Medical Officer's Comment: *The MO reviewed all deviations and agreed with the sponsor's judgement. Notable was the inclusion of patients on higher systemic steroid doses than those allowed for in the protocol. As stated previously, the MO elected not to exclude these patients but to provide a separate efficacy analysis.*

Medical Officer's Comment: *Based on the above demographic information, the MO determined that:*

- *Patients receiving steroid therapy should be evaluated in a separate analysis in order to ascertain if their inclusion in the evaluable population affected outcome.*
- *Patients who received antimicrobials for other well-documented infections (3) should be excluded from the MO evaluable population.*
- *Patients who did not have an EOS visit (16), should be excluded from the MO evaluable population.*

Overall, there was concordance between the MO and the sponsor in terms of outcome assessments and evaluability.

Sponsor's Efficacy Analysis:

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Sponsor-Defined Clinical Response:

Table 109.4
Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)

Timepoint	Trovafloxacin N= 203	Clarithromycin N = 188
Number of patients evaluated at EOT	203 (100%)	188 (100%)
Cure	87 (43%)	75 (40%)
Improvement	94 (46%)	85 (45%)
Failure	22 (11%)	28 (15%)
Success (Cure + Improvement)	181 (89%)	160 (85%)
Number of patients evaluated at EOS	197(100%)	178 (100%)
Cure	140 (71%)	110 (62%)
Improvement	18 (9%)	21 (12%)
Failure	22 (11%)	28 (16%)
Relapse	17 (9%)	19 (11%)
Success (Cure + Improvement)	**158 (80%)**	**131 (74%)**

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Clarithromycin: - 2.6%, 10.7% ($\Delta = 15$)

EOS: Trovafloxacin versus Clarithromycin: -1.9%, 15.1% ($\Delta = 15$)

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The sponsor stated that (copied from page 32 of the study report):

Comparisons (95% confidence intervals) of the difference between the two 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.

The majority of subjects in both treatment groups were clinical successes (cure + improvement) at both the end of treatment and the end of study (trovafloxacin, 89% and 80%, respectively; clarithromycin, 85% and 74%, respectively).

Medical Officer's Comment:

The MO requested that the FDA statistical reviewer, Dr. Silliman, provide a 95% CI with continuity correction factor for the above. The results were as follows:

EOT: Trovafloxacin versus Clarithromycin: - 3.1%, 11.2% (Δ = 15):

EOS: Trovafloxacin versus Clarithromycin: -2.5%, 15.7% (Δ = 15)

Based on the FDA analysis, there was therapeutic equivalence between both arms at the EOT and the EOS with trovafloxacin numerically superior to clarithromycin at both timepoints.

For the clinical ITT population, the success rates were 184/208 (88%) for the trovafloxacin-treated patients and 164/199 (82%) for the clarithromycin-treated patients at the EOT (CI: -0.8%, 12.9%). The respective values at the EOS were 145/164 (79%) and 143/199 (72%): 95% CI for this analysis: -1.45, 15.3%. The sponsor stated that this analysis also demonstrated equivalence between the 2 treatment arms.

The sponsor stated that the clinical failure rate was 11% and 15% per arm respectively, at the EOT. At the EOS, 9% and 11% of patients were relapses. Thus as per the MO calculations, the failure rate was 39/197 (20%) on the trovafloxacin arm and 47/178 (27%) on the clarithromycin arm, when failures and relapses were added together, (see introduction re definitions).

The sponsor stated that (copied from page 33 of the study report):

Of these subjects, eight trovafloxacin and 12 clarithromycin subjects had pathogens isolated at baseline. In both treatment groups, the most commonly isolated baseline pathogen was *Moraxella catarrhalis*. No pathogen with susceptibility testing done at baseline and follow-up developed resistance to trovafloxacin or clarithromycin during the study.

Clinical Relapse: Among clinically evaluable subjects who were clinical successes at the end of treatment, 17 trovafloxacin subjects and 19 clarithromycin subjects were designated as clinical relapses at the end of study. Of these subjects, eight trovafloxacin and 10 clarithromycin subjects had pathogens isolated at baseline. Among clinically evaluable subjects classified as a clinical relapse at the end of study, the most commonly isolated pathogens at baseline were *Pseudomonas aeruginosa* (3 of the 8 subjects with baseline isolates) for trovafloxacin subjects and *Haemophilus influenzae* (7 of the 10 subjects with baseline isolates) for clarithromycin subjects.

The clinically evaluable subjects with an outcome of failure and a baseline pathogen are listed below: (Outcomes are for EOS only and include patients classified as relapses by the sponsor)

Trovafloxacin (N = 16):

- #51270420: Failure: *Pseudomonas aeruginosa* at baseline, persistent. Also had *Staphylococcus aureus* which was eradicated.
- 351290382: Failure: *Haemophilus influenzae* at baseline, presumed persistent.
- #51290482: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.
- #51330345: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #51330346: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.

- #51350414: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- 351390399: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #51400357: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #50780322: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #50820093: Failure: *Pseudomonas aeruginosa* at baseline which was persistent.
- #50890170: Failure: *Klebsiella pneumoniae* at baseline which was persistent.
- #50920237: Failure: *Pseudomonas aeruginosa* at baseline, persistent. Also had *Staphylococcus aureus* which was eradicated.
- #51250365: Failure: *Pseudomonas aeruginosa* at baseline which was presumed persistent.
- #51300554: Failure: *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* serologies positive, both classified as presumed persistent.
- #51390447: Failure: *Streptococcus pneumoniae* at baseline which was eradicated.
- #51400467: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.

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Clarithromycin (N = 22):

- #50050389: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.
- #50720010: Failure: *Serratia marcescens* at baseline which was presumed persistent.
- #50790057: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #50830106: Failure: *Haemophilus parainfluenzae* at baseline which was eradicated.
- #50920197: Failure: *Staphylococcus aureus* at baseline which was eradicated.
- #51270587: Failure: *Staphylococcus aureus* at baseline which was eradicated.
- #51390356: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #51390397: Failure: *Haemophilus influenzae* at baseline which was persistent.
- #51400358: Failure: *Streptococcus pneumoniae* at baseline which was eradicated.
- #51400359: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #51400466: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #54990540: Failure: *Haemophilus influenzae* at baseline which was eradicated.
- #50320582: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #50750027: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.

