

Eligible Patients: All Treated Patients with a diagnosis of AECB at entry, defined as:

- Having evidence of purulence in an adequate pre-treatment sputum sample (>25 PMN per LPF – the original inclusion criterion required <10 epithelial cells as well, but this criterion was relaxed as previously stated).
- Having two or more of the following signs/symptoms of AECB:
 - increased dyspnea/cough;
 - increased sputum production;
 - increased sputum purulence.
- Having a pre-treatment radiograph that did not show pneumonia.

Clinically Evaluable Patients: All Eligible Patients who:

- Had a duration of dosing of at least five days (at least 3 days for treatment failures);
- Had a post-treatment clinical assessment within the Day +5 to Day +18 window for the TOC visit (except for failures); and
- Did not receive a systemic antibacterial agent between the time of the pre-treatment visit and the post-treatment assessment.

Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had at least one pathogen isolated pre-treatment non-resistant (susceptible and intermediate) pre-treatment to either study drug.

Indication: Acute Exacerbations of Chronic Bronchitis

Reviewer's comments: The 4 datasets are adequate and, except for the Test of Cure window and the relaxation of the sputum criterion, correspond to prospective definitions the sponsor and FDA had agreed upon.

Statistical Analyses

Analyses of the pre-treatment characteristics and study medication usage for All Treated, Eligible and Clinically Evaluable Patients by treatment group, were performed. Prognostic factors were also summarized.

Primary Efficacy Analysis

The primary efficacy assessment was based on the analysis of clinical response in the clinically evaluable subset. Equivalence of gatifloxacin to the control regimen was determined using the 95% confidence interval around the difference in clinical cure rates (gatifloxacin – cefuroxime axetil). The confidence intervals were computed using the DerSimonian and Laird procedure in which smoking status was used as a stratification factor. Gatifloxacin was to be considered equivalent to cefuroxime axetil if the lower confidence limit was greater than or equal to the limit specified in Table 2. Which limit applied depended on the largest observed cure rate of the two treatment arms:

Table 2

Observed Cure Rate	Lower Limit
≥90%	-10%
≥80% to <90%	-15%
<80%	-20%

Reviewer's comments: In line with the recent July 1998 Anti-infective Advisory Committee meeting, the limit of equivalence will be considered independent of the observed response. Since 15% was discussed and agreed upon by the FDA in reference to all recently submitted gatifloxacin protocols, 15% will be used in determining equivalence in this study.

Secondary Efficacy Analysis

Analysis of clinical cure rates was presented by pathogen and by prognostic factors in the Clinically Evaluable Patient subset. Bacteriologic eradication rates as well as cure rates by pathogen were determined for the Microbiologically Evaluable Patients.

Clinical response rates by site were presented for the Clinically Evaluable and Eligible Patients. The clinical cure rates for gatifloxacin and cefuroxime axetil were also compared for both the Eligible and All Treated Patients using the same statistical methods and criteria as in the primary efficacy. Ninety-five percent confidence intervals (CI) were constructed around the clinical cure rates for Eligible and All Treated Patients.

The clinical response rate by prognostic factor, by pre-treatment pathogen, and bacteriologic eradication rate by pre-treatment pathogen were also analyzed for Clinically Evaluable, Eligible and All Treated Patients by treatment and Region of Study. Relapse rates among the cured Clinically Evaluable Patients who had extended follow-up were compared using a Fisher's Exact Test. The incidence of new infections among All Treated Patients was tabulated.

The incidence of persistent pathogens and pathogens isolated from relapsed patients were displayed for Clinically Evaluable Patients, along with the study drugs' susceptibility of those organisms. The incidence of new infections, the pathogens isolated, if any, and the susceptibility of those pathogens to the study drugs were also tabulated for All Treated Patients.

Safety

All patients who received at least one dose of study medication were evaluated for safety. The frequencies of adverse clinical events were summarized by relationship to study drug and displayed by primary term within the relevant body system, as defined in the COSTART adverse clinical events classification system, which was modified by the applicant. Those adverse events that were considered by the investigator to be drug-related (i.e. certainly, probably or possibly drug-related) were also tabulated by severity. Discontinuations due to adverse events were tabulated. All adverse clinical events and all drug-related adverse events were displayed in appendices.

Changes in laboratory test results were tabulated by test. For patients with normal (Grade 0) pre-treatment laboratory test values, the frequencies of Grade 1, 2, 3, and 4 abnormalities during/post-treatment were displayed. For each patient, the most abnormal result for each test was counted. For patients with abnormal (Grades 1, 2, or 3) pre-treatment laboratory test values, the frequencies of worsening to Grade 2, 3, or 4 abnormalities during/post-treatment were displayed. For each patient, the worst grade change for each test was counted.

8.2.3.4 Results

8.2.3.4.1 Populations

This trial was conducted in the Northern and Southern Hemispheres to maximize enrollment during their respiratory infections seasons. The first patient was enrolled on August 29, 1997 and the last patient on May 11, 1998. The last visit by a patient was June 23, 1998. A total of 340 patients were enrolled in the study; all but one received at least one dose of study medication. Two hundred twelve (62%) patients were randomized at sites in North America (165 patients in the U.S. and 47 in Canada). Argentina contributed 77 patients (23%) while South Africa enrolled 24 and Mexico enrolled 23. The highest enrolling investigator entered 46 patients, 14% of the total enrollment.

Significant protocol violations were defined as those that prevented a patient from being clinically evaluable. Fifty-one protocol violations occurred (Table 3). Protocol violations are similar between the gatifloxacin and cefuroxime axetil treatment groups.

Table 3 Significant Protocol Violations, All Enrolled Patients

Violation	Number of Patients					
	Gatifloxacin N = 169		Cefuroxime Axetil N = 171		Total N = 340	
No purulent sputum pre-treatment	11	(7)	13	(8)	24	(7)
X-ray evidence of pneumonia pre-treatment	1	(<1)	1	(<1)	2	(<1)
Pre-treatment procedure outside 48 hour window	1	(<1)	1	(<1)	2	(<1)
Pre-treatment procedure not done	-		1	(<1)	1	(<1)
Does not have infection under study	-		1	(<1)	1	(<1)
No Test of Cure visit	5	(3)	9	(5)	14	(4)
Other antibiotic given	2	(1)	3	(1)	5	(1)
Insufficient therapy	-		1	(<1)	1	(<1)
Did not receive study medication	-		1	(<1)	1	(<1)
Total	20		31		51	

No interim analyses were conducted during the study. There was one instance of unblinding in a patient taking cefuroxime axetil who presented to an emergency room with apnea and was ultimately diagnosed with alcohol intoxication.

Three hundred and nine patients were Eligible and 284 patients were Clinically Evaluable. Excluding Puerto Rico, the rates of eligibility were fairly similar across countries, ranging from a low of 85% in the U.S. to 100 % in South Africa and Mexico. One hundred and thirty patients were Clinically and Microbiologically Evaluable. Of the 340 patients enrolled, 339 received at least one dose of study medication; of these 169 received gatifloxacin and 170 received cefuroxime axetil (Table 4). Thirty (9%) of the All Treated Patients were ineligible, 13 in the gatifloxacin group and 17 in the cefuroxime group.

