Medical Officer's Efficacy Analysis:

On July 31, 1997, the sponsor faxed partial tables and listings of the MO evaluable population, in accordance with the evaluability criteria laid out previously. The MO ascertained that all of the patients that the MO had requested excluded from the analyses because they did not have an EOS visit, (4) were excluded. 1 trovafloxacin-100 patient, #50590263 was not excluded but carried forward as an evaluable failure at the MO's request. The MO changed the outcome on 1 patient #50590259 to a clinical failure. The MO's evaluable population can be seen in table 101.7. Although the MO had the same # of patients evaluable on the trovafloxacin-100 arm, as the sponsor, these were not the same patients (see demographics).

Table 101.7
Clinically Evaluable Population (as per the MO)

Reason for exclusion	**Trovafloxacin- 100**	**Trovafloxacin- 300**	**Ofloxacin**
Total Randomized	N= 221		
Total Treated	N=73	N=75	N =73
Sponsor Evaluable	65	58	62
MO Excluded			
No EOS Visit	-	3	1
Antimicrobial R/x	-	1	-
Total Evaluated at EOS	**65 (89%)**	**54 (72%)**	**61 (83.5%)**

The numbers of evaluable patients per arm at the EOT were 61, 49, and 57, respectively. There were fewer patients at the EOT because the MO accepted patients in the FDA evaluable population who did not have an EOT evaluation but did have an EOS.

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 101.8:

Table 101.8
Clinically Evaluable Population by Center (as per MO)

			Trovafloxacin 100 mg				Trovafloxacin 300 mg				Ofloxacin 400 mg b. i. d.			
Center	Total Randomized N =223	(100%)	Sponsor Eval. N = 65	(100%)	MO Eval. N= 65	(100%)	Sponsor Eval. N = 58	(100%)	MO Eval. N= 54	(100%)	Sponsor Eval. N = 62	(100%)	MO Eval. N= 61	(100%)
5015	18	8.1	6	9.2	6	9.2	6	10.3	6	11.1	6	9.7	6	9.8
5016	1	0.4	0	-	0	-	0	-	0	-	0	-	0	-
5017	8	3.5	2	3.1	2	3.1	3	5.2	2	3.7	1	1.6	1	1.6
5018	16	7.0	4	6.2	4	6.2	3	5.2	2	3.7	5	8.1	5	8.2
5019	8	3.5	2	3.1	2	3.1	1	1.7	1	1.9	2	3.2	2	3.3
5021	13	5.8	4	6.2	4	6.2	4	6.9	4	7.4	2	3.2	2	3.3
5022	11	4.9	3	4.6	3	4.6	2	3.4	2	3.7	3	4.8	3	4.9
5023	4	1.8	1	1.5	1	1.5	0	-	0	-	1	1.6	1	1.6
5026	3	1.3	0	-	0	-	2	3.4	2	3.7	1	1.6	1	1.6
5033	4	1.8	0	-	0	-	2	3.4	1	1.9	1	1.6	1	1.6
5034	66	29.5	22	33.8	22	33.8	20	34.5	20	37	20	32.3	20	32.8
5047	4	1.8	1	1.5	1	1.5	1	1.7	1	1.9	1	1.6	1	1.6
5048	2	0.8	0	-	0	-	1	1.7	1	1.9	0	-	0	-
5051	4	1.8	1	1.5	1	1.5	0	-	0	-	2	3.2	2	3.3
5053	1	0.4	0	-	0	-	0	-	0	-	1	1.6	1	1.6
5054	1	0.4	0	-	0	-	0	-	0	-	0	-	0	-
5055	23	10.3	8	12.3	8	12.3	6	10.3	6	11.1	7	11.3	7	11.5
5056	4	1.8	1	1.5	1	1.5	1	1.7	1	1.9	1	1.6	1	1.6
5057	12	5.4	4	6.2	4	6.2	2	3.4	2	3.7	3	4.8	4	4.9
5058	5	2.5	2	3.1	2	3.1	1	1.7	1	1.9	1	1.6	1	1.6
5059	5	2.5	2	3.1	2	3.1	1	1.7	1	1.9	1	1.6	1	1.6
5060	10	5.0	2	3.1	2	3.1	2	3.4	1	1.9	3	4.8	2	3.3

Approximately 30% of the patients per arm were from center 5034. However, the number of patients in this study was very small and therefore all centers were pooled.

The demographics of the FDA evaluable population can be seen in Table 101.9.

Table 101.9
Demographic Characteristics of the FDA Evaluable Population:

Characteristics		Trovafloxacin-100 N = 65	Trovafloxacin-300 N = 54	Ofloxacin N = 61
Sex	(Female)	30	22	30
	(Male)	35	32	31
Age (years)	16 -44	23	21	20
	45 - 64	27	18	27
	≥ 65	15	15	14
	Mean	50.2	48.9	50.1
Race:	Asian	0	0	0
	Black	1	1	1
	White	63	53	57
	Hispanic	1	0	3
	Nat Am.	0	0	0
Body weight (kg) mean		77.5	78.2	76.9

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

Concomitant Medications:

The MO elected not to exclude patients who had been on steroids during this study. The MO's rationale was that this was a Phase II pilot study and that the number of the evaluable patients per arm on systemic steroids was proportionate. 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 MO ascertained through review of the line listings, that 12/65(18.4%) of the MO evaluable trovafloxacin-100 patients, 5/54 (9.2%) of the evaluable trovafloxacin-300 patients and 9/61 (14.7%) of the MO evaluable ofloxacin patients received systemic steroids.

6 patients on the trovafloxacin-100 arm were started on systemic steroids during the study as compared to 4 patients on the trovafloxacin-300 arm and 2 on the ofloxacin arm. The remainder had been on steroids prior to the study and continued throughout.

Of the 12 trovafloxacin-100 patients on steroids, 9 were clinically cured and 3 were failures (2 failures and 4 cures started during the study). On the trovafloxacin-300 arm, all 5 of the patients on steroids were clinical cures (4 started during the study). Of the 9 ofloxacin patients on steroids, 6 were clinical cures and 3 were failures (1 failure and 1 cure started steroids during the study).

The MO requested that a separate clinical efficacy analysis be performed excluding these patients. For accounting purposes, these patients were listed below with their clinical outcome and the time that systemic steroids were started.

Trovafloxacin-100 (N =12)

#50180086: cure, during
#50210101: cure, during
#50220050: cure, during
#50220052: cure, during
#50230040: cure, pretherapy
#50470136: failure, during
#50550270: cure, pretherapy
#50560175: cure, pretherapy
#50570189: cure, pretherapy
#50580205: failure, during
#50580208: failure, pretherapy
#50590263: failure, pretherapy

Trovafloxacin-300 (N = 5)

#50210102: cure, during
#50260026: cure, pretherapy
#50250027: cure, during
#50340236: cure, during
#50470133: cure, during

Ofloxacin (N = 9)

#50150069: cure, during
#58180085: cure, pretherapy
350180087: failure, during

#50180249: cure, pretherapy
#50230038: failure, pretherapy
#50260025: failure, pretherapy
#50570255: cure, pretherapy
#50570258: cure, pretherapy
#50600295: cure, pretherapy

Although, the MO did not exclude these patients from tables 101.7 and 101.8, a separate analysis of clinical efficacy was performed after their exclusion. In the analyses where they were excluded, the number of evaluable patients would be 53 trovafloxacin-100, 49 trovafloxacin-300, and 52 ofloxacin at the EOS.

EFFICACY:

Table 101.10
Clinical Response by Patient (as per the MO):

	Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOT	61	58	95	49	48	98	57	55	96.4
EOS	**65**	**57**	**87.7**	**54**	**52**	**96.3**	**61**	**57**	**93.4**

The MO and the FDA statistician, Dr. Nancy Silliman, applied a 95% CI using stat xact-3 to these results and found the following:

EOT: Trovafloxacin-100 versus Trovafloxacin-300: - 16.4%, 10.1% ($\Delta = 10$):
Trovafloxacin-100 versus Ofloxacin: - 15.2%, 10.7% ($\Delta = 10$)
Trovafloxacin-300 versus Ofloxacin: - 11.4%, 15.0% ($\Delta = 10$)

EOS: Trovafloxacin-100 versus Trovafloxacin-300: - 23.8%, 5.1% ($\Delta = 10$)
Trovafloxacin-100 versus Ofloxacin: - 21.1%, 7.9% ($\Delta = 10$)
Trovafloxacin-300 versus Ofloxacin: - 10.3%, 17.1% ($\Delta = 10$)

Thus, the MO's results mirrored those of the sponsor in that trovafloxacin-100 was NOT equivalent to either of the 2 other arms at the EOS for the primary efficacy variable of clinical response, and trovafloxacin-300 was marginally equivalent to ofloxacin.