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- #50870145: Failure: *Haemophilus influenzae* at baseline which was eradicated.
- #50929234: Failure: *Pseudomonas aeruginosa* at baseline which was presumed persistent.
- #51270419: Failure: *Haemophilus influenzae* and *Staphylococcus aureus* at baseline which were presumed persistent.
- #51290383: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #51290481: Failure: *Haemophilus influenzae* at baseline which was eradicated.
- #51300555: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #51300571: Failure: *Haemophilus influenzae* at baseline which was persistent.
- #51400458: Failure: *Xanthomonas maltophilia* at baseline which was presumed persistent.

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Medical Officer's Comment: *The MO elected to present only those failures and relapses with a baseline pathogen. Overall, the MO did not disagree with the sponsor's determination of outcome. The MO, however, reclassified those patients classified as relapses, into failures.*

The most common pathogen assosciated with failure on the trovafloxacin arm was Moraxella catarrhalis, followed by Pseudomonas aeruginosa. On the clarithromycin arm, the most common pathogen assosciated with failure was Haemophilus influenzae.

None of the bacterial isolates assosciated with failure were resistant or developed resistance to either study drug (as per the sponsor).

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Clinical response rates for both clinically and bacteriologically evaluable patients can be seen below:

Table 109.5
Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.3)

Timepoint	Trovafloxacin N= 93	Clarithromycin N = 81
Number of patients evaluated at EOT	93 (100%)	81 (100%)
Cure	46 (49%)	34 (42%)
Improvement	39 (42%)	35 (43%)
Failure	8 (9%)	12 (15%)
Success (Cure + Improvement)	85 (91%)	69 (85%)
Number of patients evaluated at EOS	91(100%)	78 (100%)
Cure	67 (74%)	48 (62%)
Improvement	8 (9%)	8 (10%)
Failure	8 (9%)	12 (15%)
Relapse	8 (9%)	10 (13%)
Success (Cure + Improvement)	**75 (82%)**	**56 (72%)**

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Clarithromycin: - 3.4%, 15.8% ($\Delta = 10$)

EOS: Trovafloxacin versus Clarithromycin: - 2.1%, 23.3% ($\Delta = 15$)

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Medical Officer's Comment: *Trovafloxacin appeared numerically superior to clarithromycin at the MO TOC, the EOS. However, there was no significant difference between the results of this population (clinically and bacteriologically evaluable), and the clinically evaluable population. The FDA-generated 95% CIs (with continuity correction factor) for the above were:*

EOT: Trovafloxacin versus Clarithromycin: - 4.6%, 17.0% ($\Delta = 10$)

EOS: Trovafloxacin versus Clarithromycin: - 3.3%, 24.5% ($\Delta = 15$)

Thus, the 2 agents were equivalent at both timepoints.

Clinical Response by Baseline Pathogen:

Table 109.6
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3 by MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	26	24	92.3	18	16	89
	EOS	26	24	92.3	16	7	43.7
Moraxella catarrhalis	EOT	18	14	78	20	16	80
	EOS	17	12	70.5	19	14	73.6
Streptococcus pneumoniae	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9
Haemophilus parahaemolyticus	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
Haemophilus parainfluenzae	EOT	6	6	100	7	6	85.7
	EOS	6	6	100	7	6	85.7
Klebsiella pneumoniae	EOT	5	5	100	7	7	100
	EOS	5	4	80	7	7	100
Pseudomonas aeruginosa	EOT	14	13	92.8	8	8	100
	EOS	14	10	71.4	8	7	87.5
Citrobacter amalonaticus	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Mycoplasma pneumoniae	EOT	6	6	100	2	2	100
	EOS	6	5	83.3	2	2	100
Chlamydia pneumoniae	EOT	9	8	88.8	4	3	75
	EOS	9	6	66.6	4	3	75
Klebsiella spp.	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Neisseria Meningitidis	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Pasteurella Multocida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Proteus Mirabilis	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Proteus spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pseudomonas putida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Serratia marcescens	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
Staphylococcus aureus	EOT	14	13	92.8	12	10	83.3
	EOS	13	11	84.6	12	9	75
Streptococcus pyogenes	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Xanthomonas maltophilia	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	**EOT**	**115**	**106**	**92.1**	**101**	**89**	**88.1**
	EOS	**113**	**94**	**83.1**	**98**	**75**	**76.5**

Copied below from page 42 of the study report is the sponsor's text:

Among clinically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined clinical success rates (cure + improvement) were similar (≤10 percentage-point difference) in both treatment groups at the end of treatment and at the end of study, with the following exception: a higher percentage of subjects in the trovafloxacin group with baseline isolates of *Haemophilus influenzae were* clinical successes at the end of study compared to subjects in the clarithromycin group (89%, 16/18 and 44%, 7/16, respectively).

Medical Officer's Comment: *As can be seen from the above, the clinical response by baseline pathogen was numerically superior for the trovafloxacin-treated patients as compared to the clarithromycin at both the EOT and EOS. Confidence intervals were not generated for this variable because this table was baseline pathogen and not patient driven, thus there were patients with more than 1 baseline pathogen. This decision was made in consultation with Dr. Nancy Silliman, FDA statistician.*

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

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Table 109.7
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Main Pathogens Only: Modified 5.3 by MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	26	24	92.3	18	16	89
	EOS	26	24	92.3	16	7	43.7
Moraxella catarrhalis	EOT	18	14	78	20	16	80
	EOS	17	12	70.5	19	14	73.6
Streptococcus pneumoniae	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9

Again, CIs were not applied but it appeared that trovafloxacin was superior to clarithromycin in eradicating Haemophilus influenzae at the EOS. Other than this striking difference, the 2 agents were numerically comparable with trovafloxacin being numerically slightly superior to clarithromycin in patients with Streptococcus pneumoniae and clarithromycin, numerically superior to trovafloxacin in patients with Moraxella catarrhalis. The total eradication rates for the 3 main pathogens were:

