Sponsor's Conclusion: (Copied from the Esub and modified by the MO in Times New Roman font to reflect the numerators and denominators):

Two hundred fifty-six (256) subjects were randomized to treatment with trovafloxacin 100 mg once daily (131 subjects) or ciprofloxacin 500 mg twice daily (125 subjects) for 7 days. The two treatment groups were comparable with respect to characteristics at baseline, medical history, and prior and concomitant medications.

Two hundred thirty one (231) subjects were clinically evaluable (116, trovafloxacin and 115, ciprofloxacin) and 129 subjects were bacteriologically evaluable (60, trovafloxacin and 69, ciprofloxacin). All treated subjects were included in the analysis of adverse events.

Comparisons (95% confidence intervals) of the difference between the trovafloxacin and ciprofloxacin treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the end of study supported equivalence of the two treatments for both clinically evaluable and intent-to-treat subjects.

Success rates among clinically evaluable subjects in the trovafloxacin and ciprofloxacin groups were 111/116 (96%) and 106/115 (92%), respectively, at the end of treatment and 95/110 (86%) and 81/102 (79%), respectively, at the end of study and those among clinically intent-to-treat subjects were 91% and 88%, respectively, at the end of treatment and 83% and 79%, respectively, at the end of study. These findings were supported by marked decreases in the presence of clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis from baseline to the end of treatment and to the end of study in both treatment groups.

At the end of study, the distribution of clinical cure, improvement, failure, and relapse (trovafloxacin, 79%, 7%, 5%, and 9%, respectively; ciprofloxacin, 61%, 19%, 9%, and 12%, respectively) showed a statistically significant (p=0.005) advantage for trovafloxacin.

Sponsor-defined pathogen eradication rates were similar between the two treatments in both bacteriologically evaluable and intent-to-treat subjects.

Table 141.10
Sponsor Bacteriologic Eradication Rates (as per the MO)

	Trovafloxacin-100		Ciprofloxacin	
Pathogen	EOT	EOS	EOT	EOS
Haemophilus influenzae	15/16 (94%)	13/15 (87%)	18/19 (95%)	13/16 (81%)
Moraxella catarrhalis	12/12 (100%)	10/12 (83%)	12/12 (100%)	9/12 (75%)
Streptococcus pneumoniae	2/3 (67%)	2/3 (67%)	8/9 (89%)	7/8 (88%)

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Medical Officer's Efficacy Analysis:

In accordance with the evaluability criteria previously described, the MO excluded 21 patients from the sponsor's clinically evaluable population and did not include any of the sponsor-excluded patients. The MO's evaluable population can be seen in table 141.11

Table 141.11
Clinically Evaluable Population (as per the MO)

Reason for exclusion	Trovafloxacin	Ciprofloxacin
Total Treated	N= 131	N = 125
Sponsor Evaluable	116	115
MO Excluded	7	14
No EOS Visit	6	13
Antimicrobial R/x	1	1
Total Evaluated at EOS	**109 (83.2%)**	**101 (81%)**

The numbers of evaluable patients per arm at the EOT was the same as the number at the EOS. The trovafloxacin population represented 42.5% of the randomized patients and the ciprofloxacin population was 39.4%.

The MO's bacteriologically evaluable population was a subset of the clinically evaluable.

A by-center breakdown of the MO's evaluable population is presented in Table 141.12:

Table 141.12
Clinically Evaluable Population by Center (as per MO)

Center	Total Randomized N = 256	(100%)	Trovafloxacin N = 131	100%	Ciprofloxacin N = 125	100 %
5015	26	10.1	11	10.1	12	11.9
5017	7	2.7	2	1.8	2	2.0
5034	19	7.4	6	5.5	8	7.9
5078	47	18.3	18	16.5	17	16.8
5096	3	1.1	2	1.8	1	1.0
5144	7	2.7	2	1.8	2	2.0
5145	11	4.2	5	4.6	6	5.9
5149	5	1.9	2	1.8	2	2.0
5150	5	1.9	2	1.8	3	3.0
5151	3	1.1	2	1.8	1	1.0
5152	4	1.5	2	1.8	0	0
5153	13	5.0	5	4.6	6	5.9
5154	4	1.5	2	1.8	1	1.0
5156	54	21.0	26	23.9	21	20.8
5157	1	0.3	1	0.9	0	-
5159	7	2.7	4	3.7	2	2.0
5160	27	10.5	10	9.2	12	11.9
5161	3	1.1	2	1.8	1	1.0
5210	10	3.9	5	4.6	4	4.0

As noted in the sponsor's demographics, center #5156 enrolled > 20% of the patients.

The demographics of the FDA evaluable population can be seen in Table 141.13.

Table 141.13
Demographic Characteristics of the FDA Evaluable Population:

Characteristics	Trovafloxacin N = 109	Ciprofloxacin N = 101
Sex (Female)	45	38
(Male)	64	63
Age (years) 16 -44	22	16
45 - 64	52	52
≥ 65	35	33
Mean	58.3	58.5
Race: Asian	0	1
Black	26	20
White	77	71
Hispanic	6	8
Polynes.	0	1
Body weight (kg) mean	79.5	80.8

Both arms consisted of a comparable population in terms of weight and age.

Concomitant Medications:

The MO elected (as in the review of study 154-101), not to exclude patients who had been on systemic steroids during this study. The MO's rationale was that not only was the number of evaluable patients per arm on systemic steroids proportionate, but that systemic steroids are often used in patients with CB and at increased doses during acute exacerbations. This implies a standard of care that the MO determined would be appropriate to include in the analysis. The protocol allowed for the inclusion of patients on prednisone, up to 10 mg/day. This low dose was adhered to.

The MO ascertained through review of the line listings, that 12/109 (11%) of the MO evaluable trovafloxacin patients, and 15/101 (15.8%) of the MO evaluable ciprofloxacin patients received systemic steroids during the study.

In accordance with the DAIDP's guidance document, the MO requested that a separate efficacy analysis be performed excluding these patients. These results can be found immediately following the efficacy analyses of all MO evaluable patients.

EFFICACY:

Table 141.14
Clinical Response by Patient (as per the MO):

	Trovafloxacin			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	109	104	95.4	101	92	91.1
EOS	**109**	**93**	**85.3**	**101**	**79**	**78.2**

The MO applied a 95% CI with continuity correction factor to these results and found the following:

EOT: Trovafloxacin versus Ciprofloxacin: - 3.4%, 12.1% ($\Delta = 10$)
EOS: Trovafloxacin versus Ciprofloxacin: - 4.3%, 18.5% ($\Delta = 15$)

Thus, the MO's results mirrored those of the sponsor in that trovafloxacin was equivalent to ciprofloxacin at the EOS (MO TOC), for the primary efficacy variable of clinical response. Additionally, trovafloxacin was numerically superior to ciprofloxacin at both timepoints. There were 16 failures on the trovafloxacin arm as compared to 22 on the ciprofloxacin arm at the EOS, as compared to 5 and 9 per arm respectively, at the EOT.