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Table 4 Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients

Study Population/Reason Excluded	Number of Patients (%)					
	Gatifloxacin		Cefuroxime Axetil		Total	
All Treated	169		170		339	
Untreated	-		1	(<1)	1	(<1)
Antibiotic received within 7 day pre-treatment window			1	(<1)	1	(<1)
Eligible	156	(92)	153	(90)	309	(91)
Ineligible	13	(8)	17	(10)	30	(9)
<u>Reason Ineligible:</u>						
Did Not Have Diagnosis of Chronic Bronchitis	-		1	(<1)	1	(<1)
No Pre-treatment Purulent Sputum Specimen	11	(7)	13	(8)	24	(7)
Evidence of Pneumonia on Pre-treatment X-ray	1	(<1)	1	(<1)	2	(<1)
Other	1	(<1))	2	(1)	3	(<1)
Clinically Evaluable	145	(86)	139	(82)	284	(84)
Unevaluable^a	24	(14)	31	(18)	55	(16)
<u>Reason Unevaluable:</u>						
Ineligible	13	(8)	17	(10)	30	(9)
No Post-treatment Evaluation	7	(4)	10	(6)	17	(5)
Insufficient Therapy	2	(1)	1	(<1)	3	(<1)
Other Antibiotic Received	1	(<1)	2	(1)	3	(<1)
Other	1	(<1)	1	(<1)	2	(<1)
Microbiologically Evaluable	70	(41)	60	(35)	130	(38)
Unevaluable	99	(59)	110	(65)	209	(62)
<u>Reason Unevaluable:</u>						
No Pre-treatment Pathogen	78	(46)	92	(54)	170	(50)
Clinically Unevaluable	14	(8)	12	(7)	26	(8)
Resistant Pathogen ^b	7	(4)	6	(4)	13	(4)

^a Patients may be unevaluable for more than one reason but each patient is counted based on their primary reason unevaluable.

^b Not all patients with resistant pathogens are displayed here because of mutually exclusive categories.

Reviewer's comments: Patients were well balanced between the 2 groups in terms of eligibility, clinical evaluability and microbiological evaluability. They were also well balanced in terms of the reasons for ineligibility and unevaluability. Reviewer

agrees with applicant regarding the ineligibility of 30 patients whose sputum was not purulent (24 patients), who had evidence of pneumonia on the chest X-ray (2 patients) or were not assessed adequately (4 patients). These facts were well documented on the case report forms and the databases. Reviewer also agrees regarding the unevaluability of 55 patients via the case report forms and the databases.

Data Sets

The safety data set consisted of All Treated Patients.

The primary data set for analysis of clinical efficacy consisted of the Clinically Evaluable Patients; the primary data set for analysis of bacteriologic efficacy consisted of the Microbiologically Evaluable Patients. The Eligible and All Treated Patients formed secondary efficacy data sets.

Demography and Patient Characteristics

The two treatment groups were comparable with respect to demographic characteristics. Of the 339 patients treated 55% were male and the majority were white (61%) with similar representation from Black and Hispanic populations in the two treatment groups (Table 5).

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Table 5 Demography, All Treated Patients

Characteristic	Gatifloxacin N = 169		Cefuroxime Axetil N = 170		Total N = 339	
Gender [N (%)]						
Male	94	(56)	92	(54)	186	(55)
Female	75	(44)	78	(46)	153	(45)
Race: [N(%)]						
White	103	(61)	105	(62)	208	(61)
Black	26	(15)	26	(15)	52	(15)
Hispanic	33	(20)	32	(19)	65	(19)
Asian	6	(4)	6	(4)	12	(4)
Other	1	(<1)	1	(<1)	2	(<1)
Age (years):						
Mean	55		55		55	
Median	56.0		55.0		55.0	
Min - Max	19 - 87		20 - 90		19 - 90	
Weight (kg)						
Mean	75.2		74.2		74.7	
Median	72.6		74.8		73.0	
Min - Max	42.0-135.5		34.0-136.1		34.0-136.1	
Not Recorded	-		2		2	

Reviewer's comments: Reviewer agrees that patients were well balanced between the 2 groups with respect to age, race, gender and weight.

Medical History and Presenting Conditions

Among All Treated Patients, the two treatment arms were comparable with respect to medical history. A wide variety of medical conditions were recorded with frequencies generally similar between the two groups. All but one patient had chronic bronchitis as defined previously. One patient randomized to the cefuroxime group had chronic bronchitis for one year. Other than respiratory, cardiovascular conditions were the next most commonly reported (37% in the gatifloxacin group, 40% in the cefuroxime group). Seventeen patients (9 gatifloxacin, 8 cefuroxime) had a history of neoplasia but none involved the respiratory system. None of the 7 patients with tuberculosis was considered to have active disease.

Reviewer's comments: The representation of different medical conditions was adequate, well balanced between the 2 groups, and reflected the picture encountered in clinical practice.

Microbiologic Documentation

A total of 206 pathogens were isolated from 169 (50%) patients in the All Treated group, 91 (54%) patients in the gatifloxacin group and 78 (46%) in the cefuroxime group. There were 113 isolates from the gatifloxacin group and 93 in the cefuroxime group. The types and frequencies of pathogens isolated were comparable between the treatment groups with 2 exceptions. *M. catarrhalis* was isolated more frequently from patients in the gatifloxacin group (25 vs. 12 patients) while *H. influenzae* occurred more frequently in the cefuroxime group (22 vs. 26 patients). *S. pneumoniae* was recovered in comparable frequency across treatment groups. Penicillin-resistant pneumococcus was recovered from one patient in each treatment group. Other frequently isolated respiratory organisms included *S. aureus* (28 pathogens) and *H. parainfluenzae* (22 pathogens). Of the 206 total pathogens isolated from All Treated Patients, none was resistant to gatifloxacin. Two pre-treatment pathogens, both *P. aeruginosa* and isolated from 2 gatifloxacin-treated patients had intermediate susceptibility to gatifloxacin.

Reviewer's comments: The 3 major pathogens usually involved in AECB (H. influenzae, S. pneumoniae and M. catarrhalis) are well represented in the study. There was also a good proportion of patients with H. parainfluenzae and S. aureus to allow for assessment of efficacy against those organisms.

Prognostic Factors, All Treated Patients

Most (86%) patients had Type I exacerbation; the remainder had Type II. In each treatment group, the median duration of the current episode of exacerbation prior to enrollment was eight days. Thirty-three patients (18 gatifloxacin, 15 cefuroxime) received pre-treatment systemic corticosteroids. Fifty percent of the patients were smokers or had stopped smoking within the two months before enrollment, and 84% had a history of smoking. For the majority of patients on systemic corticosteroids, these were prescribed for COPD/emphysema and/or asthma.

Reviewer's comments: The two groups were generally similar in terms of exacerbation type, smoking history, current smoking status, duration of current episode of AECB, and pre-treatment systemic corticosteroid use.

Study Therapy

Most patients received 7 (13%) or 10 (79%) days of study medication. Ten patients (7 gatifloxacin-treated, 3 cefuroxime-treated) received less than 7 days of study therapy. Eight patients discontinued treatment prematurely, 6 on the gatifloxacin arm and 2 on cefuroxime. The most frequent cause of discontinuation in both groups was adverse clinical events (4 gatifloxacin, 1 cefuroxime).

Concomitant Therapy

Nine (3%) patients used antimicrobials concomitantly, 4 in the gatifloxacin treatment group and 5 in the cefuroxime-treated group. With the exception of a gatifloxacin-treated patient who received one dose of cefuroxime, none of the patients was discontinued from study medication.

Post-treatment Therapy

Overall, post-treatment antimicrobial agents were received by 55 (16%) of All Treated Patients, 23 (14%) gatifloxacin, 32 (19%) cefuroxime. The most commonly used agents were systemic antibacterial medications: 22 (13%) gatifloxacin patients and 29 (17%) cefuroxime patients.