Trovafloxacin EOT: 44/51 (86.2%) and EOS: 42/50 (84%)
Clarithromycin EOT: 42/49 (85.7%) and EOS: 31/46 (67.3%)

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Signs and Symptoms:
(Copied from page 44 of the study report)

The percentage of clinically evaluable subjects with moderate or severe signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline was comparable between the two treatment groups and was as follows: dyspnea (trovafloxacin: 55%; clarithromycin: 60%), cough (trovafloxacin: 90% and clarithromycin: 99%), lung sounds (trovafloxacin: 62% and clarithromycin: 64%), and increase sputum volume (trovafloxacin: 85% and clarithromycin: 84%).
In both treatment groups, the percentage of subjects with signs and symptoms of infection decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among the subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects. A summary of the percentage of subjects with clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline, end of treatment and end of study is presented in the following table.

Table B. Summary of Clinical Signs and Symptoms						
	Trovafloxacin 100 mg			Clarithromycin 500 mg BID		
	Baseline (N=202)	EOT (N=203)	EOS (N=197)	Baseline (N=187)[a]	EOT (N=188)	EOS (N=179)
Sign/Symptom	Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms					
Dyspnea	82%	41%	27%	88%	47%	36%
Cough	100%	78%	52%	100%	78%	58%
Lung Sounds	89%	41%	27%	90%	52%	30%
ISV	100%	54%	30%	100%	56%	34%
	Baseline (N=208)	EOT (N=208)	EOS (N=202)	Baseline (N=199)[a]	EOT (N=197)	EOS (N=188)
Sign/Symptom	Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms					
Dyspnea	83%	42%	28%	88%	49%	37%
Cough	100%	79%	53%	100%	78%	58%
Lung Sounds	89%	43%	28%	91%	52%	29%
ISV	100%	55%	31%	100%	57%	35%

EOT= End of Treatment; EOS= End of Study; ISV= Increased Sputum Volume
a Subject 5138-0593 was not assessed for lung sounds at baseline.
Ref.: Tables 5.8.1 and 5.8.2

Medical Officer's Comment: The MO agreed with the sponsor's analysis and verified from the CRFs, that there was indeed a decrease in signs and symptoms as described above.

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Bacteriologic Response:

Sponsor-Defined Pathogen Eradication Rates at EOT and EOS can be seen in Sponsor's Table 5.4.1, copied and modified by the MO:

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Table 109.8
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population: Modified 5.4.1 by MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	26	24	92.3	16	12	89
	EOS	24	22	92.3	16	10	62.5
Moraxella catarrhalis	EOT	17	13	76	18	17	94
	EOS	16	13	70.5	18	16	89
Streptococcus pneumoniae	EOT	7	6	86	11	11	100
	EOS	7	7	100	11	11	100
Haemophilus parahaemolyticus	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
Haemophilus parainfluenzae	EOT	6	6	100	6	6	100
	EOS	6	6	100	7	7	100
Klebsiella pneumoniae	EOT	5	5	100	7	5	71
	EOS	4	3	75	7	6	83
Pseudomonas aeruginosa	EOT	13	9	69	8	6	75
	EOS	14	9	64	8	6	75
Citrobacter amalonaticus	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Mycoplasma pneumoniae	EOT	6	6	100	2	2	100
	EOS	6	5	83.3	2	2	100
Chlamydia pneumoniae	EOT	9	8	88.8	4	3	75
	EOS	9	6	66.6	4	3	75
Klebsiella spp.	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Neisseria Meningitidis	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Pasteurella Multocida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Proteus Mirabilis	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Proteus spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pseudomonas putida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Serratia marcescens	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
Staphylococcus aureus	EOT	14	14	92.8	12	12	100
	EOS	13	13	84.6	12	11	92
Streptococcus pyogenes	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Xanthomonas maltophilia	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	**EOT**	**113**	**101**	**89.3**	**96**	**85**	**88.5**
	EOS	**109**	**94**	**86.2**	**96**	**81**	**84.3**

The sponsor's text has been copied from page 45 of the study report below:

Among bacteriologically evaluable subjects, eradication rates for *Haemophilus influenzae* were higher among subjects in the trovafloxacin group compared to clarithromycin group at the end of treatment (92%, 24/26 isolates versus 75%, 12/16 isolates; 95% CI: -6.3, 40.9) and at the end of study (92%, 22/24 isolates versus 63%, 10/16 isolates; 95% CI: 3.0, 55.3).
Eradication rates for all other baseline pathogens were comparable between the two treatment groups at both the end of treatment and end of study visits.

Medical Officer's Comment: *As can be appreciated from the sponsor's text, an overall eradication rate was not provided by the sponsor in the study report. Based on the MO's analysis, the 2 agents were numerically comparable at the EOT and EOS.*

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

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Trovafloxacin EOT: 43/50 (86%) and EOS: 42/47 (89.3%)
Clarithromycin EOT: 40/45 (89%) and EOS: 37/45 (82.2%)

Although the MO appreciated the significant decrease in the eradication rate of clarithromycin versus Haemophilus influenzae at the EOS, it should be pointed out that a similar albeit slightly smaller decrease occurred for trovafloxacin versus Moraxella catarrhalis at the same timepoint.

Superinfecting Pathogens and Colonizing Organisms:
(Copied from page 46 of the study report)

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Superinfecting organisms were isolated from one subject (<1%) in the trovafloxacin group (*Escherichia coli*) and from one subject (<1%) in the clarithromycin group (*Pseudomonas aeruginosa*). Colonizing organisms were isolated from 14 subjects (7%) in the trovafloxacin group and from 27 subjects (14%) in the clarithromycin group.