The following results were obtained when patients on systemic steroids were excluded:

Table 141.15

Clinical Response at EOS by Patient Excluding Patients on Systemic Steroids (as per MO):

	Trovafloxacin-100			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	97	94	96.9	86	81	94.2
EOS	**97**	**87**	**89.7**	**86**	**73**	**84.9**

The 95% CI with continuity correction factor was:

EOT: Trovafloxacin versus Ciprofloxacin: - 4.4%, 9.8% ($\Delta = 10$)
EOS: Trovafloxacin versus Ciprofloxacin: - 6.0%, 15.6% ($\Delta = 15$)

Based on this analysis, trovafloxacin was again equivalent to ciprofloxacin at both timepoints but with an approximately 5% point difference in response rates as compared to the clinically evaluable population as a whole.

6/12 (50%) of the trovafloxacin-treated patients on systemic steroids as compared to 6/15 (40%) on the ciprofloxacin arm were clinical cures. Therefore 6 of the 16 (37.5%) failures on the trovafloxacin arm and 6 of the 22 failures (27.2%) on the ciprofloxacin arm were seen in patients on systemic steroid therapy.

Clinical response rates were higher on both treatment arms when this subgroup of patients was excluded from the analysis but the overall result was unchanged.

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Clinical Response by Baseline Pathogen:

Table 141.16
Clinical Response by Baseline Pathogen at the EOT and EOS (as per MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	16	14	87.5	19	17	89.9
	EOS	16	12	75	19	13	69
Moraxella catarrhalis	EOT	13	13	100	12	11	91.6
	EOS	13	10	76.9	12	9	75
Streptococcus pneumoniae	EOT	4	3	75	8	8	100
	EOS	4	3	75	8	5	63
Haemophilus parahemolyticus	EOT	2	2	100	6	6	100
	EOS	2	2	100	6	6	100
Haemophilus parainfluenzae	EOT	6	6	100	10	9	90
	EOS	6	6	100	10	8	80
Klebsiella pneumoniae	EOT	3	3	100	5	5	100
	EOS	3	3	100	5	4	80
Pseudomonas aeruginosa	EOT	3	3	100	5	5	100
	EOS	3	1	33	5	4	80
Mycoplasma pneumoniae	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
Chlamydia pneumoniae	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
Neisseria meningitidis	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pasteurella multocida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pseudomonas fluorescens	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Staphylococcus aureus	EOT	11	10	90.9	8	7	87.5
	EOS	11	9	82	8	7	87.5
Streptococcus pyogenes	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
Xanthomonas maltophilia	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Total	**EOT**	**67**	**62**	**92.5**	**82**	**76**	**92.6**
	EOS	**67**	**52**	**77.6**	**82**	**64**	**78**

As can be seen from the above, clinical response by baseline pathogen was essentially the same for the trovafloxacin-treated patients as compared to the ciprofloxacin both at the EOT and EOS.

For the 3 main pathogens most commonly associated with AECB and for which the sponsor is requesting approval, the MO appended a portion of the above table, below:

Table 141.17
Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically Evaluable Population/Main Pathogens Only: As per MO)

		Trovafloxacin			Ciprofloxacin		
Pathogen		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	16	14	87.5	19	17	89.9
	EOS	16	12	75	19	13	69
Moraxella catarrhalis	EOT	13	13	100	12	11	91.6
	EOS	13	10	76.9	12	9	75
Streptococcus pneumoniae	EOT	4	3	75	8	8	100
	EOS	4	3	75	8	5	63

As above, in this smaller analysis, trovafloxacin was numerically superior to ciprofloxacin in patients with *Haemophilus influenzae* at baseline, at the EOS. Clinical response in patients with *Streptococcus pneumoniae* at baseline was worse at the EOT but superior at the EOS. The total clinical response rates for the 3 main pathogens were:

Trovafloxacin EOT: 30/33 (90.9%) and EOS: 25/33 (75.7%)
Ciprofloxacin EOT: 36/39 (92.3%) and EOS: 27/39 (69.2%)

Once again the MO's results mirror those of the sponsor, in that although the 2 agents appear equivalent at the EOT, trovafloxacin appears to be numerically superior at the EOS.

Bacteriological Response:

Pathogen Eradication Rates at EOT and EOS as per the MO can be seen table 141.17:

Table 141.18

Pathogen Eradication Rates at the EOT and EOS (as per the MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	15	14	93.3	18	17	94.4
	EOS	16	14	87.5	18	14	77.8
Moraxella catarrhalis	EOT	12	12	100	12	12	100
	EOS	13	10	76.9	12	9	75
Streptococcus pneumoniae	EOT	3	2	67	8	7	87.5
	EOS	3	2	67	8	7	88
Haemophilus parahemolyticus	EOT	2	2	100	6	6	100
	EOS	2	2	100	6	6	100
Haemophilus parainfluenzae	EOT	6	6	100	10	9	90
	EOS	6	6	100	10	9	90
Klebsiella pneumoniae	EOT	2	1	50	5	5	100
	EOS	2	2	100	5	4	80
Pseudomonas aeruginosa	EOT	2	1	50	5	4	80
	EOS	2	0	0	5	4	80
Mycoplasma pneumoniae	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
Chlamydia pneumoniae	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
Neisseria meningitidis	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pasteurella multocida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pseudomonas fluorescens	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Staphylococcus aureus	EOT	11	10	90.9	7	6	85.7
	EOS	11	10	91	7	6	85.7
Streptococcus pyogenes	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
Xanthomonas maltophilia	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
Total	**EOT**	**64**	**58**	**90.6**	**80**	**74**	**92.5**
	EOS	**62**	**50**	**80.6**	**79**	**66**	**83.5**

As can be appreciated from table 141.17, the overall pathogen eradication rates were numerically comparable at the EOT and EOS. The MO's results resemble those of the sponsor, with minor differences.

The pathogen eradication rates for the 3 main pathogens only were:

Table 141.19

Pathogen Eradication Rates at the EOT and EOS (Main pathogens only: as per the MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	15	14	93.3	18	17	94.4
	EOS	16	14	87.5	18	14	77.8
Moraxella catarrhalis	EOT	12	12	100	12	12	100
	EOS	13	10	76.9	12	9	75
Streptococcus pneumoniae	EOT	3	2	67	8	7	87.5
	EOS	3	2	67	8	7	88

Trovafloxacin EOT: 28/30 (93.3%) and EOS: 26/32 (81.2%)
Ciprofloxacin EOT: 36/38 (94.7%) and EOS: 30/38 (78.9%)

The pathogen eradication rates for the 3 main pathogens only, are similar to those for all organisms as well as to the sponsor's results.