At the EOT, the trovafloxacin-100 arm was marginally equivalent to the ofloxacin arm. As in the sponsor's analysis, trovafloxacin-300 was equivalent to ofloxacin at the EOT.

At the EOS, trovafloxacin-300 was equivalent to ofloxacin but trovafloxacin-100 was NOT equivalent to either comparator arm.

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

Table 101.11
Clinical Response at EOS by Patient Excluding Patients on Systemic Steroids (as per MO):

	Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOS	53	49	92.5	49	47	95.9	52	51	98.1

The 95% CI using the previously applied exact method was:

EOS: Trovafloxacin-100 versus Trovafloxacin-300: -19.6%, 10.8% (Δ = 10)
Trovafloxacin-100 versus Ofloxacin: - 21.6%, 6.9% (Δ = 10)
Trovafloxacin-300 versus Ofloxacin: - 16.7%, 10.8% (Δ = 10)

Based on this analysis, neither trovafloxacin-100 nor trovafloxacin-300 was equivalent to ofloxacin. These results essentially mirror those of the total population.

The MO does qualify the above by stating that this was a small pilot study, not adequately powered and that 3 arms were numerically comparable.

Clinical Response by Baseline Pathogen:

Table 101.12
Clinical Response by Baseline Pathogen at the EOT and EOS (as per MO)

Pathogen		Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
		N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	12	12	100	7	7	100	6	6	100
	EOS	13	12	92.3	9	9	100	6	4	67
Moraxella catarrhalis	EOT	6	6	100	2	2	100	9	9	100
	EOS	6	5	83.3	2	2	100	9	9	100
Streptococcus pneumoniae	EOT	3	3	100	4	3	75	3	3	100
	EOS	3	2	67	5	4	80	3	3	100
Haemophilus parahaemolyticus	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
Haemophilus parainfluenzae	EOT	2	2	100	4	4	100	3	3	100
	EOS	2	2	100	4	4	100	3	3	100
Klebsiella pneumoniae	EOT	3	3	100	-	-	-	-	-	-
	EOS	4	4	100	-	-	-	-	-	-
Pseudomonas aeruginosa	EOT	1	1	100	1	1	100	3	2	67
	EOS	1	1	100	1	1	100	3	2	67
Haemophilus haemolyticus	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Mycoplasma pneumoniae	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Chlamydia pneumoniae	EOT	3	3	100	2	2	100	3	3	100
	EOS	4	3	75	2	2	100	3	3	100
Beta-hemolytic *streptococcus*	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	**EOT**	**32**	**32**	**100**	**25**	**25**	**100**	**27**	**26**	**96.2**
	EOS	**35**	**31**	**88.6**	**27**	**26**	**96.2**	**27**	**24**	**88.8**

The MO's results mirrored those of the sponsor. A 95% CI was not applied because of the small numbers. However, all 3 treatment arms were numerically comparable at the EOT. The 1 failure on the ofloxacin arm was due to a patient with a *Pseudomonas* isolate resistant to ofloxacin.

At the EOS, as in the sponsor's analysis, trovafloxacin-300 was superior to both comparators. Trovafloxacin-100 and ofloxacin appeared equal at the EOS. All failures were reviewed previously.

Bacteriological Response:

Pathogen Eradication Rates at EOT and EOS as per the MO can be seen table 101.13:

Table 101.13

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

		Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
Pathogen		N	No. Erad.	%	N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	12	12	100	6	6	100	5	5	100
	EOS	12	10	83.3	6	6	100	5	5	100
Moraxella catarrhalis	EOT	6	6	100	2	2	100	8	8	100
	EOS	6	6	100	2	2	100	8	8	100
Streptococcus pneumoniae	EOT	3	3	100	4	4	100	3	3	100
	EOS	3	2	67	4	4	100	3	3	100
Haemophilus parahaemolyticus	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
Haemophilus parainfluenzae	EOT	2	2	100	4	4	100	3	3	100
	EOS	2	2	100	4	4	100	3	3	100
Klebsiella pneumoniae	EOT	3	3	100	-	-	-	-	-	-
	EOS	3	3	100	-	-	-	-	-	-
Pseudomonas aeruginosa	EOT	1	1	100	1	1	100	3	2	67
	EOS	1	0	0	1	1	100	3	2	67
Haemophilus haemolyticus	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Beta-hemolytic *streptococcus*	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	**EOT**	**29**	**29**	**100**	**20**	**20**	**100**	**22**	**21**	**95.4**
	EOS	**29**	**25**	**86.2**	**20**	**20**	**100**	**22**	**21**	**95.4**

Once again all 3 treatment arms attained 100% efficacy at the EOT. At the EOS however, trovafloxacin-300 was numerically superior to ofloxacin and to trovafloxacin-100. Additionally, ofloxacin was numerically superior to trovafloxacin-100. The MO's results were similar to those of the sponsor. However, both trovafloxacin-300 and ofloxacin maintained almost 100% bacteriologic eradication rates at the EOS as compared to trovafloxacin-100. This loss of efficacy was not attributable to decreased eradication of any one pathogen but rather to 4 patients classified as clinical failures, with persistence or presumed persistence of their baseline pathogens, (2 isolates *Haemophilus influenzae*, 1 *Streptococcus pneumoniae* and 1 *Pseudomonas aeruginosa*).

Safety Review:

22/73 (30%) trovafloxacin-100 subjects, 52/75 (69%) of the trvofloxacin-300 subjects, and 25/73 (26%) ofloxacin subjects had at least one AE, (all causality). 4/73 (5%) trovafloxacin-100 patients, 19/75 (25%) trovafloxacin-300 patients, and 7/73 (10%) ofloxacin patients discontinued therapy because of an adverse event. All of the discontinuations on the trovafloxacin arms and 8 on the ofloxacin arm were determined to be related to the study drug. The remaining ofloxacin patient (#50210100) was discontinued because of an adverse event (exacerbation of COPD), that was not considered to be treatment-related by the investigator.

The most common adverse events leading to discontinuation on the trovafloxacin arms were related to the central nervous and peripheral nervous systems, with 3/73 (4%) subjects on the trovafloxacin-100 arm

discontinued because of headache or dizziness and 13/75 (17%) subjects on the trovafloxacin-300 arm discontinued because of dizziness, confusion, vertigo, tremor, headache, and/or abnormal gait.

On the trovafloxacin-300 arm, adverse events from the gastrointestinal system also led to discontinuation in 12/75 (16%) subjects. These events included nausea, vomiting, diarrhea, dyspepsia, abdominal pain, and/or gastritis. This is compared to 1/73 (1%) subjects on the trovafloxacin-100 arm who discontinued because of nausea, vomiting, diarrhea, and gingivitis.

On the ofloxacin arm the system most affected and leading to discontinuation was the psychiatric, with 4/73 (5%) subjects discontinued because of insomnia, impaired concentration, or nervousness.

Adverse events from the gastrointestinal tract occurred in 2/73 (3%) subjects on the ofloxacin arm, (abdominal pain, nausea, and/or vomiting).

No subjects were temporarily discontinued from therapy due to adverse events on the trovafloxacin arms. 1/73 (1%) subjects on the ofloxacin arm were temporarily discontinued because of dyspepsia (#50570203).