Medical Officer's Comment: *The MO agreed with the sponsor's determination in all cases after review of the PIDs.*

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Cross-tabulation of Sponsor-Defined Clinical Response and Pathogen Outcome:

The sponsor provided only a cross tabulation for the EOT and not the EOS. 26 patients, (11 trovafloxacin and 15 clarithromycin), had clinical responses inconsistent with pathogen outcome. The sponsor's table C has been copied from page 49 of the study report, below and modified to reflect the MO's determination of clinical and bacteriological outcome at the EOS:

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Table 109.9
Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor) and the EOS (as per the MO)

Table C. Summary of Discrepancies Between Sponsor-Defined Clinical Response and Sponsor-Defined Pathogen Outcome at the End of Treatment
Bacteriologically Evaluable Subjects

Subject Number	Baseline Pathogen	Clinical Response		Pathogen Bacteriological Response	
Trovafloxacin 100 mg		**Sponsor EOT**		**MO EOS**	
5041-0065	*Moraxella catarrhalis*	Improvement	Cure	Persistent	Pres. Erad.
5041-0069	*Moraxella catarrhalis*	Improvement	Cure	Persistent	Persistent
5041-0683	*Moraxella catarrhalis*	Improvement	Not Evaluable	Persistent	-
5092-0237	*Pseudomonas aeruginosa*	Improvement	Failure	Persistent	Persistent
5125-0365	*Pseudomonas aeruginosa*[a]	Improvement	Failure	Persistent	Pres. Pers.
5125-0367	*Pseudomonas aeruginosa*	Improvement	Cure	Persistent	Persistent
5127-0420	*Staphylococcus aureus*	Failure	Failure	Eradication	Eradicated
5135-0414	*Moraxella catarrhalis*	Failure	Failure	Eradication	Pres. Pers.
5138-0393	*Streptococcus pneumoniae*	Improvement	Cure	Persistent	Eradicated
5139-0399	*Moraxella catarrhalis*	Failure	Failure	Eradication	Eradicated
5140-0357	*Moraxella catarrhalis*	Failure	Failure	Eradication	Pres. Pers.
Clarithromycin 500 mg BID					
5076-0254	*Haemophilus influenzae*[a]	Improvement	Cure	Persistent	Pres. Erad.
5079-0057	*Moraxella catarrhalis*	Failure	Failure	Eradication	Eradicated
5081-0083	*Klebsiella pneumoniae*[a]	Improvement	Cure	Persistent	Persistent
5083-0106	*Haemophilus parainfluenzae*	Failure	Failure	Eradication	Eradicated
5092-0197	*Staphylococcus aureus*	Failure	Failure	Eradication	Eradicated
5092-0234	*Pseudomonas aeruginosa*[a]	Improvement	Failure	Persistent	Pres. Pers.
5095-0098	*Klebsiella pneumoniae*[a]	Cure	Cure	Persistent	Pres. Pers.
5125-0366	*Pseudomonas aeruginosa*[a]	Improvement	Cure	Persistent	Pres. Pers.
5127-0587	*Staphylococcus aureus*	Failure	Failure	Eradication	Eradicated
5130-0555	*Haemophilus influenzae*	Improvement	Failure	Persistent	Pres. Pers.
5138-0395	*Haemophilus influenzae*	Improvement	Cure	Persistent	Pres. Erad.
5139-0356	*Moraxella catarrhalis*	Failure	Failure	Eradication	Eradicated
5140-0358	*Streptococcus pneumoniae*	Failure	Failure	Eradication	Eradicated
5140-0359	*Moraxella catarrhalis*	Failure	Failure	Eradication	Eradicated
5499-0540	*Haemophilus influenzae*	Failure	Not Evaluable	Eradication	-

a Resistant to study drug at baseline
Ref.: Table 5.7.1 and Appendix I, Tables 8 and 8a

Medical Officer's Comment: *Based on the MO's recreation of this table, 2 patients, one from each arm were unevaluable.*

Inconsistency between clinical and bacteriologic outcome persisted in 2 of the original 11 trovafloxacin patients, both clinical cures with documented persistence of the baseline pathogen, (Moraxella catarrhalis in 1 case and Pseudomonas aeruginosa in the other (neither resistant)).

On the clarithromycin arm, inconsistencies between outcomes were seen in 10 patients, 7 were clinical failures with documented eradication of the baseline pathogen. Moraxella catarrhalis was found in 3 of the 7, Staphylococcus aureus in 2 and Haemophilus parainfluenzae and Streptococcus pneumoniae in 1 each. The remaining 3/10 patients were "cures" with "persistence"(1) or "presumed persistence" (2). All 3 of these patients had pathogens resistant to the study drug, (2 isolates Klebsiella pneumoniae and 1 Pseudomonas aeruginosa).

There were 5 baseline pathogens resistant to the study drug, all on the clarithromycin arm, 3:failures and 2 cures, (2 isolates each of Klebsiella pneumoniae and Pseudomonas aeruginosa, and 1 Haemophilus influenzae). There was also 1 resistant baseline Pseudomonas aeruginosa on the trovafloxacin arm and this patient was also a failure at the EOS.

The MO deferred to the microbiology reviewer for comment on this phenomenon. However, most isolates assosciated with AECB, did not appear to be resistant to trovafloxacin.

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

Four hundred ten (410) subjects were randomized to treatment with trovafloxacin 100 mg once daily (210 subjects) or clarithromycin 500 mg twice daily (200 subjects) for 7 days. The two treatment groups were comparable with respect to characteristics at baseline, medical history, and prior and concomitant medications.

Three hundred ninety one (391) subjects were clinically evaluable (203, trovafloxacin and 188, clarithromycin) and 174 subjects were bacteriologically evaluable (93, trovafloxacin and 81, clarithromycin). All treated subjects were included in the analysis of adverse events.

Comparisons (95% confidence intervals) of the difference between the trovafloxacin and clarithromycin 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 clarithromycin groups were 181/103 (89%) and 160/188 (85%), respectively, at the end of treatment and 158/197 (80%) and 131/178 (74%), respectively, at the end of study and those among clinically intent-to-treat subjects were 88% and 82%, respectively, at the end of treatment and 79% and 72%, 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.

The eradication rates for *Haemophilus influenzae* was higher for trovafloxacin than for clarithromycin at the end of treatment and at the end of study in both bacteriologically evaluable and intent-to-treat subjects. Eradication rates for all other baseline pathogens were comparable between the two treatment groups at both evaluation timepoints for bacteriologically evaluable and intent-to-treat subjects.