Pathogen Eradication Rates and Systemic Steroid Usage:

6 of the baseline pathogens on the trovafloxacin arm and 10 on the ciprofloxacin arm were from patients on systemic steroids with 4/6 (67%), and 3/10 (30%), eradications per arm respectively, at the EOS.

The 2 persistent organisms on the trovafloxacin arm were one each: *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

The 7 persistent isolates on the ciprofloxacin arm were 2 each *Haemophilus influenzae* and *Moraxella catarrhalis,* and 1 each *Pseudomonas aeruginosa, Serratia marcescens,* and *Mycoplasma pneumoniae.*

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 48/58 (82.7%)
Ciprofloxacin: 64/70 (91.4%)

Thus, when the baseline pathogens belonging to patients on systemic steroids were excluded, the overall bacteriologic eradication rate was numerically better for ciprofloxacin as compared to trovafloxacin.

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients on systemic steroids were:

Trovafloxacin:
Streptococcus pneumoniae: 2/3 (67%)
Haemophilus influenzae: 12/14 (85.7%)
Moraxella catarrhalis: 9/12 (75%)

Ciprofloxacin:
Streptococcus pneumoniae: 7/8 (87.5%)
Haemophilus influenzae: 13/15 (86.7%)
Moraxella catarrhalis: 9/10 (90%)

These rates were very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had no effect on either overall eradication rates or on eradication rates for the individual pathogens.

Cross-tabulation of Clinical Response and Pathogen Outcome at the EOS (MO Evaluable Population):

On the trovafloxacin arm, there were inconsistent results in 3 patients. All 3 were clinical failures with eradication of the baseline pathogen. The isolates associated with these results were 2 *Haemophilus influenzae* and 1 *Staphylococcus aureus*.

On the ciprofloxacin arm, there were 7 patients with inconsistent results (6 patients with clinical failure and bacteriologic eradication and 1 with clinical success and persistence). 2 of the clinical failures had *Haemophilus influenzae* at baseline, 2 had *Streptococcus pneumoniae*, and 1 each had *Haemophilus parainfluenzae* and *Moraxella catarrhalis*. The clinical success with persistence had *Moraxella catarrhalis*. The MO reviewed the PIDs of these patients previously.

Safety Review:

51/131 (39%) trovafloxacin subjects and 50/125 (40%) ciprofloxacin subjects had at least one AE, (all causality). 3/131 (2%) trovafloxacin patients and 7/125 (6%) ciprofloxacin patients discontinued therapy because of an adverse event. 1 of the discontinuations on the trovafloxacin arm and 5 on the ciprofloxacin arm were determined to be related to the study drug.

The most common adverse events leading to discontinuation on the trovafloxacin arm were related to the gastrointestinal system. 2/131 subjects (1%) were discontinued because of nausea, vomiting, abdominal pain, and gastroenteritis. Other events that led to discontinuation included abnormal vision, drug reactions, chest pain, and respiratory insufficiency.

On the ciprofloxacin arm the systems most affected and leading to discontinuation were the gastrointestinal and central and peripheral nervous systems, with 4/125 (3%) discontinued because of nausea, vomiting, and diarrhea and 2/125 (2%) discontinued because of dizziness and tremor. Other events that led to discontinuation, included anxiety, insomnia, pruritus, and paresthesias.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

Table 141.20
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin	Ciprofloxacin
Number of Subjects Treated	131 (100%)	125 (100%)
Subject-Days of Exposure	873	834
Subjects With At Least One Event	51 (39%)	50 (40%)
Number of Adverse Events	93	91
Subjects with Serious Adverse Events	1 (<1%)	4 (3%)
Subjects with Severe Adverse Events	1 (< 1%)	5 (4%)
Subjects Discontinued Due to Adverse Events	3 (2%)	7 (6%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0
Subjects Discontinued Due to Objective Test Findings	1 (< 1%)	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

Table 141.21
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	131 (100%)	125 (100%)
Subjects With At Least One Event	51 (39%)	50 (40%)
Subjects Discontinued due to Adverse Event	3 (2%)	7 (6%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	4 (3%)	0
Cardiovascular	4 (3%)	1 (<1%)
Centr. & Periph. Nerv.	10 (8%)	14 (11%)
Gastrointestinal	25 (19%)	27 (22%)
General	5 (4%)	6 (5%)
Hematopoietic	0	2 (2%)
Musculoskeletal	5 (4%)	3 (2%)
Other Adverse Events	2 (3%)	1 (<1%)
Psychiatric	1 (<1%)	4 (3%)
Skin/ Appendages	4 (3%)	3 (2%)
Special Senses	6 (5%)	3 (2%)
Reproductive	1 (<1%)	2 (2%)
Metabolic	1 (<1%)	0
Respiratory	5 (4%)	4 (3%)

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Table 141.22
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	131 (100%)	125 (100%)
Subjects With At Least One Event	25 (19%)	27 (22%)
Subjects Discontinued due to Adverse Event	1 (<1%)	5 (4%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	2 (2%)	0
Musculoskeletal	1 (<1%)	0
Centr. & Periph. Nerv.	3 (2%)	6 (5%)
Gastrointestinal	17 (13%)	19 (15%)
General	1 (<1%)	1 (<1%)
Psychiatric	5 (4%)	4 (3%)
Skin/ Appendages	0	1 (<1%)
Special Senses	2 (2%)	1 (<1%)
Reproductive	1 (<1%)	1 (<1%)
Respiratory	1 (<1%)	0

Overall, and as noted in previous trials, the most frequent treatment-related AEs were from the CNS and GI systems. The % of nervous system AEs was higher for the ciprofloxacin patients as compared to the trovafloxacin patients and the incidence of GI events was higher on the ciprofloxacin arm.

The further breakdown of these events can be found in the MO's Table 141.22

Table 141.23
Most Common CNS and GI AEs/Treatment-related/All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin N = 131		Ciprofloxacin N = 125	
	51	39%	50	40%
Nervous system				
Headache	5	4%	7	6%
Dizziness	5	4%	4	3%
GI System				
Nausea	11	8%	13	10%
Abdominal Pain	4	3%	2	2%
Constipation	4	3%	1	< 1%
Diarrhea	4	4%	6	5%
Dyspepsia	1	< 1%	4	3%

Other events of note included:

Insomnia in 5 (4%) of the ciprofloxacin and the trovafloxacin patients.

Serious Adverse Events:

4 trovafloxacin-treated subjects and 9 ciprofloxacin-treated subjects had serious adverse events.