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 101.14
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
Number of Subjects Treated	73 (100%)	75 (100%)	73 (100%)
Subject-Months of Exposure	24	23.4	22.3
Subjects With At Least One Event	22 (30%)	52 (69%)	26 (36%)
Number of Adverse Events	44	124	47
Subjects with Serious Adverse Events	0	0	1
Subjects with Severe Adverse Events	4 (5%)	4 (5%)	5 (7%)
Subjects Discontinued Due to Adverse Events	4 (5%)	19 (25%)	7 (10%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0	1 (1%)
Subjects Discontinued Due to Objective Test Findings	0	0	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0	0

Table 101.15
Adverse Events by Body System, All Causality (Modified Table of Sponsor Table 6.2)

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
Evaluable for Adverse Events	73 (100%)	75 (100%)	73 (100%)
Subjects With At Least One Event	22 (30%)	52 (69%)	26 (36%)
Subjects Discontinued due to Adverse Event	4 (5%)	19 (25%)	7 (10%)
ADVERSE EVENTS BY BODY SYSTEM:			
Autonomic Nervous	1 (1%)	7 (9%)	1 (1%)
Cardiovascular	1 (1%)	3 (4%)	4 (5%)
Centr. & Periph. Nerv.	8 (11%)	38 (57%)	10 (14%)
Gastrointestinal	9 (12%	27 (36%)	10 (14%)
General	2 (3%)	7 (9%)	2 (3%)
Liver/Biliary	2 (3%)	0	0
Musculoskeletal	2 (3%)	1 (1%)	0
Other Adverse Events	0	1 (1%)	0
Psychiatric	2 (3%0	4 (5%)	9 (12%0
Reproductive	3 (4%)	0	1 (1%)
Respiratory	3 (4%)	3 (4%)	3 (4%)
Skin/ Appendages	1 (1%)	4 (5%)	1 (1%)
Special Senses	2 (3%)	7 (9%)	2 (3%)

Table 101.16
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
NUMBER OF SUBJECTS:			
Evaluable for Adverse Events	73 (100%)	75 (100%)	73 (100%)
Subjects With At Least One Event	10 (14%)	46 (61%)	21 (29%)
Subjects Discontinued due to Adverse Event	4 (5%)	19 (25%)	6 (85)
ADVERSE EVENTS BY BODY SYSTEM:			
Autonomic Nervous	1 (1%)	7 (9%)	-
Cardiovascular	-	3 (4%)	-
Centr. & Periph. Nerv.	3 (4%)	34 (45%)	9 (12%)
Gastrointestinal	4 (5%)	24 (32%0	8 (11%)
General	-	5 (7%)	-
Psychiatric	1 (1%)	2 (3%)	9 (12%)
Skin/ Appendages	1 (1%)	4 (5%)	1 (1%)
Special Senses	2 (3%)	7 (9%)	2 (3%)
Liver/Biliary	1 (150	-	-
Musculoskeletal	-	1 (1%)	-
Reproductive	-	1 (1%)	1 (1%)
Respiratory	-	4 (5%)	-

Overall, and as noted in previous trials, the most frequent AEs were from the CNS and GI systems. The % of nervous system AEs was approximately five times as high for the trovafloxacin-300 patients as compared to the ofloxacin, and ten times as high as compared to the trovafloxacin-100 arm. However, the incidence of these events on the ofloxacin arm was three times that of the trovafloxacin-100 arm.

BEST POSSIBLE COPY

There was also a significantly higher incidence of GI-related AEs on the trovafloxacin –300 arm as compared to the trovaflocacin-100 and the ofloxacin arms. However, the incidence of these events was higher on the ofloxacin arm as compared to the trovafloxacin-100 arm.

The further breakdown of these events can be found on the MO's Table 101.17.

Table 101.17
Most Common CNS and GI AEs/Treatment-related/All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin-100 N = 73 10	14%	Trovafloxacin-300 N = 75 46 (61%)		Ofloxacin N = 73 21 (29%)	
Nervous system						
Headache	2	3%	7	9%	1	1%
Dizziness	3	4%	28	37%	7	10%
GI System						
Nausea	2	3%	11	15%	3	4%
Vomiting	1	1%	7	9%	2	3%
Dyspepsia	1	1%	3	4%	1	1%
Diarrhea	2	3%	1	1%	-	-
Abdominal Pain	-	-	4	4%	2	3%
Increased Appetite	-	-	2	3%	-	-

Other events of note included:

Flushing and sweating in 1% of the trovafloxacin-100 patients, 4% of the trovafloxacin-300 patients, and none of the ofloxacin patients.

Fatigue in 7% of the trovafloxacin-300 patients and none of the trovafloxacin-100 and ofloxacin patients.

Insomnia in 10% of the ofloxacin and none of the trovafloxacin-300 or trovafloxacin-100 patients.

Pruritus in 1% of the trovafloxacin-100, 5% of the trovafloxacin-300, and 1% of the ofloxacin patients.

Tinnitus in 1% of the trovafloxacin-100 and 3% of the trovafloxacin-300 patients.

Visual abnormalities in 1% of the trovafloxacin-100 and ofloxacin patients and 4% of the trovafloxacin-300 patients.

Overall, the AE profile in this trial was similar to that seen in the previously reviewed indications and no deaths were reported.

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

Trovafloxacin-100 (N= 2):

- #50340331: dizziness, day 1, therapy discontinued.
- #50560176: headache, day 3, therapy discontinued.

Trovafloxacin-300 (N =2):

- #50470134: flushing, tachycardia, dizziness, tremors, nausea, and vomiting, day 1, therapy discontinued.
- #50590261: lightheaded, day 3, therapy discontinued.

Ofloxacin (N = 4):

- #50210097: sleeplessness, day 1, therapy discontinued
- #50220051: abnormal vision, dizziness, day 3, therapy discontinued
- #50230039: insomnia, day 1, therapy discontinued
- #50340282: nervousness, day 7, therapy discontinued

Serious Adverse Events:

3 subjects had serious adverse events, one on the trovafloxacin-300 arm and 2 on the ofloxacin arm. None was considered related to therapy. In all cases the patients developed pneumonia after being discontinued from the study drugs for other adverse events within the first 2 days of therapy.

Clinical Laboratory Abnormalities:

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

The sponsor's text has been copied from page 40 of the study report:

The percentage of subjects with laboratory values that met the criteria for clinical significance during the study was ≤4% in all three treatment groups for individual laboratory parameters except erythrocyte sedimentation rate (ESR), triglycerides, urine white blood cells and urine red blood cells (trovafloxacin 100 mg and ofloxacin groups only).

For liver function parameters, the percentage of subjects with clinically significant abnormalities in alanine aminotransferase (SGPT, >2.0 x ULN), aspartate aminotransferase (SGOT, >2.0 x ULN), and lactate dehydrogenase (LDH, >2.0 x ULN) values was 1% (SGPT) in the trovafloxacin 100 mg group and 2% each for SGOT and LDH in the ofloxacin group. No other clinically significant liver function abnormalities were reported in any of the three treatment groups.

Medical Officer's Comment: *The MO reviewed table 3.3, appendix III, clinical laboratory abnormalities, and found the following:*

Trovafloxacin-100 (N = 2):

- *#50150070: increased serum creatinine after 10 days of therapy, remained elevated.* *Final value*
- *#50340246: increased ALT after 11 days of therapy.* *by the EOS.*

Trovafloxacin-300 (N = 1):

- *#50150311: increased serum creatinine after 10 days of therapy, remained elevated.* *Final value*

Ofloxacin (N = 2)

- *#50340230: increased AST after 9 days of therapy* *Final value remained elevated.*
- *#50340226: increased LDH after 11 days of therapy* *Final value had*

No other abnormalities were of significance as per the MO, including the ESR elevations which may have been due to the underlying disease process.

Conclusions:

As per the Sponsor:

The main portion of the sponsor's conclusion can be found at the conclusion of the sponsor's efficacy analysis. Before proceeding to the Phase III trials, the sponsor concluded:
(Copied from page 42 of the study report):

Trovafloxacin 100 mg or 300 mg and ofloxacin 400 mg BID were similar with respect to clinical response rates at the end of treatment and at the second follow-up evaluation for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment. At the second follow-up evaluation, bacteriologic relapses were observed in four subjects in the trovafloxacin 100 mg group. However, because of the small number of bacteriologically evaluable subjects in this treatment group (N=24), no definitive conclusions could be drawn. Both trovafloxacin 100 mg and 300 mg once daily were generally well tolerated; however, the incidence of adverse events in the 100 mg group was lower than that observed in the 300 mg group.