The 54 patients who received systemic antimicrobial agents post-treatment (23 gatifloxacin patients, 31 cefuroxime patients) fell into five main groups: Treatment failures who received an alternate antibiotic for AECB: 14 gatifloxacin patients, 22 cefuroxime patients;

Patients who were treated for new infections: 5 gatifloxacin, 5 cefuroxime patients;

Patients who discontinued study therapy prematurely due to an adverse event and received an alternate antibiotic for AECB: 2 gatifloxacin patients, 1 cefuroxime patients;

Patients who were cured at the TOC visit and relapsed: 2 gatifloxacin patients, no cefuroxime patients;

Patients who received a systemic antimicrobial agent for prophylaxis: no gatifloxacin, 3 cefuroxime patients (1 patient each for tuberculosis, epistaxis and a puncture wound).

8.2.3.4.2 Efficacy Results

Reviewer's comments:

1) Although patients were randomized according to smoking status, confidence intervals were constructed only for the group as a whole.

2) The primary efficacy analysis was not done on an intent-to-treat basis; patients who discontinued study drug before receiving 5 days of therapy because of adverse events or worsening of their condition were not considered evaluable and thus were not included in the primary efficacy analysis. The intent-to-treat population would be more closely represented by the All Treated or the Eligible subsets. Analyses of all subsets will be considered by the FDA.

3) The applicant's definition of cure included those patients whose symptoms improved as well as those whose symptoms returned to baseline. This definition without a grading system for improvement and a separate analysis for this subset of patients makes the interpretation of the trial's data difficult. For this reason a separate analysis was done that considered as cured only those patients whose 3 cardinal symptoms of cough, dyspnea and sputum production either returned to baseline at the TOC visit, or were only improved at the TOC visit but returned to baseline at the extended follow-up visit. Thus, 36 patients in gatifloxacin group (11 smokers, 25 non-smokers) and 33 patients in

cefuroxime axetil group (16 smokers and 17 non-smokers) were considered as failures. This was referred to as "reviewer's analysis #1".

4) Another separate analysis was done that considered ineligible those patients whose sputum contained >10 epithelial cells/LPF, since relaxation of this criterion was done at the end of the study. There were 16 such patients (13 of whom were evaluable) in gatifloxacin group (8 smokers, 8 non-smokers) and 13 patients (12 of whom were evaluable) in cefuroxime axetil group (9 smokers, 4 non-smokers). This was referred to as "reviewer's analysis #2".

5) A third analysis was done that took into account both above issues. This was referred to as "reviewer's analysis #3".

Clinically Evaluable Patients

Clinical cure rates for the two treatment groups were equivalent per the applicant's analysis (gatifloxacin = 86%, cefuroxime = 83%); 95% CI (-4.8%, 11.4%) (Table 6).

Table 6 Clinical Response, Clinically Evaluable Patients

	Gatifloxacin		Cefuroxime Axetil		Total		CI ^a
Clinical Response	Number of Patients (%)						
Applicant's Analysis							
	N = 145		N = 139		N = 284		
Cure	124	(86)	115	(83)	239	(84)	-4.8%, 11.4%
Failure	21	(14)	24	(17)	45	(16)	
Reviewer's Analysis #1							
	N = 145		N = 139		N = 284		
Cure	88	(61)	82	(59)	170	(60)	-19.24%, 23.28%
Failure	57	(39)	57	(61)	114	(40)	
Reviewer's Analysis #2							
	N = 132		N = 127		N = 259		
Cure	112	(85)	104	(82)	216	(84)	-5.61%, 11.75%
Failure	20	(15)	23	(18)	43	(16)	
Reviewer's Analysis #3							
	N = 132		N = 127		N = 259		
Cure	76	(58)	73	(58)	151	(58)	-24.91%, 24.87%
Failure	56	(42)	54	(42)	108	(42)	

^a 95% Confidence Interval for the difference in Cure Rate

Reviewer's comments: Cure rates were equal or slightly higher for gatifloxacin. The 95% CI for the difference in cure rates were narrow but widened when patients who were improved were considered as failures, and the lower limit exceeded -15%.

Clinical Response by Duration of Therapy

Results were comparable in patients who received 7 or 10 days of therapy. In both durations the cure rate in the gatifloxacin group was higher than that achieved with cefuroxime (Table 7).

Table 7 Clinical Cure Rate by Duration of Therapy, Clinically Evaluable Patients

Duration	Number Cured/Number of Patients (%)					
	Gatifloxacin N = 145		Cefuroxime Axetil N = 139		Total N = 284	
7 days	22/23	(96)	18/20	(90)	40/43	(93)
10 days	100/117	(85)	92/111	(83)	192/228	(84)

Clinical Response by Prognostic Factor

The clinical response rate for Clinically Evaluable Patients was generally similar across the categories of prognostic relevance and between the two treatment groups within each subset (Table 8); no difference was noted for type of exacerbation, duration of the current episode of AECB, systemic corticosteroid use, current smoking status, or smoking history. Of note, individuals who never smoked or had quit smoking had lower cure rates than patients continuing to smoke.

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Table 8 Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients

Prognostic Factor/ Subcategory	Number Cured/Number of Patients (%)		
	Gatifloxacin N = 145	Cefuroxime Axetil N = 139	Total N = 284
<u>Exacerbation Type</u>			
Type I	108/125 (86)	97/120 (81)	205/245 (84)
Type II	16/20 (80)	18/19 (95)	34/39 (87)
<u>Duration of Current Episode^a</u>			
≤7 Days	58/67 (87)	53/65 (82)	111/132 (84)
>7 Days	63/74 (85)	59/70 (84)	122/144 (85)
Not recorded	3/4 (75)	3/4 (75)	6/8 (75)
<u>Pre-treatment Systemic Corticosteroid Use</u>			
Yes	14/17 (82)	13/15 (87)	27/32 (84)
No	110/128 (86)	102/124 (82)	212/252 (84)
<u>Current Smoking Status</u>			
Smoker	66/72 (92)	60/69 (87)	126/141 (89)
Non-Smoker	58/73 (79)	55/70 (79)	113/143 (79)
<u>History of Smoking</u>			
Yes	103/118 (87)	101/122 (83)	204/240 (85)
No	21/27 (78)	14/17 (82)	35/44 (80)

^a Duration data missing for 4 (3 cured) gatifloxacin and 4 (3 cured) cefuroxime patients.

Reviewer's Comments: There was a higher response rate seen in current smokers compared to non-smokers. A separate analysis that examined the difference in cure rates between the 2 drugs according to current smoking status is presented below (Table 9). It shows that gatifloxacin had a higher cure rate in current smokers, while cefuroxime had an equal or higher cure rate in non-smokers. Since this could be due to a potential imbalance in other patient characteristics, a closer look at the distribution of smokers and non-smokers with respect to age, race, gender, history of asthma, use of other drugs concomitantly (corticosteroids, Beta adrenergics and anticholinergics) and the presence of one of the 5 major pathogens isolated, was performed retrospectively by the applicant at the reviewer's request and identified a number of differences between the 2 subsets. The most notable differences were in race (72% of non-smokers being white vs. 52% for smokers), age (mean age of 62 for non-smokers vs. 47 years for smokers), and concomitant use of respiratory drugs (72% for non-smokers vs. 36% for smokers). Logistic regression analyses on the clinical response were also performed retrospectively by the applicant for current smoking status and history of smoking using the following covariates: age, race, gender, history of asthma, use of other drugs concomitantly and

the presence of one of the 5 major pathogens isolated. Various adjustments for these characteristics minimized the impact of smoking in most analyses which eases the concerns raised by the low cure rates seen in non-smokers in reviewer's analyses #1 and #3 (table 9). Age and the presence of a major pathogen were the only independent prognostic variables identified, with those younger than 65 and those without a major pathogen isolated having higher cure rates.