Listed below are the severe adverse events that were considered treatment-related:

Trovafloxacin (N= 4):

- #50340405: post-treatment (day 27), acute MI in a 75 YO Costa Rican male with a history of hypertension, patient was hospitalized. Event was considered unrelated to the study medication but led to death.
- #51530035: theophylline toxicity day 2 of therapy. Therapy was permanently discontinued and the event resolved. This event was considered related to the study drug.
- #51560074: post-treatment (day 32), supraventricular tachycardia in an 80 YO male with a history of atherosclerosis and palpitations, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51560168: post-treatment (day 22), acute exacerbation of COPD in a 66 YO male with a history of COPD, patient was hospitalized. Event was considered unrelated to the study drug but related to the underlying disease process.

Ciprofloxacin (N = 9):

- #50150117: post-treatment (day 16), acute exacerbation of COPD in a 70 YO male with a history of COPD, patient was hospitalized. Event was considered unrelated to the study drug but related to the underlying disease process.
- #50340412: bronchospasm day 6, secondary to underlying disease process. Patient was hospitalized and study medication continued. Event resolved with therapy.
- #50780255: gun shot wound day 29. Patient was hospitalized. Event was considered unrelated to study medication and resolved with therapy.
- #50780255: exacerbation of cellulitis day 38. Patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- # 51520003: superficial femoral arterial occlusion day 5, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51560076: exacerbation of diverticulitis day 2. Patient was hospitalized and study medication discontinued. Event was considered unrelated to the study medication and resolved with therapy.
- #51560085: pneumonia day 36, considered unrelated to the study drug. Patient was hospitalized and event resolved.
- #51560180: post-treatment (day 8), exacerbation of osteoarthrosis, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

Deaths: There was one death on the trovafloxacin arm, patient #50340405: a 75 YO male with a history of COPD, HTN, and CHF. Developed an acute MI and death, 27 days post-therapy. The death was attributed to the underlying HTN and appeared unrelated to the study drug, trovafloxacin.

There were no deaths on the ciprofloxacin arm of this study.

Clinical Laboratory Abnormalities:

The sponsor has submitted tables 4.1, 4.2, 6.1, and 3.3, all of which contained listings of patients who discontinued therapy because of abnormalities. All of the above were reviewed and the MO came to the following conclusions:

Clinically significant laboratory abnormalities were observed for 16% (20/124) of subjects in the trovafloxacin group and 14% (17/118) of subjects in the ciprofloxacin group.

No subject on the trovafloxacin arm had a clinically significant SGPT or SGOT.

No subject in either treatment group had a clinically significant creatinine value.

The MO did not consider any other laboratory abnormalities found, to be related to the study drugs.

Conclusions:

As per the Sponsor:
(Copied from page 54 of the study report)

Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to that of ciprofloxacin 500 mg twice daily for 7 days for clinical success rates in subjects with acute bacterial exacerbation of chronic bronchitis. Sponsor-defined pathogen eradication rates were similar between the two treatments groups. The overall incidence of adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the ciprofloxacin group (39% and 40%, respectively), as was the frequency of treatment-related adverse events (19% and 22%, respectively) and adverse events leading to discontinuation (2% and 6%, respectively). The most commonly reported adverse event in both treatment groups was nausea. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

As per the Reviewer:

In this pivotal study comparing trovafloxacin and ciprofloxacin in the treatment of AECB for 7 days, the sponsor was able to demonstrate equivalence between the 2 antimicrobial agents.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 93/109 (85.3%) for the trovafloxacin-treated patients, and 79/101 (78.2%) for the ciprofloxacin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 4.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 104/109 (95.4%) for the trovafloxacin-treated patients versus 92/101 (91.1%) for the ciprofloxacin-treated patients. A 95% CI determined equivalence between the 2 arms at this earlier timepoint.

When patients receiving systemic steroids were excluded, the following results were obtained at the EOS: 87/97 (89.7%) trovafloxacin versus 81/86 (94.2%) ciprofloxacin. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 5.9%, 15.6% ($\Delta = 15$), trovafloxacin was again equivalent to ciprofloxacin for the primary efficacy variable of clinical response.

The overall bacteriologic efficacy analysis yielded the following by-pathogen eradication rates:
EOT: trovafloxacin 58/64 (90.6%) versus ciprofloxacin 74/80 (92.5%)
EOS: trovafloxacin 50/62 (80.6%) versus ciprofloxacin 66/79 (83.5%)

If only the 3 main pathogens were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 28/30 (93.3%) versus ciprofloxacin 36/38 (94.7%)
EOS: trovafloxacin 26/32 (81.2%) versus ciprofloxacin 30/38 (78.9%)

Specific pathogen eradication rates for the three main pathogens, were as follows:

Table 141.24
Bacteriologic Eradication Rates (as per the MO)

	Trovafloxacin-100		Ciprofloxacin	
Pathogen	EOT	EOS	EOT	EOS
Haemophilus influenzae	14/15 (93.3%)	14/16 (87.5%)	17/18 (94.4%)	14/18 (77.8%)
Moraxella catarrhalis	12/12 (100%)	10/13 (76.9%)	12/12 (100%)	9/12 (75%)
Streptococcus pneumoniae	2/3 (67%)	2/3 (67%)	7/8 (87.5%)	7/8 (87.5%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 48/58 (82.7%)
Ciprofloxacin: 64/70 (91.4%)

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients receiving systemic steroids were:

Table 141.25
Bacteriologic Eradication Rates Excluding Patients on Systemic Steroids (as per the MO)

	Trovafloxacin-100	Ciprofloxacin
Pathogen	EOS	EOS
Haemophilus influenzae	12/14 (85.7%)	13/15 (86.7%)
Moraxella catarrhalis	9/12 (75%)	9/10 (90%)
Streptococcus pneumoniae	2/3 (67%)	7/8 (87.5%)

These rates were the same as or very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had marginal (5% lower efficacy) effect on either overall eradication rates or on eradication rates for the individual pathogens.

The MO determined that the sponsor's and MO's clinical response and pathogen eradication rates were very similar for all subgroups.

The adverse events seen in this study, were similar to those noted in previous studies, with a similar overall incidence of adverse events in the trovafloxacin-treated patients (51/131: 39%) as compared to the ciprofloxacin-treated patients (50/125: 40%)

The most common complaints were from the gastrointestinal tract, with 8% (11/131) of trovafloxacin patients having nausea that was treatment-related. As seen previously, there were also complaints of dizziness and headache. In this trial, 5/131 (4%) of the episodes of dizziness and 5/125 (4%) of the episodes of headache were determined to be treatment-related.

There were no significant laboratory abnormalities.

In conclusion, trovafloxacin 100 mg PO for 7 days, was effective in the treatment of AECB caused by *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis* and was equivalent to the approved comparator, ciprofloxacin.