Reviewer's Conclusions:

Few conclusions could be drawn from this Phase II, pilot study comparing trovafloxacin 100 mg, trovafloxacin 300 mg, and ofloxacin in the treatment of AECB for 10 days. The study was not adequately powered to be able to ascertain true differences between the treatment arms.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 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. Equivalence was not shown between the trovafloxacin-100 arm and the ofloxacin 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.

Thus, the results for this variable were similar, whether or not patients on systemic steroids were included in the analyses.

The bacteriologic efficacy analysis yielded the following at the EOT, 29/29 (100%) for the trovfloxacin-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, can be seen in the table below:

Table 101.18
Bacteriologic Eradication Rates (as per the MO)

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

These results mirrored those of the sponsor.

There were no deaths in this study. The primary adverse events were from the central and peripheral nervous systems, and consisted of 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, equivalence was shown only for the trovafloxacin-300 arm versus the approved comparator, ofloxacin. Unfortunately, there was also a high incidence of adverse events on this arm. The trovafloxacin-100 arm was inferior to both comparator arms and additionally, at the EOS, the pathogen eradication rate decreased only for this arm.

Based on the above, no real conclusions could be drawn by the MO. The sponsor elected to proceed with the pivotal trials at the lower dose of trovafloxacin, 100 mg qd orally, for 7 days.

Study 154-109

TITLE:

A RANDOMIZED, DOUBLE BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study dates: November 16, 1994 – June 22, 1995

Objective: The objective of this study was to compare the safety and efficacy of trovafloxacin with clarithromycin in the treatment of subjects with acute exacerbation of chronic bronchitis.

List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5005	Willis Manfred Gooch, III, M.D.
	5011	Anthony Puopolo, M.D.
	5022	Lee Edward Payne, M.D.
	5032	Diana Dark, M.D.
	5041	Robert Fiddes, M.D.
	5042	J. Daniel Scott, M.D.
	5072	George Bensch, M.D.
	5073	Jean-Paul Bonnet, D.O.
	5074	Milan Brandon, M.D.
	5075	Edwin Bronsky, M.D.
	5076	Timothy Bruya, M.D.
	5077	Jacques Caldwell, M.D.
	5078	C. Andrew Deabate, M.D.
	5079	W. Travis Ellison, M.D.
	5080	Frank Garamy, Jr., M.D.
	5081	James Garofalo, M.D.
	5082	Mark Gotfried, M.D.
	5083	Robert Frost Jones, M.D.
	5084	Craig Laforce, M.D.
	5085	Thomas Littlejohn, III, M.D.
	5086	Michael Peveler, M.D.
	5087	Gary Post, M.D.
	5088	Robert Rosen, M.D.
	5089	David Stryker, M.D.
	5090	Alan Wanderer, M.D.
	5091	W. Murray Yarbrough, M.D.
	5092	William Ziering, M.D.
	5094	William McCall, Jr, M.D.
	5095	Robert Hippert, M.D.
	5121	Marcus Zervos, M.D.
	5124	Kent Anthony, M.D.
	5125	Steven Bowman, M.D.
	5127	Meera Dewan, M.D.
	5129	Jeffrey Hartford, M.D.
	5130	Spencer Jones, M.D.
	5132	Michael McAdoo, M.D.
	5133	Dennis Mikolich, M.D.
	5134	David Miller, D.O.

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	5135	Michael Nelson, M.D.
	5136	David Schreck, M.D.
	5137	Richard Sterling, M.D.
	5138	Randall Stoltz, M.D.
	5139	James Sullivan, M.D.
	5140	John Upchurch, M.D.
	5181	James Taylor, M.D.
	5213	Jason Chu, M.D.
	5215	George Knull, M.D.
	5250	Carlos Morales, M.D.
	5499	Harvey Tilker, Ph.D.
	5743	Boyd Harrison, M.D.
	5776	Daniel Krichbaum, PharmD.
	5777	Alan Rosenthal, PharmD.
	5853	Chandra Khurana, M.D.
	6428	Alan Storrow, M.D.

Study Design: Study 154-109 was a Phase III, randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg daily as a single dose in the morning), versus clarithromycin (1000 mg daily as 500 mg in the morning and evening), administered orally for 7 days for the treatment of AECB.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor's schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number	1	2	3	4
Study day:	Day 1	Day 4	Day 8	Day 28
Allowable Window:	-48 hours	Day 3-5	Day 7-9	Day 25-31
Treatment Period	Day 1 to Day 7			
Follow-up period	Day 8 to Day 31			
Informed consent	X			
Demographic Information	X			
Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record			X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X			
Microbiology				
Sputum Gm stain	X	X	X	X
culture & sensitivity	X	X	X	X
serology	X			X
Safety laboratory tests				
hematology	X		X	abn
biochemistry	X		X	abn
urinalysis	X		X	abn
Pregnancy test*	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's evaluation				
clinical		X	X	X

abn= abnormal at previous visit or clinically significant adverse event
*to be done by local site for women of child bearing potential

As noted from the above schedule, all baseline assessments were performed within the 48 hours prior to the start of the study.

At the baseline visit (V1, Day 1), all subjects were to have a clinical picture characterized by the following criteria:

- Clinical signs and symptoms of chronic bronchitis defined by the presence of cough, dyspnea, lung sounds (rales and rhonchi), and excessive secretion of mucus. Subjects were to have coughed up sputum on most days during three consecutive months for two or more successive years.

- Signs and symptoms characteristic of acute bacterial exacerbation, including increased dyspnea and increased sputum volume and purulence.

- Purulent sputum was to be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (LPF) [10X].

- The absence of pneumonia on chest x-ray.

Those patients who met the above definition and who gave informed consent were eligible for randomization, if they fulfilled the inclusion and exclusion criteria. Baseline visit assessments also included collection of demographic information, concurrent disease, medical history and physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature).

The clinical assessment of signs and symptoms of AECB was to include sputum characteristics, cough, dyspnea, lung sounds, and chest x-ray (unless one had been taken within 48 hours of the baseline assessment).

Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per LPF, squamous epithelial cells per LPF), of sputum were performed. Subjects with inadequate sputum specimens were not randomized and no further evaluation was performed. Hematology, serum chemistry, and urinalysis determinations were performed and serum was obtained at baseline for the determination of antibodies *to Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Susceptibility to the study drugs, trovafloxacin and clarithromycin, was determined from bacterial isolates grown from adequate sputum specimens. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. However, if no pathogen was detected on baseline culture, the continuation of the study drug was at the discretion of the investigator. If a pathogen was resistant to study medication, study treatment could have continued at the investigator's discretion, only if there was evidence of clinical improvement.

At Visits 2 (V2: Day 4) and 3 (V3: Day 8; EOT), a determination of clinical efficacy was performed. These determinations included clinical assessments of signs and symptoms of AECB and adequate sputum samples for culture and sensitivity to assess bacteriological response to study therapy. Safety was assessed through the recording of concomitant medication, vital signs, study drug dosing, and adverse events. At Visit 3, hematology, chemistry, and urinalysis tests were performed.

At Visit 4 (V4: Day 28; EOS) efficacy and safety observations were again performed as in V2 and V3 with the exception of the laboratory analyses which were only performed if a clinically significant abnormality was present at V3 (Day 8) or if the subject was experiencing a clinically significant adverse event. Final serology was performed at this visit and the investigator provided a final evaluation of clinical response.

Compliance:

This study was conducted in compliance with a local or central Institutional Review Board (IRB) and informed consent regulations.

Concomitant Illnesses and Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

Patients taking theophylline had levels monitored at each study visit. Subjects receiving warfarin had prothrombin time monitored at each study visit. Dose adjustments for theophylline or warfarin were made as clinically appropriate. The concomitant use of systemic corticosteroids was allowed in the form of 10 mg of prednisone or less daily. The use of other (non-anti-infective) medications was limited to those essential to the care of the subject. The use of any other investigational drug was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

Discontinuation of Study Therapy:

Discontinuations were allowed at the discretion of the investigator only if the patient showed no signs of clinical improvement or worsening before the EOT (V3).

Additionally, patients could discontinue therapy if they developed an adverse event or a clinically significant laboratory abnormality.

The reason for discontinuation was recorded on the CRF and the patient followed through the EOS, if possible. The investigator made a final evaluation at the time of discontinuation.

Protocol Amendments:

This protocol was amended once on October 11, 1994, as detailed below:

- Subjects receiving treatment with terfenadine or who may have required treatment were excluded from study enrollment.
- Monitoring procedures for subjects who took theophylline during the study were specified.