Table 9 Clinical Response by Smoking Status, Clinically Evaluable Patients

	Gatifloxacin		Cefuroxime		Total		CI ^a
Clinical Response	Number of Patients (%)						
Applicant's Analysis							
	N = 145		N = 139		N = 284		S(-8.7%,19.0%)
	S=72	NS=73	S=69	NS=70	S=141	NS=143	
Cure	66 (92)	58 (80)	60 (87)	55 (79)	126	113	NS(-14.6%,17.2%)
Failure	6	15	9	15	15	30	
Reviewer's Analysis #1^b							
	N = 145		N = 139		N = 284		S(-3.9%,29.6%)
	S=72	NS=73	S=69	NS=70	S=141	NS=143	
Cure	55 (76)	33 (45)	44 (64)	38 (54)	99	71	NS(-26.8%,7.7%)
Failure	17	40	25	32	42	72	
Reviewer's Analysis #2^b							
	N = 132		N = 127		N = 259		S(-9.9%,20.2%)
	S=66	NS=66	S=60	NS=67	S=126	NS=133	
Cure	60 (91)	52 (79)	52 (87)	52 (78)	112	104	NS(-14.3%,19.1%)
Failure	6	14	8	15	14	29	
Reviewer's Analysis #3^b							
	N = 132		N = 127		N = 259		S(-4.8%,31.0%)
	S=66	NS=66	S=60	NS=67	S=126	NS=133	
Cure	49 (74)	27 (41)	37 (62)	36 (54)	86	63	NS(-31.2%,4.6%)
Failure	17	39	23	31	40	70	

^a 95% Confidence Interval for the difference in Cure Rates by smoking status (S= Current smokers; NS= Non-smokers)

^b For the description of the reviewer's analyses, refer to section 8.2.3.4.2 (Efficacy Results)

Clinical Cure Rates by Pathogen

The cure rate for patients with a pathogen was 83% for gatifloxacin patients and 80% for cefuroxime-treated patients (95% CI: -9.4%, 16.3%). The overall Cure rate for all pathogens was 78% (132/169) with equal frequency (78%) in both treatment groups (Table 10). Among Clinically Evaluable Patients, the cure rate for patients without a pre-treatment pathogen was higher compared to those with a pre-treatment pathogen. For *S. pneumoniae*, the cure rate was higher for gatifloxacin-treated patients than cefuroxime-treated patients (100% vs 50%). The cure rate was unexpectedly low for *M. catarrhalis* in patients receiving gatifloxacin.

Table 10 Clinical Cure Rates by Pathogen, Clinically Evaluable Patients

Pathogen ^a /Subtype	Number Cured/Number Isolated (%)					
	Gatifloxacin		Cefuroxime Axetil		Total	
Total Patients with Pathogen^b	62/75	(83)	51/64	(80)	113/139	(81)
Total pathogens	73/93	(78)	59/76	(78)	132/169	(78)
<i>H. influenzae</i>	16/20	(80)	19/24	(79)	35/44	(80)
β-Lactamase -	13/17	(76)	11/13	(85)	24/30	(80)
β-Lactamase +	3/3	(100)	8/11	(73)	11/14	(79)
<i>M. catarrhalis</i>	15/23	(65)	8/9	(89)	23/32	(72)
β-Lactamase -	4/6	(67)	-		4/6	(67)
β-Lactamase +	11/17	(65)	7/8	(88)	18/25	(72)
β-Lactamase Unknown	-		1/1	(100)	1/1	(100)
<i>H. parainfluenzae</i>	5/7	(71)	5/7	(71)	10/14	(71)
β-Lactamase -	3/5	(60)	5/6	(83)	8/11	(73)
β-Lactamase +	1/1	(100)	-		1/1	(100)
β-Lactamase Unknown	1/1	(100)	0/1		1/2	(50)
<i>S. pneumoniae</i>	10/10	(100)	5/10	(50)	15/20	(75)
Penicillin Sensitive	7/7	(100)	3/6	(50)	10/13	(77)
Penicillin Intermediate	2/2	(100)	1/3	(33)	3/5	(60)
Penicillin Resistant	1/1	(100)	1/1	(100)	2/2	(100)
<i>S. aureus</i>	10/10	(100)	12/13	(92)	22/23	(96)
<i>K. pneumoniae</i>	1/1	(100)	3/3	(100)	4/4	(100)
<i>P. aeruginosa</i>	3/6	(50)	1/1	(100)	4/7	(57)
<i>E. cloacae</i>	0/1		0/1		0/2	-
<i>E. coli</i>	-		1/1	(100)	1/1	(100)
Other Gram-negative^c	4/6	(67)	3/3	(100)	7/9	(78)
Other Gram-positive^d	9/9	(100)	2/4	(50)	11/13	(85)

^a A patient may have had more than one organism isolated pre-treatment.

^b Total patients with pathogen; 95% CI (-9.4%, 16.3%).

^c Consisted of 9 different organisms.

^d Consisted of 5 different organisms.

Reviewer's comments: Reviewer agrees with the data presented in this table via the databases. The 95% CI for the difference in cure rates of those patients with a pathogen was acceptable (-9.4%, 16.3%).

Relapses, Clinically Evaluable Patients

Of the 237 Clinically Evaluable Patients who were evaluated as Cured at the TOC visit and had an extended follow-up assessment, 5 had relapses and all were gatifloxacin-treated patients ($p=0.061$). Only two of these five required treatment with antibiotics. Between the two treatment groups the sustained cure rate was comparable, 96% in gatifloxacin-treated patients and 100% in cefuroxime-treated patients.

Reviewer's comments: The reviewer's analysis shows that there were 1 and 2 relapses in gatifloxacin and cefuroxime groups, respectively.

Microbiologically Evaluable Patients

Clinical Cure Rates by Pathogen

The cure rate for Microbiologically Evaluable Patients was 81% for those patients treated with gatifloxacin and 80% for cefuroxime-treated patients (95% CI: -11.3%, 15.6%) (Table 11). The clinical cure rate by pathogen was higher for gatifloxacin than cefuroxime (81% vs. 77%) in Microbiologically Evaluable Patients. The cure rate for *S. pneumoniae* isolated from gatifloxacin patients was more than twice the rate for cefuroxime patients (100% vs. 44%).