Reviewer's Overall Conclusion for the Indication of Acute Exacerbation of Chronic Bronchitis:
In support of this indication, the sponsor submitted 1 phase II and 2 phase III double-blind, comparative trials. Please see MO table 141.23 for an overview.

Table 141.26
Overview of AECB (As per the MO)

Study #	154-101 Phase II, DB	154-109 Phase III, DB, pivotal	154-141 Phase III, DB, pivotal
Comparator	Ofloxacin	Clarithromycin	Ciprofloxacin
Location	US and Costa Rica (1 center)	US	US and Costa Rica (1 center)
Treatment Arms	Trovafloxacin 100 mg qd Trovafloxacin 300 mg qd Ofloxacin 400 mg bid	Trovafloxacin 100 mg qd Clarithromycin 500 mg bid	Trovafloxacin 100 mg qd Ciprofloxacin 500 mg bid
Duration of therapy	10 days	7 days	7 days
# Randomized	223	410	256
# MO Evaluable at EOS	65 54 61	196 176	109 101
# MO Evaluable on Steroids	12 5 9	32 40	12 15
# MO Evaluable w/o Steroids	53 49 52	164 136	97 86
Clinical Efficacy EOS	57/65 (87.2%) 52/54 (96.3%) 57/61 (93.4%)	157/196 (80.1%) 129/176 (73.3%)	93/109 (85.3%) 79/101 (78.2%)
Clinical efficacy EOS (excluding steroid-users)	49/53 (92.5%) 47/49 (95.9%) 51.52 (98.1%)	137/164 (83.5%) 108/136 (79.4%)	87/97 (89.7%) 73/86 (84.9%)
By-patient Bacteriologic Eradication EOS ***Haemophilus influenzae***	10/12 (83.3%) 6/6 (100%) 5/5 (100%)	22/25 (88%) 10/16 (62.5%)	14/16 (87.5%) 14/18 (77.8%)
Moraxella catarrhalis	6/6 (100%) 2/2 (100%) 8/8 (100%)	13/17 (76.5%) 16/18 (89%)	10/13 (76.9%) 9/12 (75%)
Streptococcus pneumoniae	2/3 (67%) 4/4 (100%) 3/3 (100%)	7/7 (100%) 11/11 (100%)	2/3 (67%) 7/8 (88%)
Adverse Events (Treatment-Related) (Dizziness)	3/73 (4%) 24/75 (37%) 7/73 (10%)	9 (4%) 9 (5%)	5 (4%) 4 (3%)
Comment	Underpowered pilot, dose-finding study. Trovafloxacin-100 was not equivalent to trovafloxacin-300 or ofloxacin. Trovafloxacin-300 was equivalent to ofloxacin. The use of systemic steroids did not alter these results.	2 primary efficacy variables. Trovafloxacin equivalent to comparator for both. The use of systemic steroids did not alter results (max. allowed: 10 mg). Trovafloxacin had higher efficacy relative to comparator for *Haemophilus influenzae*.	2 primary efficacy variables. Trovafloxacin equivalent to comparator for both. The use of systemic steroids did not alter results (max. allowed: 10 mg).

From the first study, 154-101, a double-blind, phase II trial comparing trovafloxacin-100, trovafloxacin-300, and ofloxacin in the treatment of AECB for 10 days, few conclusions could be drawn.

Only the trovafloxacin-300 arm was equivalent to the comparator agent, ofloxacin, with EOS clinical response rates of 57/65 (87.6%) for the trovafloxacin-100 patients, 52/54 (96.3%) for the trovafloxacin-300 patients, and 57/61 (93.4%) for the ofloxacin patients. Based on a 95% CI, trovafloxacin-300 was equivalent to both comparator arms and ofloxacin was superior to the trovafloxacin-100 arm.

When patients receiving systemic steroids were excluded, the clinical response at the EOS was 49/53 (92.4%) for the trovafloxacin-100 patients, 47/49 (95.9%) for the trovafloxacin-300 patients, and 51/52 (94.4%) for the ofloxacin patients. Based on a 95% CI, trovafloxacin-300 was superior to both comparators and ofloxacin was superior to trovafloxacin-100.

The bacteriologic efficacy analysis yielded the following at the EOT, 29/29 (100%) for the trovafloxacin-100 arm, as compared to 20/20 (100%) and 21/22 (95.4%) for the trovafloxacin-300 and ofloxacin arms respectively.

Numerically all 3 arms were comparable at the EOT.

At the EOS, the pathogen eradication rate decreased to 25/39 (86.2%) on the trovafloxacin-100 arm, but remained the same for the trovafloxacin-300 and ofloxacin arms. This decrease in eradication rate was also seen in the sponsor's analysis. Statistical significance could not be drawn from these results, as the number of bacterial isolates was very small.

Specific pathogen eradication rates for the three main pathogens (at the MO TOC, the EOS), were as follows:

Table 141.27
Bacteriologic Eradication Rates (as per the MO)

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
Pathogen	EOS	EOS	EOS
Haemophilus influenzae	10/12 (80%)	5/5 (100%)	5/5 (100%)
Moraxella catarrhalis	6/6 (100%)	2/2 (100%)	8/8 (100%)
Streptococcus pneumoniae	2/3 (67%)	4/4(100%)	3/3 (100%)

The primary adverse events were from the central and peripheral nervous systems, and consisted on multiple complaints of dizziness, visual disturbances, and headache. The trovafloxacin-300 arm had a much higher number of treatment-related adverse events from these systems, 34/75 (45%) as compared to thee trovafloxacin-100 arm 3/73 (4%). Additionally, there was a higher incidence of GI complaints on the trovafloxacin-300 arm 24/75 (32%) as compared to the trovafloxacin-100 arm, 4/73 (5%).

There were no significant laboratory abnormalities.

In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by the three main pathogens; however, marginal equivalence was shown only for the trovafloxacin-300 arm versus the approved comparator, ofloxacin.

From the second study, 154-109, a phase III, pivotal trial comparing trovafloxacin and clarithromycin in the treatment of AECB for 7 days, the sponsor was able to demonstrate equivalence between the 2 antimicrobial agents.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 157/196 (80.1%) for the trovafloxacin-treated patients, and 129/176 (73.3%) for the clarithromycin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 2.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 174/196 (88.8%) for the trovafloxacin-treated patients versus 148/176 (84.1%) for the clarithromycin-treated patients. A 95% CI determined equivalence between the 2 arms at this earlier timepoint.

When patients on systemic steroids were excluded, the following results were obtained at the EOS: 137/164 (83.5%) trovafloxacin versus 108/136 (79.4%) clarithromycin. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 5.4%, 13.7% ($\Delta = 15$), trovafloxacin was again equivalent to clarithromycin for the primary efficacy variable of clinical response.