Precautions:

Because clarithromycin may raise theophylline levels, all subjects on concomitant theophylline were to have had serum theophylline levels monitored periodically at a local laboratory. Subjects were also instructed not to donate blood during the study or for one month after the end of the study.

Study Population:

Approximately 400 subjects with acute exacerbation of chronic bronchitis were expected to be randomized to one of the treatment groups. Each study site attempted to enrol at least 10 patients.

Inclusion and Exclusion Criteria:
(Copied from page 16 of the original protocol)

Inclusion criteria

1. Age ≥ 40 at baseline.

2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or ≤ one year post-menopausal) must have a negative urine gonadotrophin pregnancy test immediately prior to entry in the study and must use adequate contraception both during and for one month after the end of the study.

3. Clinically documented acute exacerbation of chronic bronchitis. Diagnostic criteria for chronic bronchitis will include sputum production on most days during three

consecutive months for two or more successive years. The criteria for an acute exacerbation is defined as the presence of increased dyspnea, sputum volume and sputum purulence.

4. Purulent sputum must be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (10X).

5. Written informed consent must be obtained.

Exclusion Criteria

1. Pregnant women or nursing mothers.

2. Known hypersensitivity to any quinolone or macrolide antibiotic.

3. Subjects who are currently hospitalized for any reason.

4. Treatment with any other systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit.

5. Subjects with infections that may require treatment with an antibiotic other than the study drugs.

6. Subjects with any of the following conditions:

   a. pulmonary disease whose severity is sufficient to warrant initial intravenous antibiotic therapy
   b. evidence of pneumonia on chest X-ray
   c. cystic fibrosis
   d. significant gastrointestinal or other conditions which may affect study drug absorption.
   e. known Acquired Immunodeficiency Syndrome (AIDS)
   f. neutropenia, defined as a total white blood cell count less than 2500 leukocytes/mm^3 or absolute neutrophil count less than 1000/mm^3
   g. immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including treatment with greater than 10 mg/day of systemic prednisone or equivalent)
   h. history of epilepsy or seizures

7. Treatment with another investigational drug within four weeks prior to the baseline visit.

8. Prior enrollment in this protocol.

9. Evidence of recent drug or alcohol abuse or dependence.

Medical Officer's Comment: *Although this Phase III study was very similar in design to the Phase II study, 154-101, the following major differences were noted:*

- *The exclusion of patients < 40 years of age, in order to ensure the enrollment of an appropriate population.*
- *The change in the duration of therapy to 7 days.*

- *The exclusion of severity immunosuppressed patients on steroids by including only those patients on no more than 10 mg prednisone daily.*

- *The decrease in the number of visits to 4 as compared to 5.*

Overall, the MO agreed with the inclusion and exclusion criteria.

Randomization and Blinding:

The investigator sequentially assigned study numbers to the patients as they were determined to be eligible for treatment. The study number was entered onto the patient's CRF and the patient received study medication with the corresponding number. Study medication was blinded by a double-dummy technique.

Dosage Form and Administration:

Study drug was in the form of tablets and packaged in blister cards using a double dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug, dependent on the random assignment:

Trovafloxacin:	100 mg daily (1 x 100 mg tablets) as a single dose in the morning.
Clarithromycin:	1000 mg daily in two equally divided doses (morning, evening).

The blister cards contained sufficient supplies for a 7 day course of treatment.

In order to maintain blinding, subjects were instructed to take the following tablets during each day of the 7 days of treatment:

	AM Administration	PM Administration
Trovafloxacin (100 mg/d)	1-placebo for clarithromycin 1-trovafloxacin x 100 mg	1-placebo for clarithromycin
Clarithromycin (1,000 mg/d)	1-clarithromycin 500 mg	1-clarithromycin 500 mg 1-placebo for trovafloxacin

The blister card with the randomization number corresponding to that assigned to the subject was given to the subject at V1. Subjects began study drug medication with the morning dose (even if it was not the morning), and completed a full day of medication on Day 1.

The subjects were informed that compliance with taking all tablets as instructed was imperative.

Note: The concomitant use of systemic corticosteroids was allowed in patients receiving chronic, low dose oral steroids (10 mg prednisone daily or less).

The investigator was responsible for recording the receipt of study drug, its usage, and for ensuring the supervision of the storage and allocation of these supplies. At intervals as appropriate, or upon completion or termination of the study, all drug supplies unallocated or unused by the patient were returned to Pfizer.

To ensure adequate records of disposition of unused supplies at the study site and to facilitate the final drug accountability process a Drug Inventory Record was maintained by the investigator.

Compliance:

Patients were informed that compliance with taking all tablets as instructed was imperative. Outpatients were asked to bring all unused medication and empty containers to the first follow-up visit. All doses taken were charted in the case report form.

Microbiologic Methods:

Bacteriologic response was assessed at V3 (EOT) and V4 (EOS). Only those sputum specimens that were adequate, as defined previously, were cultured. If there was no obtainable "adequate" specimen, at the EOT or EOS, and the patient was cured or improved, a presumptive assignment of eradication was made.

All specimens were initially sent to the local laboratory for culture. Isolates considered significant were sent to the central laboratory where susceptibility testing was performed. Local susceptibility data was used only if the central laboratory's data was missing.

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 17 of the study report)

	Trovafloxacin	Clarithromycin	
	MIC	Zone size (mm)	MIC
Criteria	µg/mL	15 µg disc	µg/mL
Susceptible	≤2	≥18	≤2
		[≥13]	[≤8]
Intermediate	4	14-17	3-7
		[11-12]	N/A
Resistant	≥8	≤13	≥8
		[≤10]	[≥32]

Susceptibility breakpoints for trovafloxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and Zone diameter (mm) for 15 µg disk for clarithromycin are based on National Center for Clinical Laboratory Standards (NCCLS) criteria for organisms other than *Haemophilus*. The criteria for *Haemophilus* is given in brackets.

Chlamydia pneumoniae and *M. pneumoniae* serology were to be performed at baseline (Day 1) and at Visit 4 (Day 28; end of study). A four-fold increase in titer was considered positive for the presence of the organism.

Clinical Response:

Clinical response was determined by the sponsor and evaluated at the EOT: V3 (Day 8), and at the EOS: V4 (Day 28), or at the time of discontinuation from study. Clinical response was primarily based on the global assessment of the clinical presentation of the subject at the evaluation time point.

Clinical assessment was based upon resolution or improvement of clinical laboratory signs of infection such as, disappearance or decreased purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Supporting data to evaluate clinical response was to include reduction in leukocytosis. Clinical response was to be classified as cure, improvement, failure, or indeterminate, as defined in the introduction of the MOR.

Copied below, from page 18 of the original protocol, are the parameters of assessment:

Subjects were assessed for signs and symptoms, as detailed below, and these assessments were recorded on the CRF.

1. Sputum was obtained at baseline (V1) and at every visit thereafter. Macro and micro evaluations were performed.
2. Chest x-ray was obtained at baseline (V1) and at any other time point deemed necessary by the investigator.
3. Cough, dyspnea, chills/rigors, constitutional symptoms, and lung sounds were each assessed at baseline (V1) and at every visit thereafter and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Medical Officer's Comment: *For the MO's comment on both clinical and bacteriologic response, see the MOR of study 154-101. The MO points out that in this study, the determination of clinical response was made by the sponsor and not by the investigator (154-101). The sponsor's TOC visit was the EOT but as noted previously, assessments could be made at either visit. Therefore, the sponsor's population was not static but could contain patients with either visit and not necessarily both.*

Safety Assessments:

Adverse Events:

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the EOS, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the sponsor project clinician immediately by telephone. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

In addition, physical examination was performed at baseline (V1). Concomitant medication use and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were evaluated at V1 and at V2, V3 (EOT), and V4 (EOS).

Clinical Laboratory Tests:

Hematology, coagulation, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 and V3. At V4, hematology, coagulation, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Data Analysis:

See the introduction to the MOR for a review of the sponsor's subsets and their definitions.

Clinical Evaluability Criteria:

See the introduction to the MOR for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction of a review of the sponsor's criteria.