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Table 11 Clinical Cure Rates Response by Pathogen, Microbiologically Evaluable Patients

Pathogen ^a	Number Cured/Number Isolated (%)		
	Gatifloxacin	Cefuroxime Axetil	Total
Total Patients with Pathogen^b	57/70 (81)	48/60 (80)	105/130 (81)
Total Pathogens	68/84 (81)	54/70 (77)	122/154 (79)
<i>H. influenzae</i>	16/20 (80)	19/23 (83)	35/43 (81)
β-Lactamase +	3/3 (100)	8/10 (80)	11/13 (85)
β-Lactamase -	13/17 (76)	11/13 (85)	24/30 (80)
<i>M. catarrhalis</i>	15/23 (65)	8/9 (89)	23/32 (72)
β-Lactamase +	11/17 (65)	7/8 (88)	18/25 (72)
β-Lactamase -	4/6 (67)	-	4/6 (67)
β-Lactamase Unknown	-	1/1 (100)	1/1 (100)
<i>H. parainfluenzae</i>	5/7 (71)	5/7 (71)	10/14 (71)
β-Lactamase +	1/1 (100)	-	1/1 (100)
β-Lactamase -	3/5 (60)	5/6 (83)	8/11 (73)
β-Lactamase unknown	1/1 (100)	0/1	1/2 (50)
<i>S. pneumoniae</i>	9/9 (100)	4/9 (44)	13/18 (72)
Penicillin Susceptible	7/7 (100)	3/6 (50)	10/13 (77)
Penicillin Intermediate	2/2 (100)	1/3 (33)	3/5 (60)
<i>S. aureus</i>	8/8 (100)	11/12 (92)	19/20 (95)
<i>K. pneumoniae</i>	1/1 (100)	3/3 (100)	4/4 (100)
<i>P. aeruginosa</i>	2/2 (100)	-	2/2 (100)
<i>E. cloacae</i>	0/1	0/1	0/2
Other Gram-negative ^c	3/4 (75)	2/2 (100)	5/6 (83)
Other Gram-positive ^d	9/9 (100)	2/4 (50)	11/13 (85)

^a A patient may have more than one pathogen isolated pre-treatment.

^b Total patients with pathogen; 95% CI (-11.3%, 15.6%).

^c Consisted of 6 different organisms.

^d Consisted of 5 different organisms.

Reviewer's comments: There were adequate numbers of patients harboring H. influenzae, M. catarrhalis, S. pneumoniae, H. parainfluenzae or S. aureus for assessment of efficacy, although M. catarrhalis was overrepresented in gatifloxacin group. These data show effectiveness of gatifloxacin against these organisms, even after a separate analysis was done excluding patients with >10 epithelial cells/LPF and adjusting for the definition of cure. There were insufficient data to show effectiveness against penicillin-

intermediate S. pneumoniae. A review of patients with the latter organism reveals that neither of the 2 gatifloxacin patients or the levofloxacin patient who harbored it and were clinically cured had a sputum culture done post-treatment, i.e. they were all in the presumed eradicated category.

Bacteriologic Response

In general, the eradication rate was higher for pathogens isolated from gatifloxacin-treated patients than for pathogens isolated from cefuroxime-treated patients, 87% vs. 77%, respectively (Table 12). In particular, the eradication rate for *S. pneumoniae* was 100% in gatifloxacin-treated patients and 56% in cefuroxime-treated patients, while the eradication rate for *H. influenzae* was 85% in gatifloxacin patients and 74% in cefuroxime patients.

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Table 12 Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients

Pathogen ^a	Number Eradicated/Number Isolated (%)			
	Gatifloxacin	Cefuroxime Axetil	Total	
Total	73/84 (87)	54/70 (77)	127/154 (82)	
<i>H. influenzae</i>	17/20 (85)	17/23 (74)	34/43 (79)	
β-Lactamase +	3/3 (100)	7/10 (70)	10/13 (77)	
β-Lactamase -	14/17 (82)	10/13 (77)	24/30 (80)	
<i>M. catarrhalis</i>	19/23 (83)	8/9 (89)	27/32 (84)	
β-Lactamase +	13/17 (76)	7/8 (88)	20/25 (80)	
β-Lactamase -	6/6 (100)	-	6/6 (100)	
β-Lactamase Unknown	-	1/1 (100)	1/1 (100)	
<i>H. parainfluenzae</i>	5/7 (71)	5/7 (71)	10/14 (71)	
β-Lactamase +	1/1 (100)	-	1/1 (100)	
β-Lactamase -	3/5 (60)	5/6 (83)	8/11 (73)	
β-Lactamase unknown	1/1 (100)	0/1	1/2 (50)	
<i>S. pneumoniae</i>	9/9 (100)	5/9 (56)	14/18 (78)	
Penicillin Susceptible	7/7 (100)	3/6 (50)	10/13 (77)	
Penicillin Intermediate	2/2 (100)	2/3 (67)	4/5 (80)	
<i>S. aureus</i>	8/8 (100)	11/12 (92)	19/20 (95)	
<i>K. pneumoniae</i>	1/1 (100)	3/3 (100)	4/4 (100)	
<i>P. aeruginosa</i>	2/2 (100)	-	2/2 (100)	
<i>E. cloacae</i>	0/1	1/1 (100)	1/2 (50)	
Other Gram-negative ^b	3/4 (75)	2/2 (100)	5/6 (83)	
Other Gram-positive ^c	9/9 (100)	2/4 (50)	11/13 (85)	

a A patient may have more than one pathogen isolated pre-treatment.

b Consisted of 6 different organisms.

c Consisted of 5 different organisms.

Table 13: Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients (Reviewer's analysis)

Pathogen	Number Eradicated/Number Isolated (%)			
	Gatifloxacin		Cefuroxime Axetil	
<i>H. influenzae</i>	12/20	(60)	10/22	(45)
<i>M. catarrhalis</i>	14/23	(61)	5/9	(56)
<i>H. parainfluenzae</i>	4/6	(67)	3/5	(60)
<i>S. pneumoniae</i>	6/8	(75)	5/9	(56)
<i>S. aureus</i>	5/6	(84)	7/9	(78)

*Reviewer's comments: The applicant's data above (Table 12) and the reviewer's analysis of the data (Table 13) show efficacy over the 5 most frequently isolated pathogens. The reviewer's analysis excluded patients with >10 epithelial cells/LPF as ineligible, and for those patients whose outcome was changed from cure to failure (see above "Efficacy Results"), a bacteriologic outcome of "presumed eradicated" was changed to "presumed persisted". Table 13 shows superiority of gatifloxacin in eradicating the 5 major pathogens. Both cured patients in gatifloxacin group and one cured patient in levofloxacin group with penicillin intermediate *S. pneumoniae* were in the presumed eradicated category. Since the role of *S. aureus* in AECB is not entirely clear, a closer look at patients with this organism in the gatifloxacin group showed that only 7 patients had a pure growth of *S. aureus*, all of which had a presumed bacteriological eradication.*

Eligible Patients

Clinical Efficacy

Among the Eligible Patients, the overall clinical Cure rate was 80% per the applicant's analysis, and for the two treatment groups, the clinical Cure rates were equivalent (gatifloxacin = 81%, cefuroxime = 79%; 95% CI, -6.9%, 10.6%) (Table 14).