The bacteriologic efficacy analysis yielded the following pathogen eradication rates:

EOT: trovafloxacin 98/109 (90%) versus clarithromycin 76/87 (87.3%)
EOS: trovafloxacin 94/111 (84.6%) versus clarithromycin 81/87 (83.5%)

If only the 3 main pathogens were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 42/49 (85.7%) versus clarithromycin 40/45 (89%)
EOS: trovafloxacin 42/49 (85.7%) versus clarithromycin 37/45 (82.2%)

Specific pathogen eradication rates for the three main pathogens (at the MO TOC, the EOS), were as follows:

Table 141.28
Bacteriologic Eradication Rates (as per the MO)

	Trovafloxacin	Clarithromycin
Pathogen	EOS	EOS
Haemophilus influenzae	22/25 (88%)	10/16 (62.5%)
Moraxella catarrhalis	13/17 (76.5%)	16/18 (89%)
Streptococcus pneumoniae	7/7 (100%)	11/11 (100%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 81/95 (85.2%)
Clarithromycin: 61/71 (85.9%)

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients receiving systemic steroids were:

Table 141.29
Bacteriologic Eradication Rates excluding patients on Systemic Steroids (as per the MO)

	Trovafloxacin	Clarithromycin
Pathogen	EOS	EOS
Haemophilus influenzae	22/25 (88%)	8/12 (66.7%)
Moraxella catarrhalis	11/14 (78.5%)	11/12 (91.7%)
Streptococcus pneumoniae	6/6 (100%)	9/9 (100%)

The adverse events seen in this study were similar to those noted in previous studies. The most common complaints were from the gastrointestinal tract, with 5% (11/210) of trovafloxacin patients having nausea that was treatment related. As seen previously, there were also complaints of dizziness and headache. In this trial, 6/210 (3%) of the episodes of dizziness and 7/210 (3%) of the episodes of headache were determined to be treatment-related.

In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by the three main pathogens and was equivalent to the approved comparator, clarithromycin.

In the third study, 154-141, the sponsor compared trovafloxacin 100 mg daily to ciprofloxacin 500 mg bid in the treatment of AECB for 7 days, and was able to demonstrate equivalence between the 2 antimicrobial agents.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 93/109 (85.3%) for the trovafloxacin-treated patients, and 79/101 (78.2%) for the ciprofloxacin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 4.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 104/109 (95.4%) for the trovafloxacin-treated patients versus 92/101 (91.1%) for the ciprofloxacin-treated patients. A 95% CI determined equivalence between the 2 arms at this earlier timepoint.

When patients receiving systemic steroids were excluded, the following results were obtained at the EOS: 87/97 (89.7%) trovafloxacin versus 81/86 (94.2%) ciprofloxacin. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 5.9%, 15.6% ($\Delta = 15$), trovafloxacin was again equivalent to ciprofloxacin for the primary efficacy variable of clinical response.

The bacteriologic efficacy analysis yielded the following pathogen eradication rates:

EOT: trovafloxacin 58/64 (90.6%) versus ciprofloxacin 74/80 (92.5%)
EOS: trovafloxacin 50/62 (80.6%) versus ciprofloxacin 66/79 (83.5%)

If only the 3 main pathogens were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 28/30 (93.3%) versus ciprofloxacin 36/38 (94.7%)
EOS: trovafloxacin 26/32 (81.2%) versus ciprofloxacin 30/38 (78.9%)

Specific pathogen eradication rates for the three main pathogens (at the MOT TOC, EOS), were as follows:

Table 141.30
Bacteriologic Eradication Rates (as per the MO)

	Trovafloxacin	Ciprofloxacin
Pathogen	EOS	EOS
Haemophilus influenzae	14/16 (87.5%)	14/18 (77.8%)
Moraxella catarrhalis	10/13 (76.9%)	9/12 (75%)
Streptococcus pneumoniae	2/3 (67%)	7/8 (87.5%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 48/58 (82.7%)
Ciprofloxacin: 64/70 (91.4%)

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients receiving systemic steroids were:

Table 141.31
Bacteriologic Eradication Rates Excluding Patients on Systemic Steroids (as per the MO)

	Trovafloxacin	Ciprofloxacin
Pathogen	EOS	EOS
Haemophilus influenzae	12/14 (85.7%)	13/15 (86.7%)
Moraxella catarrhalis	9/12 (75%)	9/10 (90%)
Streptococcus pneumoniae	2/3 (67%)	7/8 (87.5%)

The adverse events seen in this study were similar to those noted in previous studies. The most common complaints were from the gastrointestinal tract, with 8% (11/131) of trovafloxacin patients having nausea that was treatment-related. As seen previously, there were also complaints of dizziness and headache. In this trial, 5/131 (4%) of the episodes of dizziness and 5/125 (4%) of the episodes of headache were determined to be treatment-related.

In all three trials, the MO determined that there were no significant laboratory abnormalities.

In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis* and was equivalent to the approved comparators, clarithromycin and ciprofloxacin. The clinical response and pathogen eradication rates were within 5% points difference when patients on systemic steroids were included. This decrease in efficacy was seen in both pivotal trials and was consistent on both arms.

The MO concluded that the exclusion of this patient subgroup had a consistent effect (increase) on clinical response and on overall eradication rates as well as on eradication rates for the individual pathogens thereby indicating that the use of systemic steroids has an effect on clinical response in AECB.

Overall pathogen eradication rates at the EOS were:

Streptococcus pneumoniae: 11/13 (89.6%)
Haemophilus influenzae: 46/58 (79.3%)
Moraxella catarrhalis: 29/36 (80.5%)
Staphylococcus aureus: 23/24 (95.8%)
Klebsiella pneumoniae: 10/11(90.9%)
Haemophilus parainfluenzae: 14/14 (100%)

For comparative purposes, the MO provided data pertaining to this indication, from recently approved quinolone agents.

NDA 20 - 677/Sparfloxacin: The sponsor submitted one large pivotal trial in support of this indication. The reviewing MO found an EOS clinical response rate of 244/279 (87.5%) sparfloxacin, as compared to 245/276 (88.8%) ofloxacin. Bacteriologic response by pathogen revealed the following eradication rates: *Haemophilus influenzae* 51/57 (89.5%) sparfloxacin versus 61/65 (93.8%) ofloxacin, *Moraxella catarrhalis* 36/38 (94.7%) sparfloxacin versus 33/34 (97.1%) ofloxacin, *Streptococcus pneumoniae* 30/34 (88.25) sparfloxacin versus 20/22 (90.9%) ofloxacin, *Klebsiella pneumoniae*: 15/15 (100%) sparfloxacin versus 15/17 (88.2%) ofloxacin, *Staphylococcus aureus:* 16/19 (84.2%) versus ofloxacin 13/14 (92.9%), and *Haemophilus parainfluenzae*: 115/126 (91.3%) sparfloxacin versus ofloxacin 96/108 (88.9%). This trial was similar in design to that under review and based on the above, sparfloxacin was approved for the indication of AECB caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis, Haemophilus parainfluenzae, Klebsiella pneumoniae. Enterobacter cloace*, and *Chlamydia pneumoniae*. (The MOR did not discuss whether *Staphylococcus aureus* had to be a sole pathogen in order to be considered evaluable.)