Primary and Secondary Endpoints for Efficacy:

Primary efficacy endpoints were:

- Sponsor-defined subject clinical response at the EOT and;
- Pathogen eradication rates at the EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at the EOS;
- Investigator-defined subject clinical response at the EOT, and sponsor-defined and investigator-defined subject clinical response at the EOS.

Medical Officer's Comment: *As stated in the introduction, the MO applied the TOC to the later EOS visit, therefore the primary endpoint for the MO's analysis was clinical response at that timepoint. This study differed from 154-101, in that there were 2 primary efficacy variables, that is, both clinical and bacteriological at the EOT. The MO's management of the data was unchanged.*

The MO determined that in the MO analysis, the secondary endpoints would be applied to the EOS. However, if there was a patient with a bacteriologic response at the EOT of eradication and no response at the EOS, the MO elected to carry this response forward as a "presumed eradication." Failures/persistences were always carried forward in both the sponsor's and the MO's analyses.

Definitions of Response:

Please refer to the introduction of the MOR for the sponsor's definitions.

Interim Analyses:

No interim analyses were performed.

Demographics:

As per the sponsor, 410 patients were randomized to treatment (210 subjects to receive trovafloxacin (51.2%), and 200 to receive clarithromycin (48.7%)).

Of the treated patients, 384 completed treatment (201/210 (95.7%) trovafloxacin-treated patients and 183/200 (91.5%) clarithromycin-treated patients). 26 patients were withdrawn from treatment, (9 trovafloxacin, and 17 clarithromycin), but 14 of these completed the study. In addition to these 12 (4 trovafloxacin and 8 clarithromycin patients withdrawn during the study), an additional 4 clarithromycin patients were withdrawn during follow-up, thus 16 patients were withdrawn from the study (4 trovafloxacin and 12 clarithromycin).

The MO has recreated sponsor's Table 1.1, the Disposition of Enrolled subjects.

Table 109.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin	Clarithromycin
		100 mg	500 mg bid
Subjects with Signed Consent	443		
Withdrawn Prior to Randomization	33		
Randomized		210	200
Randomized, But Not Treated		0	0
All Treated Subjects		210 (100%)	200 (100%)
Withdrawn During Treatment		9 (4%)	17 (9%)
Completed Treatment		201 (96%)	183 (92%)
Withdrawn During Follow- up		0 (0%)	4 (2%)
Completed Study		206 (98%)	188 (94%)
Completed Treatment and Study		201 (96%)	170 (90%)
Withdrawn During Treatment and Study		4 (2%)	8 (4%)

Medical Officer's Comment: *There was a higher dropout rate from the clarithromycin arm as compared to the trovafloxacin arm.*

Copied and modified below is sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

Table 109.2
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)

			Trovafloxacin		Clarithromycin	
Center	Total Randomized N = 410	(100%)	Randomized and Treated N = 210	100%	Randomized and Treated N = 200	100 %
5005	6	1.5	4	2	2	1
5022	4	1	2	1	2	1
5032	4	1	2	1	2	1
5041	12	2.9	6	2.9	6	3
5042	8	2	4	2	4	2
5072	12	2.9	6	2.9	6	3
5073	1	0.2	1	0.5	0	0
5074	6	1.5	2	1	4	2
5075	3	0.7	1	0.5	2	1
5076	40	9.7	20	9.5	20	10
5077	1	0.2	1	0.5	0	0
5078	36	8.8	18	8.6	18	9
5079	7	1.7	4	2	3	1.5
5080	24	5.8	12	5.7	12	6
5081	8	2	4	2	4	2
5082	2	0.5	2	1	0	0
5083	6	1.5	3	1.5	3	1.5
5085	2	0.5	1	0.5	1	0.5
5087	2	0.5	1	0.5	1	0.5
5089	3	0.7	1	0.5	2	1
5091	8	2	4	2	4	2
5092	16	3.9	8	4	8	4
5095	5	1.2	2	1	3	1.5
5121	3	0.7	1	0.5	2	1
5124	1	0.2	1	0.5	0	0
5125	3	0.7	2	1	1	0.5
5127	65	15.9	33	15.7	32	16
5129	14	3.4	7	3.3	7	3.5
5130	16	3.9	8	4	8	4
5132	9	2.2	4	2	5	2.5
5133	3	0.7	2	1	1	0.5
5134	5	1.2	3	1.5	2	1
5135	2	0.5	1	0.5	1	0.5
5136	1	0.2	1	0.5	0	0
5137	8	2	4	2	4	2
5138	7	1.7	3	1.5	4	2
5139	16	3.9	8	4	8	4
5140	21	5.1	10	4.8	11	5.5
5181	3	0.7	2	1	1	0.5
5213	1	0.2	1	0.5	0	0
5250	2	0.5	2	1	0	0
5499	4	1	2	1	2	1
5743	1	0.2	1	0.5	0	0
5776	1	0.2	1	0.5	0	0
5853	8	2	4	2	4	2

Medical Officer's Comment: *There were 45 centers, all of which enrolled patients. There was no center with > 20% of the patients, however, there was 1 center with approximately 15% of the patients (#5127).*

Copied below is the sponsor's table of all randomized patients and the study evaluation groups:

Table 109.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor
(Format modified by MO)

	Trovafloxacin 100 mg	Clarithromycin 500 mg bid
All Randomized Subjects	210 (100%)	200 (100%)
All Treated Subjects	210 (100%)	200 (100%)
Subjects with Inappropriate Baseline Diagnosis	2 (< 1%)	1 (<1%)
Clinically Intent- to- Treat Subjects	208 (>99%)	199 (>99%)
Clinically Evaluable Subjects	203 (97%)	188 (94%)
Clinically evaluable with baseline pathogen	93 (44%)	86 (43%)
Clinically Not Evaluable Subjects	5 (2%)	11 (6%)
Insufficient Therapy	1 (< 1%)	4 (2%)
No post-baseline clinical assessment	1 (<1%)	2 (1%)
Prior Antibiotic therapy	4 (2%)	3 (2%)
Concomitant Antibiotic therapy	0	6 (3%)
Clinically evaluable at EOS	197 (94%)	178 (89%)
Clinically evaluable at EOS with baseline pathogen	91 (43%)	80 (40%)
Bacteriologically Evaluable Subjects	93 (44%)	81 (41%)
Bacteriologically Not Evaluable Subjects	110 (52%)	107 (54%)
No Baseline Pathogen	108 (51%)	105 (53%)
Baseline culture Outside Window	2 (<1%)	1 (<1%)
No post-baseline cultures	0	2 (1%)
Bacteriologically Evaluable at EOS	87 (41%)	77 (39%)
Analyzed for Safety		
Adverse Events	210 (100%)	200 (100%)
Laboratory Data	204 (97%)	189 (95%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: *16 of the randomized subjects were not clinically evaluable, (5/210 (2%) trovafloxacin-treated subjects and 11/200 (6%) clarithromycin-treated subjects).*

The bacteriologically evaluable population was a subset of the clinically evaluable population and the bacteriological ITT population, which were both subsets of the clinical ITT population.

There were a total of 9/210 (4.2%) trovafloxacin-treated patients who discontinued therapy. 5 of these patients continued the study and 4 did not. 7/9 were clinically evaluable.

On the clarithromycin arm, 17 patients discontinued treatment. 9 of these patients continued the study and 8 did not. 11/17 were clinically evaluable.

All patients who discontinued treatment were reviewed (see below):

Trovafloxacin (N = 9):

- *#50410683: 67 YO developed nausea after 5 days and discontinued both the study and treatment. This patient had Moraxella catarrhalis in all sputum cultures. Clinically evaluable at the EOS as an improvement with presumed persistence of the pathogen. Reviewer agreed because the patient did not receive alternative therapy.*

- *#50420165: 40 YO withdrawn from treatment on day 3 because of a laboratory abnormality (low platelet count). This patient completed the study and was clinically and bacteriologically evaluable.*

specimen at the EOS. The patient was classified as a cure with presumed eradication. Reviewer disagreed because the patient did not receive the MO-specified minimum duration of therapy and therefore was unevaluable.

- *#50780282: 41 YO discontinued treatment and the study on day 5 because of nausea and vomiting. The patient was clinically and bacteriologically evaluable and had Staphylococcus aureus as the initial isolate. Sputum was not re-cultured and the patient was classified as a cure at the EOT. This patient was not evaluable for MO because there was no EOS visit.*

- *#50830108:60 YO withdrawn on day 5 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed. This patient had no baseline pathogen.*

- *#50950097: 41 YO withdrawn on day 7 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed. This patient had Candida spp. and Citrobacter as baseline pathogens and was treated with Augmentin®.*

- *#51330345: 60 YO withdrawn from treatment and study after 5 days of therapy because he was found to have pneumonia on CxR. This patient was clinically and bacteriologically evaluable. Haemophilus influenzae was isolated from the baseline and EOT sample and he was carried forward as a failure. Reviewer agreed. The patient was treated with Augmentin®.*

- *#51390399:73 YO withdrawn from treatment on day 5 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed. This patient had Moraxella catarrhalis as a baseline pathogen which was eradicated with amoxicillin.*

- *#51400457: 63 YO withdrawn from treatment on day 1 because of an adverse event. The patient completed the study but was not clinically or bacteriologically evaluable. Streptococcus pneumoniae was isolated at baseline and the patient was treated with Ceclor® and clarithromycin. Reviewer agreed.* *

- *#51810561: 70 YO withdrawn on day 3 because of an exacerbation of COPD. The patient did not complete the study and was not clinically or bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed.* *

Clarithromycin (N=17):

- *#50220524: 53 YO withdrawn from treatment on day 1 because of an exacerbation of COPD. The patient did not complete the study and was not clinically or bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed.* *

- *#50720010: 71 YO withdrawn from treatment on day 5 because he received an alternative antimicrobial in error. The patient completed the study and was clinically and bacteriologically evaluable. This patient was classified as an evaluable failure with presumed persistence of the baseline pathogen, Serratia marcescens. Reviewer agreed.*

- *#50720013: 72 YO withdrawn from treatment on day 4 because of an adverse event, (leg pain). The patient completed the study and was clinically but not bacteriologically evaluable. This patient was classified as an evaluable failure. Reviewer agreed.*

- *#50760039: 73 YO withdrawn on day 1 because of a protocol violation, (seizure disorder). The patient did not complete the study and was not clinically or bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed.* *

- *#50760221: 66 YO withdrawn from treatment on day 3 because of an adverse event, (atrial fibrillation). The patient did not complete the study and was clinically and bacteriologically evaluable. This patient was classified as an improvement with presumed eradication of the baseline pathogen, Haemophilus influenzae. No further antibiotics were prescribed. Reviewer disagreed because patient did not receive the minimum duration of therapy necessary to be evaluable per the MO. Additionally, this patient was excluded from the MO evaluable population because of a missing EOS visit.*

- *#50790059: 73 YO withdrawn from treatment on day 5 because of an adverse event, (laceration, and nausea). The patient did not complete the study and was clinically but not bacteriologically evaluable. This patient was carried forward as an evaluable failure. Reviewer agreed.*

- *#50790061: 43 YO withdrawn from treatment on day 7 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. This patient was clinically but not bacteriologically evaluable. Reviewer agreed.*

- *#50920239: 76 YP withdrawn from treatment on day 1 because of an adverse event, (hives). The patient completed the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. **

- *#50950101: 47 YO withdrawn from treatment on day 2 because of LFT elevations. The patient completed the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. **

- *#51210406: 60 YO withdrawn on day 4 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed.*

- *#51270473: 48 YO withdrawn from treatment on day 2 because of an adverse event, (nausea). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed. **

- *#51270545: 48 YO withdrawn from treatment on day 5 because of an adverse event, (nausea). The patient completed the study and was clinically but not bacteriologically evaluable. This patient was carried forward as an evaluable failure. Reviewer agreed. Patient received an additional week of ofloxacin.*

- *#51270587: 43 YO withdrawn on day 7 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. This patient was clinically and bacteriologically evaluable. Reviewer agreed. Staphylococcus aureus was isolated as the baseline pathogen and was eradicated after Augmentin® treatment.*

- *#51340454: 48 YO withdrawn from treatment on day 5 because of an adverse event, (nausea). The patient completed the study and was clinically but not bacteriologically evaluable. This patient was carried forward as an improvement at the EOS. Reviewer disagreed because the patient did not receive the minimum duration of therapy necessary as per the MO criteria and therefore was excluded.*

- *#51370508: 55 YO withdrawn from treatment on day 3 because of an adverse event, (nausea). The patient did not complete the study and was clinically but not bacteriologically evaluable. This patient was classified as an improvement at the EOT but was not seen at the EOS. This patient was unevaluable by MO criteria.*

- *#51400358: 47 YO withdrawn from treatment on day 5 because of an adverse event, (nausea). The patient completed the study and was clinically and bacteriologically evaluable. This patient was carried forward as a clinical failure with eradication of the baseline pathogen, Streptococcus pneumoniae. Reviewer agreed.*

- *#51810562: 71 YO withdrawn on day 3 because he did not meet randomization criteria (incorrectly performed Gram stain). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed. **

- *#54990539: 50 YO withdrawn on day 4 because of an adverse event. The patient was classified as a "cure" by the sponsor but was excluded by the MO because he did not receive the minimum duration of therapy necessary to be evaluable.*

*Although the 9 trovafloxacin and 17 clarithromycin patients listed above, represent discontinuations from therapy or the study, only those patients with a * are those patients who were excluded from the sponsor's clinical efficacy analysis (1 trovafloxacin and 6 clarithromycin). An additional 6 trovafloxacin-treated patients and 5 clarithromycin-treated patients were clinically unevaluable as per the sponsor. The most common reason for exclusion was prior antimicrobial therapy, (4 trovafloxacin, and 3 clarithromycin).*

All clinically unevaluable patients (as per the sponsor), are listed below:

Trovafloxacin (N = 7)

- *#50828089: Prior antibiotic therapy: Ciprofloxacin up until day –1. Pseudomonas aeruginosa at baseline. Review agreed.*

- *#51270439: Inappropriate baseline diagnosis (sputum sample was not adequate): Moraxella catarrhalis and Streptococcus pneumoniae at baseline. Moraxella eradicated but Streptococcus was persistent. Patient would have been a failure at EOS. Received ofloxacin on day 25. Reviewer agreed.*

- *#51270480: Prior antibiotic therapy: chronic suppressive therapy with Bactrim® up until day –2. Reviewer agreed.*

- *#51270490: Prior antibiotic therapy: Prior antibiotic therapy: amoxicillin up until day –1. Pseudomonas aeruginosa at baseline. Reviewer agreed.*

- *#51270547: Prior antibiotic therapy: Cefuroxime axetil® up until day –1, Reviewer agreed.*

- *#51400457: Discontinued day 2 because of an adverse event. Reviewer agreed (see above listing).*

- *#51810561: Inappropriate baseline diagnosis: COPD. Reviewer agreed (see above listing).*

Clarithromycin (N =11):

- *#50050391: Concomitant antimicrobial (Augmentin®) for infected thoracotomy site, days 9 -17. Reviewer agreed.*

- *#50220524: Developed pneumonia after 1 day and received alternative therapy. Reviewer agreed (see above listing).*

- *#50750026: Non-compliant after 1 day and changed to doxycycline. Reviewer agreed.*

- *#50760039: No post-baseline assessments. Lost to follow-up. Reviewer agreed.*

- *#50920239: Discontinued after 1 day because of an adverse event. Reviewer agreed (see above listing).*

- *#50950101: Discontinued after 3 days because of laboratory abnormalities. Reviewer agreed (see above listing).*

- *#51270473: Discontinued after 3 days because of an adverse event. Reviewer agreed (see above listing).*
- *#51270478: Concomitant antimicrobial (amoxicillin), day 1. Reviewer agreed.*
- *#51270592: Prior antibiotic therapy. Ceclor® up until day –2. Reviewer agreed.*
- *#51400465: Prior antibiotic therapy. Cefpodoxime® up until day –2. Reviewer agreed.*
- *# 51810562: Patient dropped out after 3 days and had no follow-up visit. The patient was excluded because of a protocol violation (incorrectly performed Gram stain). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed.*

Based on the above listings and in conjunction with the study report, the MO found that the sponsor's clinically evaluable trovafloxacin population consisted of 203 patients and the clarithromycin of 188. The bacteriologically evaluable population consisted of 93 trovafloxacin and 81 clarithromycin patients. The most common reason for exclusion from the bacteriologically evaluable population was "no baseline pathogen" in 108 trovafloxacin and 105 clarithromycin patients. Other reasons included "baseline culture outside of window" and "no post-baseline cultures."

The sponsor provided the Reviewer with a listing of patients that were clinically evaluable as per the sponsor but who had no EOS analysis. This listing included the following patients:

Trovafloxacin (N = 4):

- *#50410683: Improvement at EOT.*
- *#50780282: Cure at EOT.*
- *#50920235: Cure at EOT.*
- *#51270517: Improvement at EOT*

Clarithromycin (N =12)

- *#51400471: Cure at EOT.*
- *#54990538: Improvement at EOT*
- *#50720261: Improvement at EOT.*
- *#50760221: Improvement at EOT.*
- *#50410071: Improvement at EOT.*
- *#50790061: Improvement at EOT.*
- *#50910189: Improvement at EOT.*
- *#51400431: Improvement at EOT*
- *#51270551: Cure at EOT.*
- *#51210405: Cure at EOT.*

- *# 51270417: Cure at EOT.*
- *#51370508: Improvement at EOT*

The MO excluded all of the patients who did not have an EOS visit because the MO TOC was applied to the EOS. The above listing excluded failures, which were always carried forward.

Baseline Characteristics:

The 3 groups were comparable in terms of age, race, weight, sex, and smoking history. The distribution of smokers was similar between the trovafloxacin and clarithromycin groups (33% and 37% ex-smokers, 30% and 26% non-smokers, and 36% and 38% smokers, respectively.)

97 of the trovafloxacin patients were male with a mean age of 59.6 and 83% were white.
106 of the trovafloxacin patients were women with a mean age of 56 and 88% were white.

82 of the clarithromycin patients were male with a mean age of 61.4 and 84% were white.
106 of the clarithromycin patients were women with a mean age of 55.6 and 85% were white.

The median duration since the onset of the underlying primary diagnosis of CB was not provided.

The median duration since the onset of the present episode was 7 days for both treatment groups

The respective means were 11.4 days for the trovafloxacin patients and 10.2 days for the clarithromycin patients.

Duration of Treatment:

The median duration of treatment was 7 days for subjects in the both treatment groups.

Concomitant Medications:

The majority of patients were on concomitant medications during therapy. The most commonly used medications were bronchodilators (98 and 106 patients per arm, respectively

Systemic steroids were taken by 42 (21%) of the trovafloxacin-treated patients and 49 (28%) of the clarithromycin-treated patients.

Medical Officer's Comment: *The MO did not exclude patients taking systemic steroids in the pilot study 154-101 but did provide separate analyses of clinical and bacteriological response with and without these patients in the MO's efficacy analysis. The MO elected to do the same for this study. The rationale was that there was no major difference in efficacy with or without these patients. The MO found that 34 clinically evaluable trovafloxacin patients and 42 clarithromycin patients received systemic steroids.*

Concomitant Antimicrobials:

Of the clinically evaluable patients, 34 trovafloxacin-treated patients and 39 clarithromycin-treated patients received concomitant antimicrobials for the following reasons:

(This information was located in sponsor's table 2.4, appendix 1).

- inadequate response: 25 trovafloxacin and 27 clarithromycin (all carried forward as evaluable failures)
- other reason: 9 trovafloxacin and 12 clarithromycin patients.

The other category was compromised of the following patients:

Trovafloxacin (N = 9):

- #50420167: Other/relapse: Cefixime® day 28, classified as a failure. Reviewer agreed.
- #50820093: Other/relapse: Cefuroxime® day 14, classified as a failure. Reviewer agreed.
- #50920199: Other/abscessed tooth: amoxicillin day 23, classified as a failure. Reviewer agreed.
- #50920235: Other/Strep throat: amoxicillin day 45. Patient would have been excluded from MO analysis because of a missing EOS visit.
- #51270517: Other URI: erythromycin day 18. Patient would have been excluded from MO analysis because of a missing EOS visit.
- #51290384: Other/UTI: ofloxacin day 25. Reviewer agreed to include the patient as an evaluable cure because the ofloxacin was started after the EOS.
- #51330345: Other/protocol violation: Augmentin® day 5. Patient was included in the MO's analysis as an evaluable failure
- #51400468: Other/sinusitis: Cefpodoxime® day 29: Reviewer agreed to include the patient as an evaluable cure because the antimicrobial was started after the EOS.
- #54990538: Other/URI: azithromycin day 14. Classified as a cure in ITT only. Reviewer agreed.

Clarithromycin (N= 12):

- #50720013: Adverse event: amoxicillin day 8, classified as a failure. Reviewer agreed.
- #50720261: Other/sinusitis: ampicillin day 22. Classified as an improvement at EOT. The patient was excluded from the MO evaluable population because there was no EOS visit.
- #50790061: Adverse event: cefazolin day 8. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #50870145: Other/recurrence of bronchitis: amoxicillin day 26, classified as a failure. Reviewer agreed.
- #50920234: Other/sinusitis: tetracycline day 19, classified as a failure. Reviewer agreed.
- #51270417: Other/dental work: erythromycin day 26, classified as a cure. Reviewer agreed but the patient was excluded from the MO population because there was no EOS visit.
- #51270551: Other/inflammatory nodule left lung: clarithromycin day 13, classified as a cure at the EOT. The patient was excluded from the MO population because there was no EOS visit.
- #51300526: Other/sinusitis: Cefuroxime® day 26, classified as a cure. Reviewer agreed as antimicrobial was started after the EOS visit.
- #51390355: Other/sinus congestion: lincomycin day 31. Reviewer agreed as antimicrobial was started after the EOS visit.

- #51390398: Other/persistent sinus drainage: lincomycin day 30. Reviewer agreed as antimicrobial was started after the EOS visit.
- #51400358: Other/failed rescue drug: Bactrim® day 10, classified as a failure. Reviewer agreed.
- #51400431: Other/erysipelas: benzathine penicillin day 10. Patient was excluded from MO analysis because of a missing EOS visit.

Protocol Deviations:
(Copied from page 30 of the study report)

Deviations from protocol were noted for 24 subjects, two of whom had more than one deviation, during the study. These deviations were categorized as follows:

- Inclusion criteria deviations included subjects <40 years of age (3 subjects), subjects with an inappropriate diagnosis due to insufficient symptoms or inappropriate sputum histology (3 subjects);
- Other (study procedure) deviations included subjects randomized out of order (6 subjects) or sputum samples sent to laboratory for culture with at Visits 2-4 (1 subject);
- Deviations that involved taking medications other than those specified by the protocol (Seldane) (1 subject) or taking an allowed medication in amounts greater than specified by protocol (prednisone >10 mg/day) (5 subjects);
- Exclusion criteria deviations included subjects with positive chest x-ray for pneumonia (3 subjects) and history of seizures (2 subjects);
- Study drug administration deviations included administration of study drug 3 or 4 days after baseline (2 subjects).

The one trovafloxacin (5072-0011) subject with a history of seizures received 7 days of study drug and reported no seizure activity or any adverse event. The one clarithromycin (5076-0039) with a history of seizures received one day of treatment and also reported no seizure activity or any adverse event.

Subjects with an inappropriate baseline diagnosis were not included in the clinical and bacteriological intent-to-treat and evaluable analyses. All other deviations did not effect evaluability. Subjects with protocol deviations are listed in the following table.

Table A. Summary of Protocol Deviations All Randomized Subjects

Inclusion	5078-0284; 5078-0318; 5091-0190; 5127-0439; 5181-0561; 5181-0562
Other (Randomized out of order or inadequate sputum sample sent to laboratory at Visits 2-4)	5081-0083; 5082-0093; 5127-0501; 5127-0503; 5139-0529; 5140-0468; 5140-0509
Taking Medications Not Specified by Protocol or Taking an Allowed Medication in Amounts Greater Than Specified by Protocol	5032-0581; 5072-0011; 5072-0013; 5076-0036; 5076-0037; 5091-0190
Exclusion	5133-0345; 5072-0011; 5075-9005; 5076-0039; 5092-0237
Study Drug Administration	5499-0539; 6168-0598