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Table 14 Clinical Response, Eligible Patients

	Gatifloxacin		Cefuroxime Axetil		Total		CI ^a
Clinical Response	Number of Patients (%)						
Applicant's Analysis							
	N = 156		N = 153		N = 309		-6.9%, 10.6%
Cure	126	(81)	121	(79)	247	(80)	
Failure	21	(13)	25	(16)	46	(15)	
Unable to Determine	9	(6)	7	(5)	16	(5)	
Reviewer's Analysis #1^b							
	N = 156		N = 153		N = 309		-18.89%, 19.54%
Cure	90	(58)	88	(58)	247	(80)	
Failure	57	(36)	58	(37)	46	(15)	
Unable to Determine	9	(6)	7	(5)	16	(5)	
Reviewer's Analysis #2^b							
	N = 140		N = 140		N = 280		-5.54%, 12.87%
Cure	114	(81)	109	(78)	223	(80)	
Failure	20	(14)	24	(17)	44	(15)	
Unable to Determine	6	(5)	7	(5)	13	(5)	
Reviewer's Analysis #3^b							
	N = 140		N = 140		N = 280		-23.4%, 23.21%
Cure	78	(55)	78	(55)	156	(55)	
Failure	56	(40)	55	(40)	111	(40)	
Unable to Determine	6	(5)	7	(5)	13	(5)	

^a 95% Confidence Interval for the difference in Cure Rate

^b For the description of the reviewer's analyses, refer to section 8.2.3.4.2 (Efficacy Results)

Reviewer's comments: Cure rates of gatifloxacin were equal to or higher than those of cefuroxime among the clinically eligible patients in the 4 analyses, with a wide confidence interval when the improved patients were considered as failures. A separate analysis that examined the difference in cure rates between the 2 drugs according to smoking status is shown below (Table 15). Again it shows that gatifloxacin had a higher cure rate in current smokers, while cefuroxime had an equal or higher cure rate in non-smokers.

Table 15 Clinical Response by smoking status, Eligible Patients

	Gatifloxacin		Cefuroxime		Total		CI ^a
Clinical Response	Number of Patients (%)						
Applicant's Analysis							
	N = 156		N = 153		N = 309		S(-11.5%,17.6%)
	S=78	NS=78	S=76	NS=77	S=154	NS=155	
Cure	67 (86)	59 (76)	63 (83)	58 (75)	130	117	NS(-15.2%,16.1%)
Failure	6	15	9	16	15	31	
UTD	5	4	4	3	9	7	
Reviewer's Analysis #1^b							
	N = 156		N = 153		N = 309		S(-6.2%,26.3%)
	S=78	NS=78	S=76	NS=77	S=154	NS=155	
Cure	56 (72)	34 (44)	47 (62)	41 (53)	103	75	NS(-26.7%,6.6%)
Failure	17	40	25	33	42	73	
UTD	5	4	4	3	9	7	
Reviewer's Analysis #2^b							
	N = 140		N = 140		N = 280		S(-9.8%,20.8%)
	S=70	NS=70	S=67	NS=73	S=137	NS=143	
Cure	61 (87)	53 (76)	55 (82)	54 (74)	116	107	NS(-13.9%,19.0%)
Failure	6	14	8	16	14	30	
UTD	3	3	4	3	7	6	
Reviewer's Analysis #3^b							
	N = 140		N = 140		N = 280		S(-5.3%,29.2%)
	S=70	NS=70	S=67	NS=73	S=137	NS=143	
Cure	50 (71)	28 (40)	40 (60)	38 (52)	90	66	NS(-29.7%,4.6%)
Failure	17	39	23	32	40	71	
UTD	3	3	4	3	7	6	

^a 95% Confidence Interval for the difference in Cure Rates by smoking status (S= Current smokers; NS= Non-smokers)

^b For the description of the reviewer's analyses, refer to section 8.2.3.4.2 (Efficacy Results)

Bacteriologic Efficacy

For Eligible Patients, the bacteriologic eradication rate by pathogen was 70% but was greater for pathogens isolated from gatifloxacin-treated patients than for isolates from cefuroxime-treated patients, 74% vs. 66% (Table 16). The eradication rates were similar to those achieved in the evaluable population. The differences in eradication rates of *S. pneumoniae* between gatifloxacin and cefuroxime were again present.

Table 16 Bacteriologic Eradication Rates by Pathogen, Clinically Eligible Patients

Pathogen ^a	Number Eradicated/Number Isolated (%)				
	Gatifloxacin		Cefuroxime Axetil		Total
Total	75/102	(74)	55/83	(66)	130/185 (70)
<i>H. influenzae</i>	17/20	(85)	17/25	(68)	34/45 (76)
β-Lactamase +	3/3	(100)	7/11	(64)	10/14 (71)
β-Lactamase -	14/17	(82)	10/14	(71)	24/31 (77)
<i>M. catarrhalis</i>	19/25	(76)	9/12	(75)	28/37 (76)
β-Lactamase +	13/19	(68)	8/11	(73)	21/30 (70)
β-Lactamase -	6/6	(100)	-		6/6 (100)
β-Lactamase unknown	-		1/1	(100)	1/1 (100)
<i>H. parainfluenzae</i>	5/9	(56)	5/7	(71)	10/16 (63)
β-Lactamase +	1/1	(100)	-		1/1 (100)
β-Lactamase -	3/7	(43)	5/6	(83)	8/13 (62)
β-Lactamase unknown	1/1	(100)	0/1		1/2 (50)
<i>S. pneumoniae</i>	9/11	(82)	5/10	(50)	14/21 (67)
Penicillin Susceptible	7/7	(100)	3/6	(50)	10/13 (77)
Penicillin Intermediate	2/2	(100)	2/3	(67)	4/5 (80)
Penicillin Resistant	0/1		0/1		0/2
Penicillin unknown	0/1		-		0/1
<i>S. aureus</i>	8/10	(80)	11/13	(85)	19/23 (83)
<i>K. pneumoniae</i>	1/2	(50)	3/3	(100)	4/5 (80)
<i>P. aeruginosa</i>	2/7	(29)	0/3		2/10 (20)
<i>E. cloacae</i>	0/1		1/1	(100)	1/2 (50)
<i>E. coli</i>	1/1	(100)	0/1		1/2 (50)
Other Gram-negative ^b	4/7	(57)	2/3	(67)	6/10 (60)
Other Gram-positive ^c	9/9	(100)	2/5	(40)	11/14 (79)

^a A patient may have more than one pathogen isolated pre-treatment.

^b Consisted of 10 different organisms.

^c Consisted of 5 different organisms.

Reviewer's comments: Reviewer agrees with the data presented in this table via the databases.

All Treated Patients

Clinical response

Clinical responses were lower in the All Treated Patients compared to the clinically evaluable patients (Table 17).

Table 17 Clinical Response, All Treated Patients

	Number of Patients (%)		
	Gatifloxacin N=169	Cefuroxime Axetil N=170	Total N=339
Cure	136 (80)	133 (78)	269 (79)
Failure	22 (13)	29 (17)	51 (15)
UTD	11 (7)	8 (5)	19 (6)

95% Confidence Interval for difference in cure rate: (-6.3%, 10.7%)

Reviewer's comments: This group comprised patients who did not have purulent sputum or had evidence of pneumonia on chest X-ray. The response rate for gatifloxacin is slightly higher in this group, with a CI that is within acceptable limits.

New Infections

For All Treated Patients the new infection rate was comparable between treatment groups. 10 (6%) patients in the gatifloxacin group, 9 (5%) in the cefuroxime group (Table 18). Two patients developed a fungal infection: one gatifloxacin-treated patient reported oral candidiasis and a cefuroxime-treated patient developed documented vaginal candidiasis. For 4 other patients, 3 gatifloxacin, 1 cefuroxime, vaginitis was reported as an adverse event but not as a new infection.

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Table 18 New Infections, All Treated Patients

Infection Type/Diagnosis	Number of Patients (%)					
	Gatifloxacin N = 169		Cefuroxime Axetil N = 170		Total N = 339	
Any New Infection^a	10	(6)	9	(5)	19	(6)
Respiratory System						
Upper Respiratory	3	(2)	1	(<1)	4	(1)
Sinusitis	1	(<1)	3	(<1)	4	(1)
Influenza	2	(<1)	1	(<1)	3	(<1)
Pleurisy	1	(<1)	-		1	(<1)
Genitourinary System						
Urinary Tract Infection	1	(<1)	-		1	(<1)
Vaginal Candidiasis	-		1	(<1)	1	(<1)
HEENT						
Tonsillitis	-		1	(<1)	1	(<1)
Oral Candidiasis	1	(<1)	-		1	(<1)
Herpes Simplex Oral	1	(<1)	-		1	(<1)
Otitis	-		1	(<1)	1	(<1)
Dental Abscess	-		1	(<1)	1	(<1)
Other						
Herpes Zoster	-		1	(<1)	1	(<1)

^a Patients may have had more than one new infection.

Reviewer's comments: The number of new infections was low and comparable between the 2 groups, and no life-threatening infections were noted.

8.2.3.4.3 Safety Evaluation

All Adverse Clinical Events

One hundred sixty two (48%) patients experienced one or more adverse clinical events (ACE), 87 (51%) patients in the gatifloxacin treatment arm and 75 (44%) patients receiving cefuroxime (Table 19). The most commonly reported adverse events were not drug-related; dyspnea (13% vs. 9%), increased sputum (9% vs. 5%), increased coughing (11% vs. 9%) and abnormal breath sounds (11% vs. 12%) in the gatifloxacin and cefuroxime treatment groups, respectively. While the treatment groups were generally comparable with respect to distribution and frequency of adverse clinical events, there

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were a few exceptions, e.g., dizziness (7% gatifloxacin vs. 2% cefuroxime), nausea (8% vs. 4%), chest pain (8% vs. 3%) and diarrhea (5% vs. 8%).

Drug-Related Adverse Clinical Events

Adverse events were more frequently attributed to gatifloxacin than cefuroxime (30% vs. 23%, respectively) (Table 20). The majority were either mild or moderate in severity as judged by the investigator.

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Table 19 Adverse Clinical Events^a of All Causes, All Treated Patients

Adverse Clinical Event ^a	Number of Patients (%)							Number of Patients (%)								
	Gatifloxacin N = 169							Cefuroxime Axetil N = 170								
	Drug-related		Not Drug-related		Unassessed	Total		Drug-related		Not Drug-related		Unassessed	Total			
Any Adverse Clinical Event	50	(30)	37	(22)	-	87	(51)	39	(23)	35	(21)	1	(<1)	75	(44)	
Dyspnea	3	(2)	19	(11)	-	22	(13)	-	-	16	(9)	-	-	16	(9)	
Increased Coughing	3	(2)	16	(10)	-	19	(11)	-	-	15	(9)	-	-	15	(9)	
Breath Sounds Abnormal	1	(<1)	17	(10)	-	18	(11)	1	(<1)	19	(11)	-	-	20	(12)	
Increased Sputum	1	(<1)	15	(9)	-	16	(9)	-	-	8	(5)	-	-	8	(5)	
Nausea	11	(7)	3	(2)	-	14	(8)	4	(2)	2	(1)	-	-	6	(4)	
Chest Pain	2	(1)	11	(7)	-	13	(8)	1	(<1)	4	(2)	-	-	5	(3)	
Dizziness	6	(4)	5	(3)	-	11	(7)	2	(1)	1	(<1)	-	-	3	(2)	
Rhinitis	3	(2)	5	(3)	-	8	(5)	-	-	11	(6)	-	-	11	(6)	
Diarrhea	8	(5)	-	-	-	8	(5)	14	(7)	3	(2)	-	-	14	(8)	
Pharyngitis	2	(1)	6	(4)	-	8	(5)	-	-	7	(4)	-	-	7	(4)	
Headache	5	(3)	2	(1)	-	7	(4)	4	(2)	4	(2)	-	-	8	(5)	
Dry mouth	4	(2)	1	(<1)	-	5	(3)	-	-	-	-	-	-	-	-	
Tremor	3	(2)	1	(<1)	-	4	(2)	-	-	-	-	-	-	-	-	
Malaise	-	-	3	(2)	1	(<1)	4	(2)	2	(1)	6	(4)	1	(<1)	9	(5)
Insomnia	3	(2)	1	(<1)	-	4	(2)	2	(1)	2	(1)	-	-	4	(2)	
Asthcna	2	(1)	2	(1)	-	4	(2)	-	-	-	-	-	-	-	-	
Vaginitis ^b	3	(4)	-	-	-	3	(4)	2	(3)	-	-	-	-	2	(3)	
Vomiting	2	(1)	1	(<1)	-	3	(2)	-	-	2	(1)	-	-	2	(1)	
Somnolence	2	(1)	1	(<1)	-	3	(2)	-	-	-	-	-	-	-	-	
Dyspepsia	3	(2)	-	-	-	3	(2)	3	(2)	1	(<1)	-	-	4	(2)	
Pain	1	(<1)	1	(<1)	-	2	(1)	1	(<1)	3	(2)	-	-	4	(2)	
Abdominal Pain	1	(<1)	1	(<1)	-	2	(1)	4	(2)	1	(<1)	-	-	5	(3)	
Sinusitis	-	-	1	(<1)	-	1	(<1)	-	-	3	(2)	-	-	3	(2)	
Anorexia	-	-	-	-	-	-	-	1	(<1)	2	(1)	-	-	3	(2)	

^a All Adverse clinical events occurring in $\geq 2\%$ of the total number of patients in either treatment group.

^b Percent calculated on number of female patients; in each treatment group: 75 gatifloxacin, 78 cefuroxime.

Table 20 Drug-related Adverse Clinical Events, All Treated Patients

Adverse Clinical Event ^a	Gatifloxacin N = 169					Cefuroxime Axetil N = 170				
	Mild	Moderate	Severe	Very Severe	Total	Mild	Moderate	Severe	Very Severe	Total
Any Drug-related Adverse Clinical Event	31 (18)	18 (11)	1 (<1)	-	50 (30)	23 (14)	14 (8)	1 (<1)	-	39 (23)
Nausea	9 (5)	1 (<1)	1 (<1)	-	11 (7)	4 (2)	-	-	-	4 (2)
Diarrhea	6 (4)	2 (1)	-	-	8 (5)	7 (4)	4 (2)	-	-	11 (6)
Dizziness	2 (1)	4 (2)	-	-	6 (4)	1 (<1)	1 (<1)	-	-	2 (1)
Headache	4 (2)	1 (<1)	-	-	5 (3)	1 (<1)	2 (1)	1 (<1)	-	4 (2)
Dry mouth	3 (2)	1 (<1)	-	-	4 (2)	-	-	-	-	-
Vaginitis ^b	2 (3)	1 (1)	-	-	3 (4)	-	1 (1)	1 (1)	-	2 (1)
Dyspepsia	3 (2)	-	-	-	3 (2)	2 (1)	1 (<1)	-	-	3 (2)
Insomnia	2 (1)	1 (<1)	-	-	3 (2)	2 (1)	-	-	-	2 (1)
Tremor	1 (<1)	2 (1)	-	-	3 (2)	-	-	-	-	-
Coughing	3 (2)	-	-	-	3 (2)	-	-	-	-	-
Dyspnea	1 (<1)	2 (1)	-	-	3 (2)	-	-	-	-	-
Rhinitis	2 (1)	1 (<1)	-	-	3 (2)	-	-	-	-	-
Taste Perversion	2 (1)	-	-	-	2 (1)	-	-	-	-	-
Abnormal Vision	2 (1)	-	-	-	2 (1)	-	-	-	-	-
Chest Pain	-	2 (1)	-	-	2 (1)	-	-	-	-	-
Constipation	2 (1)	-	-	-	2 (1)	-	1 (<1)	-	-	1 (<1)
Flatulence	2 (1)	-	-	-	2 (1)	-	-	-	-	-
Gingivitis	1 (<1)	1 (<1)	-	-	2 (1)	-	-	-	-	-
Vomiting	2 (1)	-	-	-	2 (1)	-	-	-	-	-
Paresthesia	1 (<1)	1 (<1)	-	-	2 (1)	-	-	-	-	-
Somnolence	2 (1)	-	-	-	2 (1)	-	1 (<1)	-	-	1 (<1)
Pharyngitis	1 (<1)	1 (<1)	-	-	2 (1)	-	-	-	-	-
Asthenia	2 (1)	-	-	-	2 (1)	-	-	-	-	-
Abdominal Pain	1 (<1)	-	-	-	1 (<1)	1 (<1)	3 (2)	-	-	4 (2)
Chills	-	1 (<1)	-	-	1 (<1)	-	-	-	-	-
Malaise	-	-	-	-	-	2 (1)	-	-	-	2 (1)

^a All adverse clinical events occurring in $\geq 1\%$ of the total number of patients in each treatment group.

^b Percent calculated on number of female patients in each treatment group: 75 gatifloxacin, 78 cefuroxime.

Deaths and Serious Adverse Events (SAE)

Two deaths occurred within 30 days of the end of treatment while patients were on study, both in the gatifloxacin treatment group. One patient had a history of pneumonia, ulcer, hernia repair, cholecystectomy and arthritis, died of a myocardial infarction after 5 days of gatifloxacin therapy. The second patient had a history of hypertension, pyelonephritis, benign prostatic hypertrophy and inguinal hernia repair. He was withdrawn from study therapy because the pre-treatment pathogen showed resistance to cefuroxime; he subsequently received ciprofloxacin to continue treatment of the acute infection. The patient died on Day +14 of underlying COPD. Neither patient's death was judged related to gatifloxacin by the investigator.

Ten (3%) patients experienced 11 serious adverse events, 7 gatifloxacin patients and 3 cefuroxime. One (cefuroxime) of the ten patients experienced two SAE's: alcohol intoxication and respiratory arrest. None of the serious adverse events in either treatment group was attributed to study medication by the investigator. In gatifloxacin group, there was one event each of dyspnea, syncope and pneumonia, and two events each of asthma and myocardial infarction. In cefuroxime axetil group, there was one event each of alcohol intolerance, diabetes mellitus, apnea and AECB.

Adverse Events Leading to Discontinuation of Study Therapy

Five patients discontinued study therapy due to an adverse event, 4 in the gatifloxacin treatment group (dizziness, insomnia, nervousness, nausea, chills, tremor, thirst) and 1 in the cefuroxime treatment group (abdominal pain).

Reviewer's comments: Most adverse events in the gatifloxacin group were non-serious in nature. Nausea, vomiting, dizziness and tremor were more frequent with gatifloxacin. There was also a trend towards more adverse events that could be related to the underlying disease in the gatifloxacin group (sputum production, dyspnea and cough), which raises the possibility of a lower efficacy rate for gatifloxacin compared to cefuroxime. Drug class-related events, namely phototoxicity, tendinitis, and seizures, were not encountered. Discontinuations were infrequent. Both death occurrences seemed unrelated to gatifloxacin but such a relation cannot be definitely excluded. From this study, it appears that gatifloxacin has a favorable adverse clinical event profile.

Pregnancies

One pregnancy was confirmed in a gatifloxacin-treated patient on Day +20 after the patient had completed 10 days of dosing. The patient elected to terminate the pregnancy.

Laboratory Test Results

Patients with Normal Pre-treatment Values

Overall, very few patients with normal baseline values developed abnormal laboratory test results during or post-treatment. The frequencies of abnormal laboratory values were

comparable between the two treatment groups. The abnormalities that did occur usually were mild (Grade 1). In the gatifloxacin group, the most common mild abnormalities were anemia (10%), decreased bicarbonate (14%), hypernatremia (10%) and increased bicarbonate (10%). Of 147 tested in the gatifloxacin-treated group, 5 patients (3%) experienced moderately elevated total bilirubin (up to 1.4 mg/dL) and 2 patients had Grade 3 total bilirubin (1.8 and 2.3 mg/dL). Of 138 and 141 gatifloxacin patients tested for AST and ALT respectively, 8 (6%) and 6 (4%) had grade 1 abnormalities, respectively. Of 137 gatifloxacin patients tested for Alkaline Phosphatase levels, 4 and 1 had grade 1 and grade 4 abnormalities respectively. Two gatifloxacin patients (of 142 tested) experienced Grade 3 or 4 hypochloremia. Of 26 gatifloxacin patients tested for fasting blood sugar, two (8%) had elevated values (116 and 125 mg/dL, neither was diabetic). Of 149 gatifloxacin patients tested for creatinine, 5 (3%) and 1 had grade 1 and grade 2 abnormalities respectively. Of 151 gatifloxacin patients tested for neutrophils, 6 (4%) and 2 had grade 1 and grade 2 abnormalities respectively.

Patients with Abnormal Pre-treatment Values

Overall, very few patients who had abnormal (Grade 1, 2 or 3) pre-treatment laboratory values experienced worsening to a higher grade during or post-treatment in either treatment group. One gatifloxacin patient experienced a Grade 4 toxicity (hyponatremia to 114 mEq/dL, pre-treatment level being 130 mEq/dL). Three gatifloxacin-treated patients developed Grade 3 toxicity (one case of neutropenia and hypernatremia each, both worsening from grade 1 to grade 3, and one case of bilirubin elevation from grade 2 to grade 3).

Reviewer's comments: Gatifloxacin appears to have a favorable adverse event profile in terms of laboratory parameters. Hepatic and renal abnormalities were infrequent and mild. Among patients with normal pre-treatment values, none of the patients in the gatifloxacin group had an elevation of both ALT and AST whereas this occurred in 3 patients in the cefuroxime group. The number of patients who had a pre and post-treatment Fasting Blood Sugar done was relatively small, 29 in gatifloxacin group and 27 in cefuroxime axetil group.

8.2.3.5 Conclusions

The applicant's conclusion was that "the results of this study indicate that gatifloxacin 400 mg daily for 7 or 10 days is safe and effective compared to cefuroxime for the treatment of acute exacerbations of chronic bronchitis. The drug demonstrated a favorable safety profile and excellent clinical and bacteriologic efficacy in a highly representative cohort of patients with this disease. Efficacy was documented for the respiratory pathogens *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*, as well as for *H. parainfluenzae* and *S. aureus*. Seven-day therapy was as efficacious as ten days."

Reviewer's comments: Data in this study were well presented in tables and appendices in hard copy and electronic format, which allowed easy derivation for further analysis. Individual patient data were well documented on Case Report Forms, as shown by a thorough review of 10% of those, representing patients from all the countries where

the study was conducted. The study was well designed, but separating cured patients from those who were only improved would have been a better approach. Cure rates were slightly higher for gatifloxacin, and the lower limits for the 95% Confidence Intervals were within the designated limit but exceeded it when patients who were improved were considered as failures. Data regarding microbiologic efficacy were supportive of effectiveness against the major pathogens involved in AECB, namely H. influenzae, S. pneumoniae and M. catarrhalis, but also against S. aureus and H. parainfluenzae. The safety profile seemed favorable but should be examined more thoroughly through the review of the data from the the integrated safety summary.

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