NDA 20 – 634/Levofloxacin: The sponsor submitted 2 US pivotal studies (an open-label, multicenter trial with cefaclor as the comparator, and the other, an open study with cefuroxime as the comparator.) Additionally, a supportive double-blind foreign study was also submitted with amoxicillin as the comparator. As per the reviewing MO, the clinical cure rate of levofloxacin (280/291:98%) met the 95% CI versus the approved comparators, cefaclor (123/127:97%) and cefuroxime 188/203 (93%). By pathogen eradication rates were: *Haemophilus influenzae* 47/52 (90%) versus combined comparators (cefaclor/cefuroxime 36/46 (78%), *Moraxella catarrhalis*, 30/30 (100%) versus 26/29 (90%) combined comparators, *Streptococcus pneumoniae* 16/18 (89%) versus 15/15 (100%) combined comparators, and Haemophilus parainfluenzae, 27/32 (84%) versus 28/39 (72%) combined comparators. Based on the above, an approval was granted for levofloxacin in this indication. The sponsor also requested approval for AECB caused by *Staphylococcus aureus*. This approval was granted by the MTL. The eradication rates were 9/12 (75%) versus comparator 31/34 (91%). Although the 95% CI was met, the reviewing MO recommended that approval should not be granted because of the low numbers of individual isolates and the inability to calculate valid CIs around the difference in eradication rates. Additionally, the decision to not grant approval was based on concerns about the development of resistance and the MO recommended that if approval was granted, that a rigorous subsequent study be imposed to further characterize the microbiology of clincial and microbiological failures. Eradication rates for other organisms were not addressed in the conclusion of the review. An eradication rate was provided for levofloxacin versus *Klebsiella pneumoniae* in 1 study alone: 13/13 (100%).

The clincial success rates for trovafloxacin (both pivotal studies combined), were 250/305 (82%) for all patients and 224/261 (85.9%), when patients receiving systemic steroids were excluded. The MO determined that both the clincial success rates and the pathogen eradication rates were comparable between trovafloxacin and those reported in recent fluoroquinolone NDAs.

RECOMMENDED REGULATORY ACTION:

The following statement can be added to the labeling:

/S/ 12.9.97

Regina Alivisatos, MD
Medical Officer, DSPIDPs

APPEARS THIS WAY
ON ORIGINAL

Orig. NDA #20-759
Orig. NDA #20-760
HFD-590
HFD-590/Div. Dir./MGoldberger /S/ 12/17/97
HFD-590/Dep. Dir./RAlbrecht
HFD-590/MTL/BLeiss
HFD-590/MO/RAlivisatos /S/ 12/17/97
HFD-590/CSO/PFogarty
HFD-725/Biostat/Silliman
HFD-344/Thomas

APPEARS THIS WAY
ON ORIGINAL

Addendum to MOR of NDA 20 – 759/Acute Exacerbations of Chronic Bronchitis

On November 14, 1997, (Telecon), the sponsor's representatives made a request to add *Haemophilus parainfluenzae* and *Staphylococcus aureus* to the list of requested pathogens for this indication.

This request was made because the sponsor wanted their label to be consistent with those of previously approved quinolones. Specifically, these organisms are included in the AECB indication of both sparfloxacin and levofloxacin.

As noted in the conclusion of the MOR for AECB, the bacteriologic response by pathogen for these organisms was:

Sparfloxacin: *Staphylococcus aureus:* 18/22 (84%)
Haemophilus parainfluenzae: 115/126 (91.3%)

Levofloxacin: *Staphylococcus aureus:* 9/12 (75%)
Haemophilus parainfluenzae: 32/32 (100%)

As noted in the overall conclusion of the MOR of NDA 20 – 759/AECB, there were 279 clinically evaluable sparfloxacin patients in NDA 20 – 677 and 291 in the levofloxacin NDA 20 – 634. Neither approval of *Staphylococcus aureus* (22 and 12 isolates respectively), was based on the number of isolates representing 10% of the evaluable isolates. Rather, approval was granted based on the number of these isolates exceeding 10 (alternative interpretation of the PTC Rule of 10).

A review of these organisms in the original submission revealed the following bacteriologic eradication rates (EOS/MO TOC):

Table 1

Bacteriologic Eradication Rates of Staphylococcus aureus and Haemophilus influenzae (as per MO)

Study	Drug Regimen	*Staphylococcus aureus*	*Haemophilus parainfluenzae*
154-101	Trovafloxacin-100	-	2/2 (100%)
	Trovafloxacin-300	-	3/3 (100%)
	Ofloxacin	-	4/4 (100%)
154-109	Trovafloxacin	11/13 (84.6%)	6/6 (100%)
	Clarithromycin	9/12 (75%)	6/7 (85.7%)
154-141	Trovafloxacin	10/11 (91%)	6/6 (100%)
	Ciprofloxacin	6/7 (85.7%)	9/10 (90%)
Total	Trovafloxacin-100	23/24 (95.8%)	14/14 (100%)

The following can be stated:

In study 154-101, the eradication rates for *Haemophilus parainfluenzae* alone were equal between the arms.

In study 154-109, there was numerical superiority of trovafloxacin versus the comparator for both organisms.

In study 154-141, there was numerical superiority of trovafloxacin versus the comparator for both organisms.

Total trovafloxacin, 100 mg PO qd, (EOS) pathogen eradication rates for these isolates were:

Staphylococcus aureus: 23/24 (95.8%)
Haemophilus parainfluenzae: 14/14 (100%)

The inclusion of *Haemophilus parainfluenzae* in the labeling for AECB is acceptable to the MO. The sponsor was able to show equivalent efficacy for this organism which is well recognized as a pathogen in this disease. Additionally, the eradication rate was numerically superior to those of previously approved agents. The number of isolates did not meet the standard of the PTC Rule of 10 in terms of percentage of isolates (14/202 (6.9%)), however it did meet the standard of at least 10 evaluable isolates.

The issue of the inclusion of *Staphylococcus aureus* was discussed in the MOR of AECB. At this time there is no clear standard as to the evaluabiltiy criteria necessary to be met in terms of sputum quality or organism quantity that can be adhered to. The approval for this organism in the sparfloxacin NDA 20 –677 was granted without the application of specific criteria. It was the current MO's determination that based on numbers alone, it was highly unlikely that the evaluable by the RMO isolates were sole pathogens.