EOT Trovafloxacin (bacteriologically evaluable):
Haemophilus influenzae: 24/26 (92.3%)
Moraxella catarrhalis: 13/17 (76%)
Streptococcus pneumoniae: 6/7 (86%)

EOS Trovafloxacin (bacteriologically evaluable):
Haemophilus influenzae: 22/24 (92.3%)
Moraxella catarrhalis: 13/16 (70.5%)
Streptococcus pneumoniae: 7/7 (100%)

EOT Clarithromycin (bacteriologically evaluable):
Haemophilus influenzae: 12/16 (89%)
Moraxella catarrhalis: 17/18 (94%)
Streptococcus pneumoniae: 11/11 (100%)

EOS Clarithromycin (bacteriologically evaluable):
Haemophilus influenzae: 10/16 (62.5%)
Moraxella catarrhalis: 16/18 (89%)
Streptococcus pneumoniae: 11/11 (100%)

Medical Officer's Efficacy Analysis:

In accordance with the evaluability criteria previously described, the MO excluded 19 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 109.10.

Table 109.10
Clinically Evaluable Population (as per the MO)

Reason for exclusion	Trovafloxacin	Clarithromycin
Total Treated	N=210	N=200
Sponsor Evaluable	203	188
MO Excluded	7	12
No EOS Visit	4	12
Antimicrobial R/x	3	-
Total Evaluated at EOS	**196 (93.3%)**	**176 (88%)**

The numbers of evaluable patients per arm at the EOT was the same as the number at the EOS. The trovafloxacin population represented 47.8% of the randomized patients and the clarithromycin population was 43%.

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 109.11:

Table 109.11
Clinically Evaluable Population by Center (as per MO)

			Trovafloxacin				Clarithromycin			
Center	Total Randomized N =223 (100%)		Sponsor Eval. N = 203 (100%)		MO Eval. N= 196		Sponsor Eval. N = 188 (100%)		MO Eval. N= 176	
5005	6	1.5	4	2	4	2	1	0.5	1	0.6
5022	4	1	2	1	2	1	1	0.5	1	0.6
5032	4	1	2	1	2	1	2	1.1	2	1.1
5041	12	2.9	6	2.9	5	2.6	6	3.2	5	2.8
5042	8	2	4	2	3	1.5	4	2.1	4	2.3
5072	12	2.9	6	2.9	6	3.1	6	3.2	5	2.8
5073	1	0.2	1	0.5	1	0.5	0	0	0	0
5074	6	1.5	2	1	2	1	4	2.1	4	2.3
5075	3	0.7	1	0.5	1	0.5	1	0.5	1	0.6
5076	40	9.7	20	9.5	20	10.2	19	10.1	18	10.2
5077	1	0.2	1	0.5	1	0.5	0	0	0	0
5078	36	8.8	18	8.6	17	8.7	18	9.6	18	10.2
5079	7	1.7	4	2	4	2	3	1.6	2	1.1
5080	24	5.8	12	5.7	12	6.1	12	6.4	12	6.8
5081	8	2	4	2	4	2	4	2.1	4	2.3
5082	2	0.5	2	1	1	1	0	0	0	0
5083	6	1.5	3	1.5	3	1.5	3	1.6	3	1.7
5085	2	0.5	1	0.5	1	0.5	1	0.5	1	0.6
5087	2	0.5	1	0.5	1	0.5	1	0.5	1	0.6
5089	3	0.7	1	0.5	1	0.5	2	1.1	2	1.1
5091	8	2	4	2	4	2	4	2.1	3	1.7
5092	16	3.9	8	3.9	7	3.6	7	3.7	7	4
5095	5	1.2	2	1	2	1	2	1.1	2	1.1
5121	3	0.7	1	0.5	1	0.5	2	1.1	1	0.6
5124	1	0.2	1	0.5	1	0.5	0	0	0	0
5125	3	0.7	2	1	2	1	1	0.5	1	0.6
5127	65	15.9	29	14.3	28	14.3	29	15.4	27	15.3
5129	14	3.4	7	3.4	7	3.6	7	3.7	7	4.0
5130	16	3.9	8	3.9	8	4.1	8	4.3	8	4.5
5132	9	2.2	4	2	4	2	5	2.7	5	2.8
5133	3	0.7	2	1	2	1	1	0.5	1	0.6
5134	5	1.2	3	1.5	3	1.5	2	1.1	1	0.6
5135	2	0.5	1	0.5	1	0.5	0	0	0	0
5136	1	0.2	1	0.5	1	0.5	0	0	0	0
5137	8	2	4	2	4	2	4	2.1	3	1.7
5138	7	1.7	3	1.5	3	1.5	4	2.1	4	2.3
5139	16	3.9	8	3.9	8	4.1	8	4.5	8	4.5
5140	21	5.1	9	4.4	8	4.1	10	5.3	9	5.1
5181	3	0.7	1	0.5	1	0.5	0	0	0	0
5213	1	0.2	1	0.5	1	0.5	0	0	0	0
5250	2	0.5	2	1	2	1	0	0	0	0
5499	4	1	2	1	2	1	2	1.1	1	0.6
5743	1	0.2	1	0.5	1	0.5	0	0	0	0
5776	1	0.2	1	0.5	1	0.5	0	0	0	0
5853	8	2	4	2	4	2	4	2.1	4	2.3

As noted in the sponsor's demographics, no single center enrolled > 20% of the patients. Because the number of patients per center was small, all centers were pooled.

The demographics of the FDA evaluable population can be seen in Table 109.12

Table 109.12
Demographic Characteristics of the FDA Evaluable Population:

Characteristics	Trovafloxacin N = 196	Clarithromycin N = 176
Sex (Female)	102	97
(Male)	94	79
Age (years) 16 -44	33	30
45 - 64	103	83
≥ 65	60	63
Mean	57.9	58.2
Race: Asian	1	3
Black	16	20
White	169	148
Hispanic	10	4
Polynes.	0	1
Body weight (kg) mean	88.6	82.7

All 3 arms consisted of a comparable population in terms of weight and age.

Additionally, the MO's population was sufficiently similar to that of the sponsor so that a separate analysis of smokers was not provided.

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 not always adhered to

The MO ascertained through review of the line listings, that 32/196(18.4%) of the MO evaluable trovafloxacin-100 patients, and 40/176 (14.7%) of the MO evaluable clarithromycin patients received systemic steroids during the study.

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

EFFICACY:

Table 109.13
Clinical Response by Patient (as per the MO):

	Trovafloxacin			Clarithromycin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	196	174	88.8	176	148	84.1
EOS	**196**	**157**	**80.1**	**176**	**129**	**73.3**

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

EOT: Trovafloxacin versus Clarithromycin: - 2.8%, 12.2% ($\Delta = 10$)

EOS: Trovafloxacin versus Clarithromycin: - 2.3%, 15.9% ($\Delta = 15$)

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Thus, the MO's results mirrored those of the sponsor in that trovafloxacin was equivalent to clarithromycin at the EOS (MO TOC), for the primary efficacy variable of clinical response. Additionally, trovafloxacin was numerically superior to clarithromycin at the EOT. There were 39 failures on the trovafloxacin arm as compared to 47 on the clarithromycin arm at the EOS, as compared to 22 and 28 per arm respectively, at the EOT.

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

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Table 109.14
Clinical Response at EOS by Patient Excluding Patients on Systemic Steroids (as per MO):

	Trovafloxacin-100			Clarithromycin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	164	149	90.8	136	113	83
EOS	**164**	**137**	**83.5**	**136**	**108**	**79.4**

The 95% CI with continuity correction factor was:

EOT: Trovafloxacin versus Clarithromycin: - 6.9%, 7.7% ($\Delta = 10$)

EOS: Trovafloxacin versus Clarithromycin: - 5.4%, 13.7% ($\Delta = 15$)

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Based on this analysis, trovafloxacin was again equivalent to clarithromycin at both timepoints.

20/32 (62.5%) of the trovafloxacin-treated patients on systemic steroids as compared to 21/40 on the clarithromycin arm were clinical cures. Therefore 12 of the 39 (30.7%) failures on the trovafloxacin arm and 19 of the 47 failures (40.4%) on the clarithromycin arm were in patients on systemic steroid therapy.

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

Clinical Response by Baseline Pathogen:

Table 109.15
Clinical Response by Baseline Pathogen at the EOT and EOS (as per MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	25	23	92	16	14	87.5
	EOS	25	23	92	16	7	43.7
Moraxella catarrhalis	EOT	17	13	76.5	19	15	78.9
	EOS	17	12	70.5	19	14	73.6
Streptococcus pneumoniae	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9
Haemophilus parahaemolyticus	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
Haemophilus parainfluenzae	EOT	6	6	100	7	6	85.7
	EOS	6	6	100	7	6	85.7
Klebsiella pneumoniae	EOT	5	5	100	7	7	100
	EOS	5	4	80	7	7	100
Pseudomonas aeruginosa	EOT	14	13	92.8	8	8	100
	EOS	14	10	71.4	8	7	87.5
Citrobacter amalonaticus	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Mycoplasma pneumoniae	EOT	6	6	100	2	2	100
	EOS	6	5	83.3	2	2	100
Chlamydia pneumoniae	EOT	8	7	87.5	4	3	75
	EOS	8	5	62.5	4	3	75
Klebsiella spp.	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Neisseria Meningitidis	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Pasteurella Multocida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Proteus Mirabilis	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Proteus spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pseudomonas putida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Serratia marcescens	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
Staphylococcus aureus	EOT	13	12	92.3	12	10	83.3
	EOS	13	11	84.6	12	9	75
Streptococcus pyogenes	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Xanthomonas maltophilia	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	**EOT**	**111**	**102**	**91.8**	**98**	**83**	**84.6**
	EOS	**111**	**93**	**83.7**	**98**	**76**	**77.5**

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

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

Table 109.16
Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Main Pathogens Only: As per MO)

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Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	25	23	92	16	14	87.5
	EOS	25	23	92	16	7	43.7
Moraxella catarrhalis	EOT	17	13	76.5	19	15	78.9
	EOS	17	12	70.5	19	14	73.6
Streptococcus pneumoniae	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9

As above, in this smaller analysis, trovafloxacin was numerically superior to clarithromycin in patients with *Haemophilus influenzae* at baseline, both at the EOT and the EOS. The difference between the 2 agents at the EOS is striking and the MO's analysis confirmed that of the sponsor. Clinical response in patients with *Streptococcus pneumoniae* at baseline was slightly better at the EOT but slightly worse at the EOS with trovafloxacin numerically superior to clarithromycin at the EOT but not the EOS. Clarithromycin was numerically superior to trovafloxacin in patients with *Moraxella catarrhalis* at baseline at both timepoints. The total clinical response rates for the 3 main pathogens were:

Trovafloxacin EOT: 43/49 (87.7%) and EOS: 41/49 (83.6%)
Clarithromycin EOT: 39/46 (84.7%) and EOS: 31/46 (67.3%)

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Bacteriological Response:

Pathogen Eradication Rates at EOT and EOS as per the MO can be seen table 109.17:

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Table 109.17
Pathogen Eradication Rates at the EOT and EOS (as per the MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	25	23	92	16	12	89
	EOS	25	22	88	16	10	62.5
Moraxella catarrhalis	EOT	17	13	76.5	18	17	94
	EOS	17	13	76.5	18	16	89
Streptococcus pneumoniae	EOT	7	6	85.7	11	11	100
	EOS	7	7	100	11	11	100
Haemophilus parahaemolyticus	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
Haemophilus parainfluenzae	EOT	6	6	100	6	6	100
	EOS	6	6	100	7	7	100
Klebsiella pneumoniae	EOT	5	5	100	7	5	71
	EOS	5	4	80	7	6	83
Pseudomonas aeruginosa	EOT	13	9	69	8	6	75
	EOS	14	9	64	8	6	75
Citrobacter amalonaticus	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Mycoplasma pneumoniae	EOT	6	6	100	2	2	100
	EOS	6	6	100	2	2	100
Chlamydia pneumoniae	EOT	8	7	84.5	4	3	75
	EOS	8	5	62.5	4	3	75
Klebsiella spp.	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Neisseria Meningitidis	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Pasteurella Multocida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Proteus Mirabilis	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Proteus spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Pseudomonas putida	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Serratia marcescens	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
Staphylococcus aureus	EOT	13	13	100	12	12	100
	EOS	13	13	84.6	12	11	92
Streptococcus pyogenes	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Xanthomonas maltophilia	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	**EOT**	**109**	**98**	**90**	**87**	**76**	**87.3**
	EOS	**111**	**94**	**84.6**	**97**	**81**	**83.5**

As can be appreciated from table 109.17, the overall pathogen eradication rates were numerically comparable at the EOT and EOS, with numerical superiority of trovafloxacin versus clarithromycin at both timepoints. The MO's results resemble those of the sponsor, with minor differences. However equivalence was shown between the 2 agents at the EOS for this second primary efficacy variable (as defined in the protocol).

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

Table 109.18

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

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	25	23	92	16	12	89
	EOS	25	22	88	16	10	62.5
Moraxella catarrhalis	EOT	17	13	76.5	18	17	94
	EOS	17	13	76.5	18	16	89
Streptococcus pneumoniae	EOT	7	6	85.7	11	11	100
	EOS	7	7	100	11	11	100

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Trovafloxacin EOT: 42/49 (85.7%) and EOS: 42/49 (85.7%)
Clarithromycin EOT: 40/45 (89%) and EOS: 37/45 (82.2%)

As in the sponsor's analysis, the MO also appreciated the significant decrease in the eradication rate of clarithromycin vs., *Haemophilus influenzae* at the EOS. The lower eradication rate should also be pointed out for trovafloxacin vs. *Moraxella catarrhalis* as compared to clarithromycin at both timepoints.

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Pathogen Eradication Rates and Systemic Steroid Usage:

13 of the baseline pathogens on the trovafloxacin arm and 25 on the clarithromycin arm were from patients on systemic steroids with 10/13 (77%) and 20/25 (80%) eradication per arm respectively, at the EOS.

The 3 persistent organisms on the trovafloxacin arm were one each: *Chlamydia pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

The 5 persistent isolates on the clarithromycin arm were 2 *Haemophilus influenzae* and 1 each: *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

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

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

Thus, equivalence was again shown between the 2 agents at the EOS. Additionally, the rates are comparable to those attained when the systemic steroid users were included in the analysis.

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

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Trovafloxacin:
Streptococcus pneumoniae: 6/6 (100%)
Haemophilus influenzae: 22/25 (88%)

Moraxella catarrhalis: 11/14 (78.5%)

Clarithromycin:
Streptococcus pneumoniae: 9/9 (100%)
Haemophilus influenzae: 8/12 (66.7%)
Moraxella catarrhalis: 11/12 (91.7%)

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 5 patients, (3 clinical successes with persistence of the baseline pathogen and 2 clinical failure with eradication). The clinical successes had 1 each: *Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa.* The clinical failures with eradication both had *Staphylococcus aureus* at baseline.

On the clarithromycin arm, there were 11 patients with inconsistent results (5 patients with clinical success and bacteriologic persistence and 6 with clinical failure and eradication). 2 of the clinical successes had *Haemophilus influenzae* at baseline, 2 had *Klebsiella pneumoniae*, and 1 had *Pseudomonas aeruginosa.* 3 of the clinical failures with eradication had *Haemophilus influenzae*, 2 had *Staphylococcus aureus,* and 1 had *Haemophilus parainfluenzae.*

The MO reviewed the PIDs of these patients previously.

Safety Review:

85/210 (40%) trovafloxacin subjects and 101/200 (51%) clarithromycin subjects had at least one AE, (all causality). 4/210 (2%) trovafloxacin patients and 8/200 (4%) clarithromycin patients discontinued therapy because of an adverse event. 3 of the discontinuations on the trovafloxacin arm and 6 on the clarithromycin arm were determined to be related to the study drug. An additional clarithromycin patient (#50760221) was discontinued because of an adverse event (atrial fibrillation secondary to exacerbation of CHF) that was not considered to be treatment-related by the investigator and was not included in the summary tables.

The most common adverse events leading to discontinuation on the trovafloxacin arm were related to the gastrointestinal system. 2/210 subjects (1%) were discontinued because of nausea and 1 patient was discontinued because of an event assosciated with the central nervous and peripheral nervous systems (vertigo). One additional patient discontinued therapy because of an exacerbation of COPD (#51810561)

On the clarithromycin arm the system most affected and leading to discontinuation was the gastrointestinal with 5/200 (3%) discontinued because of nausea, vomiting, and diarrhea). 2 of these 5 also had 'other" events, 1 with taste perversion and 1 with an injury. In addition, 1 subject each was discontinued because of respiratory decompensation, generalized pain, and urticarial rash.

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 109.19
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin	Clarithromycin
Number of Subjects Treated	210 (100%)	200 (100%)
Subject-Days of Exposure	1440	1339
Subjects With At Least One Event	85 (40%)	101 (51%)
Number of Adverse Events	145	205
Subjects with Serious Adverse Events	1 (<1%)	6 (3%)
Subjects with Severe Adverse Events	5 (2%)	13 (7%)
Subjects Discontinued Due to Adverse Events	4 (2%)	8 (4%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0
Subjects Discontinued Due to Objective Test Findings	1 (<1%)	2 (1%)
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

Table 109.20
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Trovafloxacin	Clarithromycin
Evaluable for Adverse Events	210 (100%)	200 (100%)
Subjects With At Least One Event	85 (40%)	101 (51%)
Subjects Discontinued due to Adverse Event	4 (2%)	8 (4%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	5 (2%)	6 (3%)
Cardiovascular	1 (<1%)	7 (4%)
Centr. & Periph. Nerv.	36(17%)	23 (12%)
Gastrointestinal	26(12%)	47 (24%)
General	9 (4%)	13 (7%)
Hematopoietic	2 (1%)	1(< 1%)
Musculoskeletal	2 (3%)	0
Other Adverse Events	2 (3%)	1(< 1%)
Psychiatric	1(<1%)	0
Metabolic	9 (4%)	17 (9%)
Respiratory	0	1 (<1%)
Skin/ Appendages	20 (10%)	17 (9%)
Special Senses	8 (4%)	11 (6%)
Insertion site	10 (5%)	32 (16%)
Urinary Tract	0	1 (<1%)
	3 (1%)	0

Table 109.21
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin	Clarithromycin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	210 (100%)	200 (100%)
Subjects With At Least One Event	42 (20%)	76 (38%)
Subjects Discontinued due to Adverse Event	3 (1%)	6 (6%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	4 (2%)	4 (2%)
Cardiovascular	-	1 (< 1%)
Centr. & Periph. Nerv.	18 (9%)	12 (6%)
Gastrointestinal	15 (7%)	40 (20%)
General	2 (<1%)	5 (3%)
Psychiatric	7 (3%)	7 (4%)
Skin/ Appendages	2 (<1%)	5 (3%)
Special Senses	4 (2%)	31 (16%)

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 trovafloxacin patients as compared to the clarithromycin patients; however, the incidence of GI events was higher on the clarithromycin arm.

The further breakdown of these events can be found in the MO's Table 109.22

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Table 109.22
Most Common CNS and GI AEs/Treatment-related/All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin N = 210		Clarithromycin N = 200	
	42	20%	76	38%
Nervous system				
Headache	7	3%	2	1%
Dizziness	6	3%	5	3%
Vertigo	3	1%	4	2%
GI System				
Nausea	11	5%	18	9%
Vomiting	-	-	5	3%
Constipation	-	-	5	3%
Diarrhea	1	< 1%	16	8%

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Other events of note included:

Dry mouth in 1 (<1%) trovafloxacin patient and 3 (2%) of the clarithromycin patients.

Insomnia in 5 (3%) of the clarithromycin and 2 (< 1%) of the trovafloxacin patients.

Taste perversion on 4 (2%) of the trovafloxacin and 31 (16%) of the clarithromycin patients.

Moniliasis in 1 (<1%) trovafloxacin patient and 4 (2%) clarithromycin patients.

Serious Adverse Events:

3 trovafloxacin-treated subjects and 11 clarithromycin-treated subjects had serious adverse events.

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

Trovafloxacin (N= 3):

- #50820089: post-treatment (day 16), exacerbation of COPD, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #50950097: post-treatment (day 21), exacerbation of bronchitis with bronchospasm, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51810561: exacerbation of COPD day 3, patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.

Clarithromycin (N = 11):

- #50050391: acute pneumothorax study day 1 secondary to underlying bullous lung disease. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- #50220524: respiratory failure day 2, secondary to pneumonia. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- #50790061: nausea and vomiting, day 6, related to the study drug. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- #50760221: atrial fibrillation day 3 secondary to underlying CHF. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- # 50950098: post-treatment (day 31), exacerbation of COPD, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51300377: exacerbation of angina day 6. Patient was hospitalized and study medication continued. Event was considered unrelated to the study medication and resolved with therapy.
- #51320375: Aspiration and death secondary to cardiac arrest day 104 (97 days after therapy). Considered unrelated to the study drug.

- #51370426: post-treatment (day 10), exacerbation of bronchitis with bronchospasm, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51390397: post-treatment (day 11), exacerbation of bronchitis with bronchospasm, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51380397; post-treatment fever (day 23). No etiology, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

- #51390445: post-treatment (day 31), exacerbation of bronchitis and depression, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

- #54990540: cerebral vascular accident day 20. Patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

Deaths: There was one death on the clarithromycin arm, patient #51320375: a 76 YO male with a history of cardiovascular disease, sinus infections, peptic ulcer disease, and AECB. Developed pulmonary aspiration and death, 97 days post-therapy. No further information was provided and the event appeared unrelated to the study drug, clarithromycin.

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

Clinical Laboratory Abnormalities:

The sponsor submitted tables 4.1, 4.2, 6.1, and 3.3, all of which contain listings of patients who discontinued therapy because of abnormalities.

The sponsor's text has been copied from page 55 of the study report:

One subject in each treatment group was discontinued from treatment due to abnormal laboratory results (objective test finding), as summarized in the following narratives.

Trovafloxacin 100 mg Group

Subject 5042-0165, a 40 year-old white female with a history of non-thrombocytopenic purpuras, non-infectious gastroenteritis/colitis, rheumatism, and involuntary movements of limbs, received trovafloxacin 100 mg daily for 3 days (Days 1 - 3) for acute bacterial exacerbation of chronic bronchitis. On Day 1, the subject was diagnosed with severe thrombocytopenia (platelets:). The subject's platelet counts remained low on Day at which time the subject was discontinued from treatment, and at the follow-up visit on Day 30 This subject's thrombocytopenia was determined to have an unknown etiology.

Clarithromycin 500 mg BID Group

Subject 5095-0101, a 47 year-old white female with a history of hypertension, received clarithromycin 500 mg twice daily for 2 days (Days 1 and 2) and once daily for 1 day (Day 3) for acute bacterial exacerbation of chronic bronchitis. On Day 1, the subject had elevated SGOT , SGPT , and alkaline phosphatase levels. On Day 3, the subject was discontinued from treatment due to these abnormal laboratory values. Each of these laboratory parameters was within the normal range on Day 8 (SGOT ; SGPT, alkaline phosphatase,) and at the follow-up visit on Day 31 (SGOT, ; SGPT, alkaline phosphatase,). This subject's laboratory abnormalities were determined to have an unknown etiology.

Clinically significant post-baseline laboratory abnormalities were observed for 14% (28/204) of subjects in the trovafloxacin group and 13% (25/189) of subjects in the clarithromycin group.

No subject in either group had a clinically significant alanine aminotransferase value (SGPT).

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.