In the 11/14/97, the MO requested that Pfizer provide additional data pertaining to the quality of the specimens as well as to document the presence of *Staphylococcus aureus* as a sole pathogen in as many evaluable cases as possible. It was determined that although this information would be helpful in strengthening the sponsor's case, it was not imperative given recent regulatory precedence. However, the resubmitted data was intended to reset this precedence if possible and to impose a new standard to which other agents need apply given the issue of potential development of resistance.

This data are reviewed below:

The sponsor submitted (FAX/November 20, 1997), clinical response and bacteriologic eradication tables for all patients with *Staphylococcus aureus* isolated either as a sole pathogen or as a co-pathogen (patient line listings were also provided). Please note that the primary determinant of efficacy for this indication was clinical response at the EOS, as opposed to bacteriologic eradication (see Introduction to MOR of AECB). Additionally, the MO extrapolated bacteriological response from the clinical response unless there was an EOS culture result. This method of assessment differed from that of previously reviewed NDAs, where bacteriologic response was assessed separately.

Also of note is that the total number of evaluable *Staphylococcus aureus* isolates (24) represented 11.9% of the total number of evaluable pathogens (202/all studies). However as no *Staphylococcus aureus* was isolated in study 101, the total number of isolates from the 2 pivotal studies (109 and 141) was 173. Thus the 24 isolates of *Staphylococcus aureus* represented 13.9% of the evaluable isolates and when only those isolates that were sole pathogens were taken into account, 13, they represented 7.5% of the total number of isolates,

All of the sputum specimens evaluated in both studies were of good quality, as per protocol, consisting of > 25 WBCs/HPF and < 10 epithelial cells/HPF. Further information with regards to a predominant morphology on Gram stain could not be obtained from this submission. In the CRFs, the reporting of Gram stain bacterial morphology was performed erratically with some investigators reporting this information whereas others merely documented the adequacy of the specimen.

The MO elected to presented bacteriological eradication rates as well as clinical response rates by study below:

Table 2
Study 154 – 109
***Staphylococcus aureus* Bacteriologic Eradication and Clinical Response at the EOS (as per the MO)**

	Trovafloxacin	Clarithromycin
Clinical Response (success)		
Sole pathogen	4/4 (100%)	7/9 (77.8%)
Co-infection	7/9 (77.8%)	2/3 (66.7%)
Total	**11/13 (84.6%)**	**9/12 (75%)**
Bacteriologic Response (Eradication)		
Sole Pathogen	4/4 (100%)	9/9 (100%)
Co-infection	9/9 (100%)	2/3 (66.7%)
Total	**13/13 (100%)**	**11/12 (91.7%)**

In both trovafloxacin-treated patients where *Staphylococcus aureus* was mixed with another isolate, *Pseudomonas aeruginosa* was the co-pathogen. In both of these cases, the *Staphylococcus aureus* was eradicated but the *Pseudomonas aeruginosa* was not, thus the patients were assigned an outcome of failure as per the MO (according to the clinical outcome).

Table 3
Study 154 – 141
***Staphylococcus aureus* Bacteriologic Eradication and Clinical Response at EOS (as per the MO)**

	Trovafloxacin	Ciprofloxacin
Clinical Response (success)		
Sole pathogen	7/9 (77.8%)	7/8 (87.5%)
Co-infection	2/2 (100%)	5/5 (100%)
Total	**9/11 (81.8%)**	**12/13 (92.3%)**
Bacteriologic Response (Eradication)		
Sole Pathogen	8/9 (88.9%))	5/5 (100%)
Co-infection	2/2 (100%)	1/2 (50%)
Total	**10/11 (90.9%)**	**6/7 (85.7%)**

In both instances of clinical failure in the trovafloxacin-treated patients, *Haemophilus influenzae* was the co-pathogen.

Table 4
Combined Results (studies 154-109 and 154-141)
***Staphylococcus aureus* Bacteriologic Eradication and Clinical Response at EOS (as per the MO)**

	Trovafloxacin	Comparators
Clinical Response (success)		
Sole pathogen	11/13 (84.6%)	14 /17 (82.3%)
Co-infection	9/11 (81.8%)	7/8 (87.5%))
Total	**20/24 (83.3%)**	**21/25 (84%)**
Bacteriologic Response (Eradication)		
Sole Pathogen	12/13 (92.3%)	14/14 (100%)
Co-infection	11/11 (100%)	3/5 (60%)
Total	**23/24 (95.8%)**	**17/19 (89.4%)**

From the above, it became apparent that trovafloxacin was as effective in the eradication of *Staphylococcus aureus* (either as a sole pathogen or as a co-pathogen), versus not only the comparator agents but also versus sparfloxacin and levofloxacin. The MO determined that the sponsor met the "Rule of 10" in terms of 10% of the evaluable isolates when all isolates were taken into account and additionally, that at least 10 isolates (sole isolates n = 13) were provided. Although the MO recognizes that as recommended in PTC, the greater of the 2 should be met and that the sponsor does not meet this goal based on "sole isolates" only, regulatory precedence indicates that the sponsor provided greater information than that contained in previous applications receiving approval. Additionally, the sponsor provided valuable information with regards to clinical response in either setting. This information cannot be compared to that in previously reviewed NDAs because the sponsors of those NDAs did not provide these data.

The MO determined that the information provided was adequate to recommend an approval for trovafloxacin in the treatment of AECB caused by *Staphylococcus aureus*, either as a sole pathogen or as a co-pathogen. However, the real value in this submission lies in the resetting of regulatory precedence in that other submissions should also provide adequate information with regards to the number of isolates that occurred as sole pathogens as well as their eradication rates and the clinical response rates assosciated with them.

RECOMMENDED REGULATORY ACTION:

The following statement can be added to the labeling:

Trovafloxacin is indicated for the treatment of Acute Exacerbation of Chronic Bronchitis caused by *Haemophilus influenzae, Haemophilus parainfluenzae, Staphylococcus aureus, Streptococcus pneumoniae,* and *Moraxella catarrhalis* at a dose of 100 mg PO daily for 7 – 10 days.

/S/ 12/5/97

Regina Alivisatos, MD
Medical Officer, DSPIDPs

APPEARS THIS WAY
ON ORIGINAL

Orig. NDA #20-759
Orig. NDA #20-760
HFD-590
HFD-590/Div. Dir./MGoldberger /S/
HFD-590/Dep. Dir./RAlbrecht
HFD-590/MTL/BLeissa /S/ 12/17/97
HFD-590/MO/RAlivisatos
HFD-590/CSO/PFogarty
HFD-725/Biostat/Silliman
HFD-344/Thomas

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL