The primary difference between the sponsor's and the MO's assessments was that of timing. The sponsor applied the TOC to the EOT visit whereas the MO applied the TOC to the EOS.

Definitions of Response:

Please see the introduction to the MOR (pages 384 – 386) for the sponsor's definitions and the Reviewer's comments.

Interim Analyses:

No interim analyses were performed.

Demographics:

As per the sponsor, 274 patients signed consent, 7 of these however, were withdrawn prior to randomization because they did not meet the study entry criteria. Thus 269 subjects were randomized, 129/269 (47.9%) to receive alatrofloxacin/trovafloxacin and 138/269 (51.3%) to receive ciprofloxacin. 2 randomized subjects on the trovafloxacin arm (#51150121 and #59850262) and 1 subject (#54670139), on the ciprofloxacin arm did not receive treatment. Thus 127 of the randomized trovafloxacin and 137 of the randomized ciprofloxacin subjects were treated (Total treated = 264).

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

Table 113.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Alatro/Trovafloxacin 300 mg → 200 mg	Ciprofloxacin 400 mg bid→ 750 mg bid
Subjects with Signed Consent	274		
Withdrawn Prior to Randomization	7		
Randomized		129	138
Randomized, But Not Treated		2	1
All Treated Subjects		127 (100%)	137 (100%)
Withdrawn During Treatment		53 (42%)	43 (31%)
Completed Treatment		74 (58%)	94 (69%)
Withdrawn During Follow- up		9 (7%)	24 (18%)
Completed Study		86 (68%)	90 (66%)
Completed Treatment and Study		65 (51%)	70 (51%)
Withdrawn During Treatment and Study		32 (25%)	23 (17%)

Medical Officer's Comment:

There were a larger number of patients withdrawn during treatment on the trovafloxacin arm as compared to the ciprofloxacin arm. 17/53 (32%) of the discontinuations on the trovafloxacin arm were considered related to the study drug and included 5 withdrawals (4%) for an AE, 11 for an insufficient response, and 1 because of a laboratory abnormality. 36/53 discontinuations on this arm were considered unrelated to the study drug and included 6 withdrawals because of an AE, 12 deaths, 15 "other", 1 protocol violation and 2 withdrawn consents.

On the ciprofloxacin arm, 9/43 discontinuations from treatment (21%) were considered related to the study drug. 8 of these were due to insufficient response and 1 to a laboratory abnormality. Of the 34/43 discontinuations unrelated to ciprofloxacin therapy, 8 were due to an AE, 1 patient was lost to follow-up, 12 "other," 10 deaths, 2 protocol violations, and 1 withdrawn consent.

Of the 53 trovafloxacin patients withdrawn from treatment, 21 completed the study as compared to 20/43 of the ciprofloxacin patients.

Discontinuation form treatment or the study had no predetermined effect on evaluability. Evaluability was determined solely by the previously described criteria.

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

Table 113.2
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

	Alatro/Trovafloxacin	Cipro/Ciprofloxacin
All Randomized Subjects	129 (100%)	138 (100%)
All Treated Subjects	127 (98%)	137 (>99%)
Subjects with Inappropriate Baseline Diagnosis	2 (2%)	3 (2%)
Clinically Intent- to- Treat Subjects	127 (985)	135 (98%)
Subjects with Negative Baseline Culture	56 (43%)	67 (49%)
Bacteriologically ITT Subjects	71 (55%)	68 (49%)
Clinically Evaluable Subjects	88 (68%)	103 (75%)
Clinically evaluable with baseline pathogen	47 (36%)	52 (38%)
Clinically Not Evaluable Subjects	39 (30%)	32 (23%)
Insufficient Therapy	27 (21%)	23 (17%)
No post-baseline clinical assessment	20 (16%)	16 (12%)
Prior Antibiotic therapy	0	1 (<1%)
Concomitant Antibiotic therapy	14 (11%)	9 (7%)
No post-baseline clinical assessment in evaluable analysis window	20 (16%)	16 (12%)
Other	1 (< 1%)	4 (3%)
Clinically evaluable at EOS	72 (56%)	79 (57%)
Clinically evaluable at EOS with baseline pathogen	39 (30%)	38 (28%)
Bacteriologically Evaluable Subjects	47 (36%)	52 (38%)
Bacteriologically Not Evaluable Subjects	41 (32%)	51 (37%)
No Baseline Pathogen	41 (32%)	51 (37%)
No post-baseline cultures	1 (<1%)	1 (<1%)
Bacteriologically Evaluable at EOS	39 (30%)	38 (28%)
Baseline Blood Cultures Performed	124 (96%)	125 (91%)
Analyzed for Safety		
Adverse Events	127 (100%)	137 (100%)
Laboratory Data	115 (91%)	126 (92%)

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

Medical Officer's Comment: *It can be appreciated from table 113.2 that on the trovafloxacin arm there were 39/127 (30.7%) randomized and treated subjects with an appropriate baseline diagnosis who were clinically unevaluable at the EOT and an additional 16/127 (12.5%) clinically unevaluable at the EOS, thus there were a total of 55/127 (43.3%) that were clinically unevaluable.*

On the ciprofloxacin arm, there were 32/135(23.7%) randomized and treated subjects with an appropriate baseline diagnosis, who were clinically unevaluable at the EOT and an additional 24/135 (17.7%) subjects clinically unevaluable at the EOS. Thus, on the ciprofloxacin arm there were 56/135 (41.4%) subjects who were clinically unevaluable.

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

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 113.3
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)

Center	Total Randomized N = 267	(100%)	Alatrofloxacin/Trovafloxacin Randomized and Treated N = 129 (100%)		N = 127 (100%)		Ciprofloxacin/Ciprofloxacin Randomized and Treated N = 138 (100%)		N = 137 (100 %)	
5423	1	0.4	1	0.7	1	0.7	0	-	0	-
5467*	3	1.1	1	0.7	1	0.7	2	1.4	1	0.7
5483*	15	5.6	7	5.4	7	5.5	8	5.8	8	5.8
5508	1	0.4	1	0.7	1	0.7	0	-	0	-
5510	3	1.1	2	1.4	2	1.5	1	0.7	1	0.7
5511	3	1.1	2	1.4	2	1.5	1	0.7	1	0.7
5513	2	0.7	0	-	0	-	2	1.4	2	1.4
5515	1	0.4	0	-	0	-	1	0.7	1	0.7
5516	1	0.4	0	-	0	-	1	0.7	1	0.7
5541*	2	0.7	0	-	0	-	2	1.4	2	1.4
5546*	4	1.4	2	1.4	2	1.5	2	1.4	2	1.4
5623	18	6.7	9	6.9	9	7.1	9	6.5	9	6.6
5627	4	1.5	1	0.7	1	0.7	3	2.2	3	2.9
5628*	1	0.4	0	-	0	-	1	0.7	1	0.7
5834	3	1.1	2	1.7	2	1.5	1	0.7	1	0.7
5835	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
5837*	1	0.4	0	-	0	-	1	0.7	1	0.7
5903	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5970*	1	0.4	1	0.7	1	0.7	0	-	0	-
5984*	1	0.4	1	0.7	1	0.7	0	-	0	-
5985*	3	1.1	2	1.4	1	0.7	1	0.7	1	0.7
5987*	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
6111	1	0.4	1	0.7	1	0.7	0	-	0	-
6112	1	0.4	1	0.7	1	0.7	0	-	0	-
6127*	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
6367*	3	1.1	0	-	0	-	3	2.2	3	2.9
6376*	1	0.4	0	-	0	-	1	0.7	1	0.7
5030	2	0.7	2	1.4	2	1.5	0	-	0	-
5034	3	1.1	1	0.7	1	0.7	2	1.4	2	1.4
5079*	5	1.8	3	2.3	3	2.3	2	1.4	2	1.4
5106*	4	1.5	2	1.4	2	1.5	2	1.4	2	1.4
5111*	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0
5112*	14	5.2	7	5.4	7	5.5	7	5.0	7	5.1
5115*	2	0.7	1	0.7	0	-	1	0.7	1	0.7
5117*	1	0.4	1	0.7	1	0.7	0	-	0	-
5118*	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5119*	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0
5121*	5	1.8	3	2.3	3	2.3	2	1.4	2	1.4
5173*	5	1.8	2	1.4	2	1.5	3	2.2	3	2.9
5174*	6	2.2	3	2.3	3	2.3	3	2.2	3	2.9
5175*	19	7.1	10	7.7	10	7.9	9	6.5	9	6.6
5181*	1	0.4	0	-	0	-	1	0.7	1	0.7
5188*	11	4.1	6	4.6	6	4.7	5	3.6	5	3.6
5191*	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0

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5193*	1	0.4	0	-	0	-	1	0.7	1	0.7
5211*	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
5249*	3	1.1	2	1.4	2	1.5	1	0.7	1	0.7
5384*	1	0.4	1	0.7	1	0.7	0	-	0	-
5386*	20	7.5	9	6.9	9	7.1	11	8.0	11	8.0
5395	1	0.4	0	-	0	-	1	0.7	1	0.7
5396	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5407	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5409	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0
5410	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
6404	11	4.1	5	3.9	5	3.9	6	4.3	6	4.4
6455*	1	0.4	0	-	0	-	1	0.7	1	0.7
6543	7	2.6	4	3.1	4	3.1	3	2.2	3	2.9

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* Designates US centers

***Medical Officer's Comment**: No center had > 8% of the patients and that the patients were well distributed over the 57 centers listed. 34 of these centers were located in the US. The 34 US centers randomized 180/267 of all of the patients or 67.4% of the total.*

The MO found that the number of centers decreased from 84, as found in the initial study report to 57. The total number of US centers decreased from 48 to 34. The sponsor was queried as to this change on September 25, 1997. The sponsor responded that there was difficulty in enrollment at many of the centers with a resultant high attrition rate. These difficulties wee mostly associated with "consent" issues.

At this point and because of the overall concurrence between the MO and the sponsor as to the design and implementation of this trial, the MO elected to review a selected sample of patients. This random sample was generated by the FDA statistician, Dr. Nancy Silliman, and is representative in terms of demographic content with the randomized population. This list was generated and reviewed in a blind manner.

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Alatrofloxacin/Trovafloxacin (N = 15):

- *#51110083: 84 YO male, never smoked, who received study drug for 4 days. The patient had findings consistent with a new right upper lobe pneumonia and had Morganella morganii isolated from the sputum. The patient was withdrawn from therapy because of a variety of AEs including an infection of a right groin surgical site and tremor. In addition to the study drug, the patient received vancomycin for a coagulase negative staphylococcus isolated in the blood. This patient was neither clinically nor microbiologically evaluable. The investigator and the sponsor rated this patient as an "improvement at the EOT. The patient did not receive any other antimicrobial specifically directed against the initial sputum isolate. The Reviewer agreed with the unevaluability in this case, as the patient did not receive the appropriate duration of therapy.*

- *#51110108: 69 YO male, smoker, both clinically and bacteriologically evaluable. The patient received a 10 day course of therapy for a new left and right lower lobe pneumonia. The initial sputum sample had growth of Acinetobacter anitratus which was persistent at the EOT but presumed eradicated at the EOS where the patient was unable to produce a sample. The patient was rated as an improvement at the EOT and a cure at the EOS. The Reviewer agreed.*

- *#51120277: 78 YO male, ex-smoker, who was neither clinically nor bacteriologically evaluable despite a 10 day course of therapy. The initial CxR reveled patchy fibronodular infiltrates thoughout the left lung and at the right base, however the patient was unable to produce a sputum sample. The patient was characterized as an "improvement" at the EOS as opposed to a "cure" at the EOT. A UTI developed on study day 13 for which the patient received intravenous cefotaxime, followed by oral ciprofloxacin. The Reviewer agreed with the unevaluability of this patient in the face of concomitant antimicrobial therapy.*

- *#51210230: 80 YO male, never smoked, clinically and bacteriologically evaluable. This patient received 15 days of therapy. Initial sputum was unobtainable, however later specimens were positive for Pseudomonas aeruginosa and Staphylococcus aureus. Additionally, Escherichia coli and Enterococcus faecalis were isolated from the blood and subsequently eradicated at day 4. The Pseudomonas aeruginosa was eradicated on day 8 but the Staphylococcus aureus was never eradicated. Initial CxR revealed a left lower lobe density which worsened over the course of therapy, at both the EOT and EOS. The patient received vancomycin, aztreonam, and metronidazole after the 12th day of study drug. This patient was rated as a "failure" at both the EOT and EOS. Reviewer agreed.*

- *#51880004:41 YO male, smoker, neither clinically nor bacteriologically evaluable. This patient was withdrawn form the study within the first 24 hours because of his poor prognosis. Patient had sustained a fatal brain injury. Bilateral airspace disease was noted on CxR and a bronchoscopy specimen was notable for growth of Proteus mirabilis. In the ITT analysis this patient was rated as a failure, however, the Reviewer agreed with the unevaluability of this patient who did not receive enough study drug to determine any outcome.*

- *#54090358: 65 YO female, never smoked, both clinically and bacteriologically evaluable after 10 days of study drug. Pseudomonas aeruginosa was isolated at baseline and presumed eradicated at the EOS when the patient was unable to produce a specimen. Initial CxR revealed bilateral patchy alveolar infiltrates which improved. No other antimicrobial was utilized. The Reviewer agreed with the evaluability of this patient as well as with the outcome of cure at the EOS.*

- *#54100363:49 YO female, smoker, clinically evaluable only after 8 days of therapy. This patient had a history of metastatic esophageal cancer and had a new right lower lobe pneumonia on CxR. No concurrent antimicrobials were given and the sponsor rated the patient as a cure at the EOT. This patient was unevaluable for the Reviewer, in accordance with the previously specified MO TOC at the EOS. The patient did not have an EOS visit as all therapy was withdrawn and she died before the EOS. The infiltrate did completely resolve.**

- *#54830113:84 YO male, ex-smoker, neither clinically nor bacteriologically evaluable. The patient received 5 days of therapy but initial CxR was negative for a new infiltrate. Staphylococcus aureus was isolated from an initial sputum sample despite previous antimicrobials for 96 hours prior to enrollment. This patient died of respiratory failure on day 5. The Reviewer agreed that this patient was unevaluable in view of the negative CxR and the previous antimicrobial therapy.*

- *#54830115: 54 YO male, ex-smoker, clinically evaluable only as per the sponsor after 11 days of therapy as a cure. This patient was unevaluable as per the Reviewer because he had no EOS visit. The patient did have a new middle lobe (L) pneumonia on CxR, which resolved at the EOT.**

- *#55080613: 70 YO female, never smoked, clinically evaluable only, after 3 days of therapy as a failure. The patient was withdrawn for insufficient response and treated with amikacin and cefotaxime for a patchy left lower lobe infiltrate. The CxR cleared on the rescue regimen and the patient was carried forward as a failure. Reviewer agreed.*

- *#55460090:98 YO male, never smoked, neither clinically nor bacteriologically evaluable after 4 days of therapy. The patient's family withdrew him from the study and he subsequently died of his underlying CHF. No isolates were grown from the sputum or the blood and the initial CxR revealed bilateral alveolar densities, the etiology of which appeared unclear. This patient was characterized as a "failure" in the ITT analysis. The reviewer agreed with the unevaluability of this patient because there does not appear to be a confirmed diagnosis of pneumonia as opposed to CHF.*

- *#55460091: 77 YO female, never smoked, clinically evaluable only as a cure at the EOT and EOS. The patient received 10 days of study drug for a new left lower lobe infiltrate, without bacteriologic*

confirmation, which completely resolved by the EOT without any other antimicrobial coverage. Reviewer agreed.

- *#65430538: 72 YO female, never smoked, clinically evaluable only after 11 days of study drug as a cure at the EOS. The patient was treated for a new right middle lobe infiltrate of uncertain bacterial etiology, which resolved completely by the EOS. Reviewer agreed.*

- *#65430540: 69 YO male, never smoked, clinically evaluable only after 7 days of therapy as a cure at the EOS. This patient had a right middle lobe pneumonia which resolved by the EOS. This patient was unevaluable as per the Reviewer because he did not receive the minimum required 80% of therapy.**

- *#65430809: 85 YO female, never smoked, clinically evaluable only after 10 days of study drug for a new left lower lobe pneumonia which resolved by the EOS. Reviewer agreed.*

Ciprofloxacin/Ciprofloxacin (N = 12):

- *#51110106: 70 YO male, smoker, clinically evaluable only after 7 days of therapy as a cure for new bibasilar infiltrates without a bacterial isolate. The patient was withdrawn after 7 days for unknown reasons but he did not receive alternative antimicrobials and had improvement on the repeat CxR. This patient would be unevaluable as per the Reviewer because he did not receive the minimum duration of therapy (80%) to be considered evaluable as a cure. **

- *#51150122: 75 YO female, smoker, clinically and bacteriologically evaluable after 10 days of therapy as a cure at the EOS. The patient presented with bilateral infiltrates on initial CxR, which improved and had growth of Haemophilus influenzae in the initial sputum. The isolate was presumed eradicated in the face of clinical improvement and the inability to produce additional sputum. Reviewer agreed.*

- *#51180069: 61 YO female, never smoked, clinically evaluable only after 24 days of therapy for a new left lower lobe infiltrate that resolved. The patient was assessed as a cure at both the EOT and EOS. Reviewer agreed.*

- *#52110782: 71 YO male, never smoked, clinically and bacteriologically unevaluable after 1 day of therapy for a questionable new infiltrate. The patient died. Initial sputum revealed mixed flora, and a severe pneumothorax developed on the first day which appeared related to the cause of death. Reviewer agreed.*

- *#53860247:80 YO female, never smoked, clinically evaluable only as a cure at the EOT and EOS. The patient received 14 days of study drug for a right lower lobe pneumonia which resolved completely. Reviewer agreed.*

- *#54090345: 72 YO male smoker, clinically evaluable only after 8 days of therapy as an improvement. Initial CxR revealed ARDS with bilateral infiltrates and no bacterial etiology. The patient was withdrawn from the study because of respiratory failure and despite improvement on the CxR. No further antimicrobial therapy was given. Reviewer considered this patient unevaluable because there was no EOS evaluation.**

- *#54830116: 28 YO female, never smoked, clinically evaluable only after 10 days of therapy as an EOT improvement. The patient was treated for a new right basilar infiltrate without a bacterial pathogen. This patient was unevaluable per the Reviewer because there was no EOS visit.**

- *#54830254:72 YO male, never smoked, clinically and bacteriologically evaluable after 8 days of therapy as an EOS cure with presumed eradication of the baseline sputum isolate, Aerococcus spp. Had new bilateral infiltrates at onset which completely resolved and no further therapy was provided. Reviewer agreed.*

- *#55100609: 80 YO male, smoker, clinically evaluable only after 7 days of therapy for a right upper lobe pneumonia. This patient was classified as a failure and therapy was changed to piperacillin on day 8. Reviewer agreed that this patient should be carried forward as a failure.*

- *#55110619: 59 YO male, never smoked, neither clinically nor bacteriologically evaluable after 11 days of therapy. This patient was withdrawn from the study during the post-therapy period because he developed septic shock associated with a central line and died. No baseline pathogen was isolated and the patient was treated in violation of the protocol from day 1 with vancomycin, aztreonam, and clindamycin. Reviewer agreed with the unevaluability of this patient in view of the treatment with multiple antimicrobials in violation of the protocol.*

- *#55130622: 41 YO male, smoker, clinically and bacteriologically evaluable after 14 days of therapy for a bilateral pneumonia which completely resolved. The patient was classified as an EOT and EOS "cure" with presumed eradication of the baseline pathogens, Haemophilus parainfluenzae and Morganella morganii. Reviewer agreed.*

- *#56280117: 35 YO male, smoker, clinically and bacteriologically evaluable after 14 days of therapy for a bilateral pneumonia apparently due to Haemophilus influenzae, which completely resolved. This patient was lost to follow-up and therefore unevaluable as per the reviewer's criteria.**

***Medical Officer's Comment**: As can be appreciated by the synopsis of the above 27 patients, there was concordance between the MO and the sponsor both in terms of evaluability and outcome assessments. The only exceptions were in 3 trovafloxacin-treated and 4 ciprofloxacin-treated patients who were excluded from the MO's evaluable population because they either had no EOS visit or they did not receive the minimum duration of therapy necessary to be assessed as "cures".*

The MO was satisfied however, that all cases evaluated were seen in patients already hospitalized, that all failures were carried forward and that the sponsor generally adhered to the protocol. Because of the above, the MO elected to accept the sponsor's determinations of evaluability and outcome in all cases. The only exceptions to the above were the exclusion from the MO's evaluable population of those 16 trovafloxacin and 24 ciprofloxacin patients who did not have an EOS visit and therefore did not meet the MO's evaluability criteria. An additional 4 patients were excluded from the MO's population because they were classified as cures after 7 days of therapy only and therefore did not meet the pre-specified minimum duration of therapy necessary to be evaluable as per the MO.

The patients who did not have an EOS visit are listed by study arm below:

Trovafloxacin (N = 16):

- *#51110129: cure*
- *#51120280: improvement*
- *#51190227: cure*
- *#51740016: improvement*
- *#51910196: improvement*
- *#53860207: cure*
- *#54070351: cure*
- *#54090346: cure*
- *#54090348: cure*
- *#54100363: cure*
- *#54830115: improvement*
- *#56230311: improvement*
- *#58350329: improvement*
- *#59850145: cure*
- *#64040533: cure*

- *#64040802: improvement*

Ciprofloxacin (N = 24)

- *#51110107: cure*
- *#51120221: cure*
- *#51120279: improvement*
- *#51740014: cure*
- *#51880002: cure*
- *#51910040: improvement*
- *#51930029: cure*
- *#53860033: improvement*
- *#53860252: improvement*
- *#54090345: improvement*
- *#54100362: improvement*
- *#54830116: improvement*
- *#54830125: improvement*
- *#54830256: cure*
- *#55130621: improvement*
- *#55410735: cure*
- *#56230306: cure*
- *#56270302: cure*
- *#56280117: cure*
- *#58340605: improvement*
- *#59870258: improvement*
- *#61270211: improvement*
- *#64040535: cure*
- *#65430539: cure*

The 4 additional patients excluded from the MO evaluable population are listed below:

Trovafloxacin (N=2)

- *#53860200: cure*
- *#65430540: cure*

Ciprofloxacin (N = 2)

- *#51110106: cure*
- *#54830769: cure*

Sponsor's Evaluable Populations: As per the sponsor, of the 129 trovafloxacin and 138 ciprofloxacin subjects who were randomized, 2 trovafloxacin and 3 ciprofloxacin subjects had an inappropriate baseline diagnosis and were excluded from the ITT and evaluable analyses.

Of the 127 trovafloxacin and 135 ciprofloxacin clinical ITT patients, 39 trovafloxacin and 32 ciprofloxacin patients were not clinically evaluable at the EOT therefore, 88 trovafloxacin-treated subjects and 103 ciprofloxacin-treated subjects were clinically evaluable at the EOT.

The most common reasons for exclusion from the clinical efficacy analyses can be seen in table 113.2.

71/127 trovafloxacin ITT subjects and 68/103 ciprofloxacin ITT subjects were included in the bacteriological ITT analysis. The remaining patients (56 and 67 per arm respectively, had negative baseline cultures.

Of the 88 clinically evaluable as per the sponsor, trovafloxacin patients, and the 103 ciprofloxacin patients, 41 and 51 per arm respectively, were not included in the bacteriologically evaluable analysis. Therefore, 47 trovafloxacin-treated subjects and 52 ciprofloxacin-treated subjects, were bacteriologically evaluable.

Baseline Characteristics:

78/127 alatrofloxacin/trovafloxacin-treated subjects (61%) were male and 49 (39%) were female. 76/137 ciprofloxacin-treated subjects (55%) were male and 61 (45%) were female. Treated subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups were generally comparable with respect to age, race, weight, and smoking classification.

The distribution of treated subjects according to smoking classification was similar between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups (38% and 39% ex-smoker, 42% and 40% never smoked, and 20% and 21% smoker, respectively).

The primary diagnosis for the clinically intent-to-treat subjects was nosocomial-acquired pneumonia. The median duration (range) since onset of pneumonia was 2 days (1-13 days), for subjects in the alatrofloxacin/trovafloxacin group and 2 days (1-12 days), for subjects in the ciprofloxacin group.

There were no marked differences between subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups with respect to medical history at baseline.

Copied below, from page 34 of the study report, is Sponsor's Table A:

Table A. Summary of Baseline Characteristics and Selected Underlying Diseases and Syndromes at Baseline All Treated Subjects

	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
Baseline Characteristic	**Number and Percentage (%) of Subjects**			
Age (years)				
Mean	68.2		70.7	
Minimum				
Maximum				
16-44	16	(13%)	15	(11%)
45-64	28	(22%)	19	(14%)
≥65	83	(65%)	103	(75%)
Smokers	25	(20%)	29	(21%)
Chronic Obstructive Lung Disease	33	(26%)	43	(31%)
Congestive Heart Failure	38	(30%)	45	(33%)
Diabetes Mellitus	28	(22%)	34	(25%)
Asthma	9	(7%)	12	(9%)

Ref.: Table 2.1.1 and Appendix I, Table 1

Evidenced by this table is that the 2 treatment groups were comparable in terms of age and underlying disease.

Of the clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups, 24/88 (27%) and 29/103 (28%) subjects, respectively, had post-surgical nosocomial pneumonia, 18/88 (20%) and 28/103 (27%) subjects, respectively, had nosocomial pneumonia resulting from suspected aspiration, 11/88 (13%) and 9/103 (9%) subjects, respectively, had nosocomial pneumonia resulting from mechanical ventilation, and 35/88 (40%) and 38/103 (37%) subjects, respectively, had nosocomial

pneumonia resulting from "other" reasons. (Subjects may have had more than one reason for nosocomial pneumonia.)

Severity Factors and APACHE II Scores at Baseline:

Of the clinically evaluable subjects, 29/88 (33%) of the alatrofloxacin/trovafloxacin subjects and 35/103 (34%) of the ciprofloxacin subjects required respiratory supportive therapy as baseline. This support was in the form of supplemental oxygen therapy or mechanical ventilation. 24/88 (27%) of the alatrofloxacin/trovafloxacin subjects and 22/103 (21%) of the ciprofloxacin subjects required mechanical ventilation.

The mean APACHE score at baseline for both treatment groups was 13.09.

In addition, among clinically evaluable subjects, 33/88 (38%) on the alatrofloxacin/trovafloxacin arm and 49/103 (48%) on the ciprofloxacin arm had bilateral pneumonia at baseline. 15/88 (17%) on the alatrofloxacin/trovafloxacin arm and 20/103 (19%) on the ciprofloxacin arm had abnormalities in ≥3 lobes at baseline.

Duration of Treatment:

On the alatrofloxacin/trovafloxacin arm, the subjects were treated for a median number of 5 days with alatrofloxacin and 7 days with trovafloxacin. The total median number of days of treatment was 10 (range 1 – 16). On the ciprofloxacin arm, the subjects were treated with a median number of 6 days intravenously and 7 days orally. The total median number of days of therapy was 10 on this arm also (range 1 – 17).

Concomitant Medications:

Protocol-specified Antimicrobials:
(Copied from page 38 of the study report):

Among treated subjects, 27 alatrofloxacin/trovafloxacin and 29 ciprofloxacin/ ciprofloxacin subjects received additional protocol-specified therapy with aztreonam (for documented baseline *Pseudomonas* infection), vancomycin (for documented baseline methicillin-resistant *Staphylococcus aureus*), clindamycin/placebo (for suspected anaerobic infections), and/or metronidazole/placebo (for suspected anaerobic infections). (Subjects in the alatrofloxacin/trovafloxacin group may have received aztreonam, vancomycin, and/or placebo; subjects in the ciprofloxacin group may have received aztreonam, vancomycin, clindamycin, and/or metronidazole.)

- Additional Therapy with Aztreonam and/or Vancomycin

  Nine (9) subjects in the alatrofloxacin/trovafloxacin group and 11 subjects in the ciprofloxacin group received additional therapy with aztreonam and nine subjects in the alatrofloxacin/trovafloxacin group and seven subjects in the ciprofloxacin group received additional therapy with vancomycin.

  The median number of days that subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups were treated with aztreonam was 6 and 8 days, respectively, and that for vancomycin was 8 days for subjects in both treatment groups.

- Additional Therapy with Clindamycin/Placebo and/or Metronidazole/Placebo

  Eleven (11) subjects in the alatrofloxacin/trovafloxacin group received clindamycin placebo and 14 subjects in the ciprofloxacin group received additional therapy with clindamycin. The median number of days that subjects in the alatrofloxacin/trovafloxacin

were treated with placebo was 6 days and the median number of days that subjects in the ciprofloxacin group were treated with clindamycin was 7 days.

No subjects in the alatrofloxacin/trovafloxacin group received metronidazole placebo and two subjects in the ciprofloxacin group received additional therapy with metronidazole. The median number of days that subjects in the ciprofloxacin group were treated with metronidazole was 4 days.

Medical Officer's Comment: From the sponsor's submission, it was apparent that approximately the same numbers of patients (10%) in each treatment group received protocol-specified concomitant antimicrobials. The investigators adhered to the use of additional anaerobic coverage only in the ciprofloxacin-treated patients, thus creating a "worst case" scenario in favor of that arm.

Other Medications:

One hundred twenty-seven (127/127, 100%) subjects in the alatrofloxacin/trovafloxacin group and 137 (137/137, 100%) subjects in the ciprofloxacin group received concomitant medications during study therapy. The most commonly used medications during therapy were analgesics, antibacterial drugs, anticoagulants, diuretics, electrolyte and water replacement, hypnotics, oxygen treatment, and ulcer-healing drugs.

Concomitant Antimicrobials:

During the study, 84 subjects in the alatrofloxacin/trovafloxacin group and 86 subjects in the ciprofloxacin group received antibiotics or other anti-microbials other than study drug for the following reasons:

- inadequate response (19, alatrofloxacin/ trovafloxacin; 14, ciprofloxacin),
- early discontinuation of study drug due to an adverse event (8, alatrofloxacin/trovafloxacin; 4, ciprofloxacin)
- other reasons (57, alatrofloxacin/trovafloxacin; 68, ciprofloxacin).

These numbers included subjects whose last dose of prior antibiotic therapy was taken on Day 1 of the study.

Medical Officer's Comment: The MO performed a separate audit on the CRFs of those patients on concomitant, non-protocol-specified antimicrobials and found that 59/84 trovafloxacin patients were clinically evaluable. Of the trovafloxacin patients who received alternative antimicrobials for other reasons, the most common reason was the development of a new and different infectious process. This is an expected phenomenon in this group of patients. On the ciprofloxacin arm, 59/86 subjects were clinically evaluable. Once again, the use of the category "other" predominantly referred to other infectious processes.

All cases where antimicrobials were utilized for "inadequate response" were carried forward as failures. Additionally, all of the "other" category of patients who received antimicrobials for a pulmonic process were carried forward as failures.

Protocol Deviations:
(Copied from page 38 of the study report and modified in Times New Roman font by the MO)

Deviations from protocol were noted for 51 subjects, of whom four subjects had more than one protocol deviation, during the study. These deviations were categorized as follows.

Subjects with nursing home acquired pneumonia, meeting inclusion criteria #2, were in some cases allowed to be treated in the nursing home rather than being transferred to a hospital. This was approved by Pfizer in cases where the nursing home was in the immediate vicinity of the hospital, study drug was prepared in the hospital pharmacy, and it was already customary to treat patients in the nursing home with intravenous antibiotics.

Subjects given optional study antibiotics (aztreonam or vancomycin) without meeting study defined requirements for use are included below. These patients were made not evaluable if they had a baseline pathogen potentially treatable by the optional antibiotic or if they had no identified baseline pathogen. Subjects with a baseline pathogen for which the optional antibiotic would have no activity were kept evaluable (e.g. vancomycin use in a subject with a gram negative infection).

- Inclusion criteria deviations included five subjects who were nursing home patients not admitted to the hospital, but approved for treatment in the nursing home; one subject who acquired nosocomial pneumonia when hospitalized for less than 48 hours; one subject who was admitted to the hospital with pneumonia acquired on prior admission; two subjects who had no baseline chest x-ray findings recorded; and three subjects who had no pneumonia on chest x-rays (1 trovafloxacin and 4 ciprofloxacin).

- Exclusion criteria deviations included two subjects who had recent alcohol abuse or dependence (1 trovafloxacin and 1 ciprofloxacin); two subjects who had past history of seizures (1 trovafloxacin and 1 ciprofloxacin); three subjects who had prior antibiotic use for >72 hours (; two subjects who received prior and/or concurrent systemic antibiotics (both ciprofloxacin, one with a baseline pathogen and evaluable); and two subjects who were on immunosuppressive therapy (2 ciprofloxacin).

- Study drug administration deviations included 11 subjects who received vancomycin without documented MRSA (6 trovafloxacin and 5 ciprofloxacin); eight subjects who received aztreonam without documented *Pseudomonas* (3 trovafloxacin and 5 ciprofloxacin); one subject who received both vancomycin and aztreonam with no positive cultures (ciprofloxacin); and one subject who was given 600 mg ciprofloxacin for the evening dose for 4 days in error (no known adverse consequences).

- Other deviations (study procedure) included two subjects who were unblinded; four subjects who were randomized out of sequence; one subject who was randomized but not treated; and five subjects who were withdrawn prior to consent due to missed randomization numbers.

Subjects with protocol deviations are listed in the following table.

Table B. Summary of Protocol Deviations All Randomized Subjects	
Inclusion Criteria	5112-0055; 5112-0056; 5112-0223; 5112-0222; 5112-0278; 5119-0227; 5188-0189; 5249-0158; 5396-0333; 5467-0139[a]; 5483-0771; 6404-0534
Exclusion Criteria	5115-0122; 5175-0047[b]; 5175-0155[c]; 5395-0338; 5409-0348; 5467-0137; 5628-0117; 6127-0212; 6376-0709[d]
Study Drug Administration	5111-0107; 5174-0015; 5174-0241; 5191-0040; 5175-0718; 5386-0202; 5386-0246; 5386-0250; 5467-0138; 5511-0617; 5511-0619; 5546-0091; 5546-0092; 5623-0307; 5623-0310; 5623-0311; 5623-0320; 5623-0324; 5623-0684; 5627-0301; 6376-0709[d]
Other: Study Procedure Randomization	5119-0226; 5191-0038 5173-0149; 5173-0150; 5175-0155[c]; 5175-0156; 5396-0334; 5407-0350; 5410-0343; 5467-0139[a]; 5834-0607; 6404-0815

a Subject 5467-0139 had one inclusion criteria deviation and one "other" deviation.
b Subject 5175-0047 had two exclusion criteria deviations.
c Subject 5175-0155 had one exclusion criteria deviation and one "other" deviation.
d Subject 6376-0709 had one exclusion criteria deviation and one study drug administration deviation
Ref.: Appendix II. E

Sponsor's Efficacy Analysis:

Sponsor-Defined Clinical Response:

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Table 113.4

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

Timepoint	Trovafloxacin N= 88	Ciprofloxacin N = 103
Number of patients evaluated at EOT	88 (100%)	101 (100%)
Cure	42 (48%)	51 (50%)
Improvement	26 (30%)	28 (28%)
Failure	20 (23%)	22 (22%)
Success (Cure + Improvement)	68 (78%)	79 (78%)
Number of patients evaluated at EOS	72 (100%)	79 (100%)
Cure	42 (58%)	53 (67%)
Improvement	8 (11%)	1 (1%)
Failure	20 (28%)	22 (28%)
Relapse	2 (3%)	3 (4%)
Success (Cure + Improvement)	50 (69%)	54 (68%)

The sponsor provided the following CIs without continuity correction factor:

EOT: Trovafloxacin versus Ciprofloxacin: -12.8%, 10.9% (Δ = 20)
EOS: Trovafloxacin versus Ciprofloxacin: -13.7%, 15.9% (Δ = 20)

The sponsor stated that (copied from page 41 of the study report):

Sponsor-defined clinical success rates (cure + improvement) were comparable between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups at the end of treatment (77% and 78%, respectively) and at the end of study (69% and 68%, respectively).

Medical Officer's Comment: The MO agreed with the sponsor's determination that the 2 agents were equivalent at both timepoints. CIs with continuity correction factor, were provided by the FDA statistician, Dr. Nancy Silliman:

EOT: Trovafloxacin versus Ciprofloxacin: -13.9%, 12.0% (Δ = 20)
EOS: Trovafloxacin versus Ciprofloxacin: -15.0%, 17.2% (Δ = 20)

The results seen in the ITT population were similar, with an overall success rate at the EOT of 80/127 (63%) for the trovafloxacin-treated patients as compared to 94/135 (70%) for the ciprofloxacin-treated patients (CI: -18.8%, 5.6% with continuity correction factor (Δ = 20). Thus indicating equivalence of ciprofloxacin at this early timepoint.

At the EOS, the overall success rate was 77/127 (61%) trovafloxacin versus 91/135 (67%) ciprofloxacin, (CI: -19.1%, 5,6% with continuity correction factor (Δ = 20). Once again it appeared as if trovafloxacin was equivalent to ciprofloxacin in this broader population at the MO TOC, the EOS.

Although clinical response by severity of illness can be found below, the MO found that patients on ciprofloxacin with mild disease had a higher response rate as compared to the trovafloxacin-treated patients, thus accounting for the numerical superiority of ciprofloxacin in the ITT population.

Clinical Response by Baseline Severity:

Table 113.5

Sponsor-Defined Clinical Response/Clinically Evaluable Population with Mild/Moderate Disease at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Trovafloxacin N= 59	Ciprofloxacin N = 68
Number of patients evaluated at EOT	59 (100%)	66 (100%)
Cure	29 (49%)	39 (59%)
Improvement	20 (34%)	17 (26%)
Failure	10 (17%)	10 (15%)
Success (Cure + Improvement)	49 (83%)	56 (85%)
Number of patients evaluated at EOS	51 (100%)	53 (100%)
Cure	31 (61%)	39 (74%)
Improvement	8 (16%)	1 (2%)
Failure	10 (20%)	10 (19%)
Relapse	2 (4%)	3 (6%)
Success (Cure + Improvement)	39 (76%)	40 (75%)

Medical Officer's Comment: The clinical success rates were comparable between the 2 arms for this subgroup of patients. Interestingly, and as stated above, ciprofloxacin was numerically superior to trovafloxacin in the ITT population for this subgroup only.

Below is the sponsor's table of clinical response for those patients with "severe" disease. Patients were defined as having severe disease if they required mechanical ventilation or on a fractional inspired oxygen concentration of ≥ 0.35 to maintain an arterial oxygen tension of 60 mmHg.

Table 113.6
Sponsor-Defined Clinical Response/Clinically Evaluable Population with Severe Disease at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Trovafloxacin N= 29	Ciprofloxacin N = 35
Number of patients evaluated at EOT	29 (100%)	35 (100%)
Cure	13 (49%)	12 (34%)
Improvement	6 (34%)	11 (31%)
Failure	10 (17%)	12 (34%)
Success (Cure + Improvement)	19 (66%)	23 (66%)
Number of patients evaluated at EOS	21 (100%)	26 (100%)
Cure	11 (52%)	14 (54%)
Improvement	-	-
Failure	10 (48%)	12 (46%)
Relapse	-	-
Success (Cure + Improvement)	11 (52%)	14 (54%)

Medical Officer's Comment: From this table, it can be appreciated that the 2 treatment arms were numerically equivalent for this subgroup of patients and that overall response was approximately 10 percentage points less at both the EOT and the EOS. Similarly equivalent results also occurred in the ITT population.

Sponsor-Defined Clinical Response for Clinically and Bacteriologically Evaluable subjects:

Table 113.7
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= 47	Ciprofloxacin N = 52
Number of patients evaluated at EOT	47 (100%)	52 (100%)
Cure	19 (40%)	21 (40%)
Improvement	14 (305)	18 (35%)
Failure	14 (30%)	13(25%)
Success (Cure + Improvement)	33 (70%)	39 (75%)
Number of patients evaluated at EOS	39 (100%)	38 (100%)
Cure	19 (49%)	24 (63%)
Improvement	3 (13%)	0
Failure	14 (36%)	13 (34%)
Relapse	1(3%)	1 (3%)
Success (Cure + Improvement)	24 (62%)	24 (63%)

Medical Officer's Comment: *It appeared as if in this subpopulation, there was a slight numerical superiority of ciprofloxacin to trovafloxacin at the EOT, however, this difference was no longer apparent at the EOS. Overall, the results of this subpopulation mirror those for all clinically evaluable patients.*

Clinical Response by Baseline Pathogen:

Table 113.8
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3.1 by MO)

		Trovafloxacin			Ciprofloxacin		
Pathogen		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	8	7	88	9	8	89
	EOS	6	5	83	7	6	86
Moraxella catarrhalis	EOT	1	0	0	4	3	75
	EOS	1	0	0	2	1	50
Streptococcus pneumoniae	EOT	4	2	50	6	5	83
	EOS	4	2	50	4	3	75
Stenotrophomonas maltophilia	EOT	2	2	100	1	1	100
	EOS	2	2	100	1	1	100
Haemophilus parainfluenzae	EOT	5	5	100	3	2	67
	EOS	5	5	100	2	1	50
Klebsiella pneumoniae	EOT	4	3	75	7	3	43
	EOS	4	2	50	5	1	20
Pseudomonas aeruginosa	EOT	15	10	67	11	6	55
	EOS	13	8	62	8	2	25
Klebsiella oxytoca	EOT	3	2	67	2	2	100
	EOS	3	2	67	-	-	-
Escherichia coli	EOT	7	5	71	5	4	80
	EOS	6	3	50	5	4	80
Proteus mirabilis	EOT	3	2	67	1	1	100
	EOS	2	2	50	1	1	100
Morganella morganii	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Acinetobacter spp.	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
Staphylococcus aureus	EOT	11	7	64	10	8	80
	EOS	8	4	50	6	4	67
Serratia marcescens	EOT	2	2	100	1	1	100
	EOS	1	1	100	1	1	100
Enterococcus faecalis	EOT	2	1	50	1	0	0
	EOS	2	1	50	1	0	0
Enterobacter cloace	EOT	1	1	100	4	3	75
	EOS	1	1	100	2	1	50
Enterobacter aerogenes	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Neisseria meningitidis	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Providencia spp.	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Aerococcus spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Citrobacter diversus	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Corynebacterium spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
Haemophilus parahemolyticus	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Legionella pneumophilia	EOT	2	2	100	-	-	-
	EOS	2	2	100	-	-	-
Streptococcus anginosus	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Total	EOT	74	55	74.3	74	52	70.3
	EOS	67	42	62.6	53	30	56.6

Medical Officer's Comment: *The results in table 113.8 closely mirror those in table 113.4, with a clinical response in the 70% range at the EOT which decreased by the EOS to 62.6% for the trovafloxacin-treated patients as compared to a much lower 56.6% for the ciprofloxacin-treated patients.*

Notable to the MO was the lower clinical response rate of the patients treated with ciprofloxacin who had Enterobactericiae.

CIs were not applied to this variable as each patient could have had more than 1 bacterial isolate.

Table 113.9
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Requested Pathogens Only: Modified 5.3.1 by MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	8	7	88	9	8	89
	EOS	6	5	83	7	6	86
Escherichia coli	EOT	7	5	71	5	4	80
	EOS	6	3	50	5	4	80
Klebsiella pneumoniae	EOT	4	3	75	7	3	43
	EOS	4	2	50	5	1	20
Staphylococcus aureus	EOT	11	7	64	10	8	80
	EOS	8	4	50	6	4	67
Pseudomonas aeruginosa	EOT	15	10	67	11	6	55
	EOS	13	8	62	8	2	25
Total	EOT	45	32	71.1	42	29	69
	EOS	37	22	59.4	31	17	54.8

Medical Officer's Comment: *When only clinical response by requested pathogen was assessed, the clinical response rates are essentially unchanged although slightly lower. It appeared as if trovafloxacin had better activity versus Pseudomonas aeruginosa and that ciprofloxacin had better activity versus Staphylococcus aureus.*

CIs were not applied to this variable as each patient could have had more than 1 bacterial isolate.

Clinical Response by Ventilator Status:

The MO requested that the sponsor provide an assessment of clinical response for this subpopulation.

Table 113.10
Sponsor-Defined Clinical Response/Clinically Evaluable Population requiring Mechanical Ventilation at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Trovafloxacin N= 24	Ciprofloxacin N = 22
Number of patients evaluated at EOT	24 (100%)	22 (100%)
Cure	10 (50%)	8 (36.4%)
Improvement	6 (31.2%)	6 (27.3%)
Failure	8 (18.8%)	8 (36.4%)
Success (Cure + Improvement)	**16 (66.7%)**	**14 (63.6%)**
Number of patients evaluated at EOS	18 (100%)	16 (100%)
Cure	10 (59.3%)	8 (50%)
Improvement	-	-
Failure	8 (22.2%)	8 (50%)
Relapse	-	-
Success (Cure + Improvement)	**10 (55.6%)**	**8 (50%)**

Medical Officer's Comment: As expected, clinical response was worse overall in this apparently more ill population by about 10 percentage points at both the EOT and the EOS. Trovafloxacin appeared numerically superior to ciprofloxacin at the MO TOC, the EOS.

Signs and Symptoms:
(Copied from page 50 of the study report)

The percentage of clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups with moderate or severe signs and symptoms of pneumonia at baseline was as follows: dyspnea (54%, each group), cough (63% and 58%, respectively), pleuritic chest pain (16%, each group), chills/rigor (14%, each group), and increased sputum volume (58% and 56%, respectively).

In both treatment groups, the percentage of subjects with these signs and symptoms of pneumonia decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects.

The percentage of clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups with additional signs and symptoms present at baseline, including fever, focal abnormal auscultatory findings (FAAF), and diffuse abnormal auscultatory findings (DAAF) was as follows: documented fever (54% and 50%, respectively), FAAF (73% and 84%, respectively), and DAAF (56% and 50%, respectively). The percentage of subjects with these signs and symptoms decreased from baseline to the end of treatment, with further decreases generally noted at the end of study. Similar trends were observed among clinically intent-to-treat subjects.

In addition, among the clinically evaluable subjects who were febrile within 24 hours of the baseline visit, the mean (± standard deviation) time to afebrile was 3.51 days (± 2.79) and 4.04 days (± 2.95) for subjects in the alatrofloxacin/trovafloxacin (n=47) and ciprofloxacin (n=51) groups, respectively. Among the clinically intent-to-treat subjects, the mean (± standard

deviation) time to afebrile was 3.84 days (± 2.92) and 4.08 days (± 2.97) for subjects in the alatrofloxacin/trovafloxacin (n=61) and ciprofloxacin (n=63) groups, respectively.

A summary of the percentage of subjects with mild, moderate, or severe clinical signs and symptoms of pneumonia at baseline, end of treatment, and end of study is presented in the following table.

Table C. Summary of Clinical Signs and Symptoms

	Alatrofloxacin ↓ Trovafloxacin			Ciprofloxacin ↓ Ciprofloxacin		
	Baseline	EOT	EOS	Baseline	EOT	EOS
Sign/Symptom[a]	Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms					
Dyspnea	77%	37%	14%	71%	23%	25%
Cough	79%	37%	22%	87%	39%	24%
PCP	28%	1%	0%	25%	2%	0%
Chills/Rigors	32%	2%	0%	28%	2%	0%
ISV	80%	23%	13%	81%	27%	14%
Fever	54%	6%	4%	50%	6%	1%
FAAF	73%	14%	13%	84%	29%	16%
DAAF	56%	22%	10%	50%	22%	21%
	Baseline	EOT	EOS	Baseline	EOT	EOS
Sign/Symptom[a]	Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms					
Dyspnea	74%	41%	16%	71%	28%	24%
Cough	79%	40%	24%	83%	40%	26%
PCP	25%	2%	0%	23%	3%	0%
Chills/Rigors	29%	5%	0%	24%	2%	0%
ISV	82%	32%	17%	81%	34%	15%
Fever	55%	14%	4%	50%	9%	3%
FAAF	75%	20%	16%	82%	31%	17%
DAAF	57%	30%	10%	53%	24%	20%

EOT=End of Treatment; EOS = End of Study; PCP=Pleuritic Chest Pain; ISV=Increased Sputum Volume; FAAF= Focal Abnormal Auscultatory Findings; DAAF=Diffuse Abnormal Auscultatory Findings

a Not all subjects were evaluated for all signs/symptoms at all timepoints.

Ref.: Tables 5.8.1a, 5.8.1b, 5.8.2a, and 5.8.2b

Medical Officer's Comment: *As can be appreciated from sponsor's Table C, the decrease in signs and symptoms was comparable between the 2 study arms. It appeared as if the ciprofloxacin patients had a more rapid initial decrease which however was matched by trovafloxacin by the EOS.*

Radiographic Changes (Copied from pages 50 and 51 of the study report):

Three clinically evaluable subjects in the ciprofloxacin group had positive baseline chest X-rays findings that were not obtained within the assessable window (Day -1 to Day 1).

All other clinically evaluable subjects (alatrofloxacin/trovafloxacin, 88 and ciprofloxacin, 100) had x-rays obtained within the appropriate window at baseline. Of these, 55 (63%) alatrofloxacin/trovafloxacin subjects and 51 (50%) ciprofloxacin subjects had unilateral abnormalities and 33 (38%) alatrofloxacin/trovafloxacin subjects and 49 (48%) ciprofloxacin

subjects had bilateral abnormalities. Fifteen (15) subjects (17%) in the alatrofloxacin/trovafloxacin group and 20 subjects (19%) in the ciprofloxacin group had abnormalities in ≥3 lobes at baseline. The mean number of lobes involved at baseline was 1.8 for subjects in the alatrofloxacin/trovafloxacin group and 1.9 for subjects in the ciprofloxacin group.

The majority of subjects in both treatment groups with positive baseline x-ray findings showed improvement (better or complete resolution) from baseline to the end of treatment (63%, each group) and to the end of study (68%, alatrofloxacin/trovafloxacin; 76%, ciprofloxacin). In addition, among clinically evaluable subjects in the alatrofloxacin/trovafloxacin group with abnormalities in ≥3 lobes at baseline, nine were clinically cured or improved and six were clinical failures at the end of treatment. Among clinically evaluable subjects in the ciprofloxacin group with abnormalities in ≥3 lobes at baseline, 11 were clinically cured or improved, eight were clinical failures, and one was not assessed at the end of treatment.

With the exception of two clinical intent-to-treat subjects in the alatrofloxacin/trovafloxacin group who had positive chest X-rays findings that were not recorded at baseline (both subjects were randomized but not treated), all clinical intent-to-treat subjects (alatrofloxacin/trovafloxacin, 125 and ciprofloxacin, 135) had positive x-rays findings recorded at baseline. Of these, 70 (55%) alatrofloxacin/trovafloxacin subjects and 65 (48%) ciprofloxacin subjects had unilateral abnormalities and 55 (43%) alatrofloxacin/trovafloxacin subjects and 70 (52%) ciprofloxacin subjects had bilateral abnormalities. In addition, 20 subjects (16%) in the alatrofloxacin/trovafloxacin group and 24 subjects (18%) in the ciprofloxacin group had abnormalities in ≥3 lobes at baseline. The mean number of lobes involved at baseline was 1.8 for subjects in the alatrofloxacin/trovafloxacin group and 1.9 for subjects in the ciprofloxacin group.

The majority of subjects in both treatment groups with positive baseline x-ray findings showed improvement (better or complete resolution) from baseline to the end of treatment (74%, alatrofloxacin/trovafloxacin; 76%, ciprofloxacin) and to the end of study (79%, alatrofloxacin/trovafloxacin; 89%, ciprofloxacin). Among clinically intent-to-treat subjects with abnormalities in ≥3 lobes at baseline, with the exception of five subjects in the alatrofloxacin/trovafloxacin group and four subjects in the ciprofloxacin group who were not clinically evaluable, nine in the alatrofloxacin/trovafloxacin group were clinically cured or improved and six were clinical failures at the end of treatment and 11 in the ciprofloxacin group were clinically cured or improved, eight were clinical failures, and one was not assessed at the end of treatment.

Medical Officer's Comment: *As expected the radiographic findings followed the clinical. The MO concurred with the sponsor's analysis.*

Bacteriologic Response:

As per the sponsor, the pathogen eradication rates were comparable at both the EOT and the EOS. The pathogen eradication rates were derived by collapsing pathogen outcomes of eradication and presumed eradication for a response of eradication, and by collapsing the outcomes of persistence and presumed persistence for a response of persistence. That is, the results were not necessarily based on actual repeat positive culture results.

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Table 113.11
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically Evaluable Population: Modified 5.4.1 by MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	8	7	88	9	9	100
	EOS	5	6	83	7	7	100
Moraxella catarrhalis	EOT	1	0	0	4	3	75
	EOS	1	0	0	2	1	50
Streptococcus pneumoniae	EOT	4	2	50	6	6	100
	EOS	4	2	50	4	4	100
Stenotrophomonas maltophilia	EOT	2	2	100	1	1	100
	EOS	2	2	100	1	1	100
Haemophilus parainfluenzae	EOT	5	5	100	3	2	67
	EOS	5	5	100	2	1	50
Klebsiella pneumoniae	EOT	4	2	50	7	3	43
	EOS	4	2	50	4	1	25
Pseudomonas aeruginosa	EOT	15	9	60	11	3	27
	EOS	13	10	77	8	2	25
Klebsiella oxytoca	EOT	3	2	67	1	1	100
	EOS	3	2	67	-	-	-
Escherichia coli	EOT	6	4	67	5	5	100
	EOS	4	3	75	5	5	100
Proteus mirabilis	EOT	3	3	100	1	1	100
	EOS	2	2	100	1	1	100
Morganella morganii	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
Acinetobacter spp.	EOT	1	0	0	0	0	0
	EOS	1	1	100	0	0	0
Staphylococcus aureus	EOT	11	6	55	9	6	67
	EOS	8	3	38	6	4	67
Serratia marcescens	EOT	2	1	50	1	1	100
	EOS	1	1	100	1	1	100
Enterococcus faecalis	EOT	1	0	0	1	0	0
	EOS	1	0	0	1	0	0
Enterobacter cloace	EOT	1	1	100	4	3	75
	EOS	1	1	100	2	1	50
Enterobacter aerogenes	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Neisseria meningitidis	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Providencia spp.	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
Aerococcus spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Citrobacter diversus	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Corynebacterium spp.	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
Haemophilus parahemolyticus	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Legionella pneumophilia	EOT	2	2	100	-	-	-
	EOS	2	2	100	-	-	-
Streptococcus anginosus	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Total	EOT	72	49	68	72	52	72.2
	EOS	61	44	72.1	52	34	55.3

Medical Officer's Comment: *MO table 113.11 mirrors MO table 113.8 with minor numeric differences. Interestingly however, the overall bacteriologic eradication rate of trovafloxacin at the EOS appeared superior to that of ciprofloxacin. Contributing to this may have been the low eradication rate of Pseudomonas aeruginosa on the ciprofloxacin arm as compared to the trovafloxacin arm.*

Table 113.12
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population/Requested Pathogens Only: Modified 5.4.1 by MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	8	7	88	9	9	100
	EOS	6	5	83	7	7	100
Escherichia coli	EOT	6	4	67	5	5	100
	EOS	4	3	75	5	5	100
Klebsiella pneumoniae	EOT	4	2	50	7	3	43
	EOS	4	2	50	4	1	25
Staphylococcus aureus	EOT	11	6	55	9	6	67
	EOS	8	3	38	9	6	67
Pseudomonas aeruginosa	EOT	15	9	60	11	3	27
	EOS	13	10	77	8	2	25
Total	EOT	44	28	63.6	41	26	63.4
	EOS	35	23	65.7	33	21	63.6

Medical Officer's Comment: *In table 113.12, the MO has shown only the eradication rates for the requested pathogens. Overall bacteriologic eradication rates were changed only slightly when the bacterial spectrum was narrowed to those organisms that appear to be clearly assosciated with NP. Additionally, both arms appear to be numerically equivalent. As noted in table 113.8, (clinical response by pathogen), trovafloxacin did not appear as active versus Staphylococcus aureus as compared to ciprofloxacin. Additionally, ciprofloxacin appeared numerically superior versus Escherichia coli and Haemophilus influenzae, but performed very poorly against Pseudomonas aeruginosa. The number of pathogens however was too small to be able to draw any valid conclusions.*

Bacteriologic Response in Subjects with *Pseudomonas aeruginosa* at Baseline:
(Copied from page 54 of the study report)

Of the 15 evaluable alatrofloxacin/trovafloxacin subjects and 11 ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, six alatrofloxacin/trovafloxacin (40%) and four ciprofloxacin (36%) received optional aztreonam therapy (dual therapy).

There appeared to be no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy in sponsor-defined clinical response at end of treatment or end of study. Subjects in both treatment groups who received dual therapy had a lower rate of persistence and presumed persistence for *Pseudomonas aeruginosa* at the end of treatment; however, due to the small number of subjects no definitive conclusions could be drawn.

Medical Officer's Comment: *The MO independently audited the 15 trovafloxacin and 11 ciprofloxacin subjects who had Pseudomonas aeruginosa isolated at baseline. The MO concurred with the sponsor that 6 and 4 patients per arm respectively, received aztreonam as per protocol.*

Of the 6 patients who received aztreonam on the trovafloxacin arm, 3 were clinical failures with eradication of the Pseudomonas, 2 were clinically improved at both the EOT and EOS visits with eradication and 1 patient was improved with persistence of the Pseudomonas aeruginosa. Resistance had not developed in this patient and no further therapy was utilized.

Of the remaining 9 patients on trovafloxacin who had Pseudomonas aeruginosa at baseline, 5 were clinical cures and the baseline pathogen was eradicated in 4 of these cases and persisted in one, once again without

further antimicrobial therapy being prescribed. 2 patients were clinical failures with persistence and 2 were clinically improved with eradication in 1 and persistence in 1.

On the ciprofloxacin arm, of the 4 patients who received aztreonam, only 1 was a clinical failure with persistence. 2 were clinical cures with eradication and 1 was clinically improved with persistence.

Of the remaining 7 patients on this arm, 6 were failures with persistence and 1 was a relapse at the EOS who had had persistence of the Pseudomonas in the sputum and who was subsequently treated with gentamicin.

Based on the above, the MO agreed with the sponsor that the number of patients evaluated was too small to make any firm statements. However, that the MO agreed to that the statement appended by the sponsor to the *draft labeling* ("As with other antibiotics, treatment of nosocomial infections due to Pseudomonas aeruginosa infections, may require combination therapy.") *was accurate.*

Superinfecting Pathogens and Colonizing Organisms:

3 patients on the trovafloxacin arm and 1 subject on the ciprofloxacin arm had superinfecting pathogens at the EOS requiring further therapy. Specifically, of the trovafloxacin-treated patients, one patient had *Morganella morganii*, 1 had *Proteus mirabilis* and *Enterobacter aerogenes*, and 1 patient had *Staphylococcus aureus* and *Serratia marcescens*. The ciprofloxacin patient was found to have *Enterococcus faecalis* and a *Pseudomonas* spp.

23 trovafloxacin-treated subjects were found to have colonizing organisms not requiring treatment as compared to 22 ciprofloxacin subjects.

Mortality:

The sponsor stated that amongst the 88 clinically evaluable trovafloxacin patents, there were 12 (14%) deaths within 5 days of the initiation of study therapy as compared to 17/103 (17%) on the ciprofloxacin arm.

Amongst the clinically ITT subjects, there were 30 deaths on the trovafloxacin arm and 34 on the ciprofloxacin arm. Copied below is sponsor's table D (page 59 of the study report):

Table D. Summary of Mortality

	Clinically Evaluable Subjects	
	Alatrofloxacin ↓ Trovafloxacin (N=88)	Ciprofloxacin ↓ Ciprofloxacin (N=103)
Number of Deaths[a]	12 (14%)	17 (17%)
≤48 Hours	0	0
Day 3 to 7	2 (2%)	0
Day 8 to 15	3 (3%)	3 (3%)
Day 16 to 45	7 (8%)	14 (14%)
	Clinically Intent-to-Treat Subjects	
	Alatrofloxacin ↓ Trovafloxacin (N=127)	Ciprofloxacin ↓ Ciprofloxacin (N=135)
Number of Deaths[a]	30 (24%)	34 (25%)
≤48 Hours	3 (2%)	3 (2%)
Day 3 to 7	11 (9%)	8 (6%)
Day 8 to 15	8 (6%)	7 (5%)
Day 16 to 45	8 (6%)	16 (12%)

a Number of deaths that occurred from initiation of study therapy.
Ref.: Appendix I, Tables 9.1 and 9.2

Medical Officer's Comment: Of note from table D is that most of the deaths on both treatment arms occurred after the conclusion of active therapy. The MO reviewed all deaths in the safety section of this review.

Clinical Failures:

The sponsor provided an analysis of the 20 trovafloxacin and 22 ciprofloxacin-treated subjects who were clinical failures at the EOT and carried forward as such to the EOS. This analysis has been copied from page 59 of the study report:

Eleven (11) of the 20 alatrofloxacin/trovafloxacin subjects designated as clinical failures were discontinued from treatment between Days 2 and 9 due to inadequate response. Three (3) subjects (Subjects 5106-0050, 5623-0323, and 5623-0682) who were clinical failures received optional aztreonam. Eighteen (18) subjects who were clinical failures received additional antibiotics for inadequate response. No subject was re-hospitalized or had hospitalization prolonged due to worsening of condition. Five subjects (Subjects 5174-0241, 5175-0719, 5175-0154, 5511-0618, and 5623-0682) died due to the disease under study.

Nine (9) of the 22 ciprofloxacin subjects designated as clinical failures were discontinued from treatment between Days 3 and 12 due to inadequate response. Of the subjects designated as

clinical failures, one subject (Subject 5175-0163) received optional vancomycin, one subject (Subject 5546-0092) received optional clindamycin and vancomycin, and one subject (Subject 6367-0745) received optional aztreonam and clindamycin. Nineteen (19) ciprofloxacin subjects who were clinical failures received additional antibiotics for inadequate response and two subjects (Subjects 5173-0150 and 5175-0163) were re-hospitalized or had hospitalization prolonged due to worsening of condition. Four subjects (Subjects 5174-0242, 5407-0349, 6127-0786, and 5175-0163) died due to the disease under study.

Medical Officer's Comment: *The MO reviewed all failures and found that 13/20 of the EOT failures on the trovafloxacin arm as well as 1 patient who was a relapse (EOS) were found to have had a baseline pathogen and thus were bacteriologically as well as clinically evaluable. On the ciprofloxacin arm, 13/22 EOT failures as well as 1/3 EOS relapses were in the same category. The MO elected to review these patients below:*

Trovafloxacin (N = 14)

Subject Number	Baseline Pathogen (Source)	Days on Treatment	Subject Clinical Response	Pathogen Bacteriologic Outcome
51060050	*Pseudomonas aeruginosa* (sputum)	9	Failure	Eradication (documented by culture at EOT and EOS, with superinfection with *Serratia marcescens.*
51190064	*Staphylococcus aureus* (sputum)	6	Failure	Presumed Persistence (patient died on day 6 after Vancomycin® started. No further cultures obtained)
51210230	*Escherichia coli* (blood)	15	Failure	Eradication (also had *Enterococcus faecalis* in blood repeatedly and MO determined that patient had an abdominal mass which appeared to be the cause of sepsis. Initial sputum not obtained but at day 7 until the EOS, the patient had persistent *Staphylococcus aureus* and intermittent *Pseudomonas aeruginosa.*
51210232	*Haemophilus influenzae* (blood)	9	Failure	Presumed Persistence (MO agreed with determination).
51750154	*Proteus mirabilis* (LRT, sputum)	8	Failure	Eradication (at EOT and EOS, patient was changed to gentamicin at day 8).
51880192	*Staphylococcus aureus* (LRT, sputum)	3	Failure	Persistent (MO agreed. Patient had *Staphylococcus aureus* in the EOT sputum at day 3, as well as *Pseudomonas aeruginosa.* Alternative therapy with gentamicin and Nafcillin® were instituted.
51910039	*Staphylococcus aureus* (bronchoscopy, sputum)	10	Failure	Presumed Persistent (MO agreed. Patient received Timentin®, Vancomycin®, clindamycin, and metronidazole. Repeat cultures were not obtained).
53860251	*Pseudomonas aeruginosa* (lung, sputum)	14	Failure	Persistent (MO agreed. Patient had *Pseudomonas aeruginosa* in EOT and EOS specimens and was treated with ciprofloxacin)
55100610	*Moraxella catarrhalis* *Streptococcus pneumoniae* (LRT, lung)	5	Failure	Presumed Persistent: both isolates (MO agreed that by default would apply this outcome. However, in all specimens after day 5, the patient had *Enterobactericiae* isolated. Therapy was guided against these organisms with ultimate resolution
55110618	*Klebsiella oxytoca* *Pseudomonas aeruginosa* *Staphylococcus aureus* (bronchoscopy)	2	Failure	All isolates Presumed Persistent (septic shock required the addition of multiple antimicrobials.)

56230323	*Pseudomonas aeruginosa* (LRT)	10	Failure	Eradication (MO agreed. *Pseudomonas* was eradicated prior to the institution of other antimicrobials including ciprofloxacin).
56230682	*Pseudomonas aeruginosa* (LRT, sputum)	5	Failure	Eradication (MO agreed with EOT result, *Pseudomonas* was again present at the EOS and after multiple other anti-pseudomonal antimicrobials.
61270209	*Enterococcus faecalis* (blood) *Escherichia coli* (blood, lung) *Klebsiella pneumoniae* (blood, lung) *Streptococcus pneumoniae* (lung, sputum)	3	Failure	Presumed Persistence all isolates.(MO Agreed with outcome assessment. Patient was treated with multiple other antimicrobials)
50300265	*Escherichia coli* *Klebsiella pneumoniae* (sputum)	9	Improvement Relapse	Eradication of *Escherichia coli* but Persistence of *Klebsiella pneumoniae.*

Ciprofloxacin (N = 14)

Subject Number	Baseline Pathogen (Source)	Days on Treatment	Subject Clinical Response	Pathogen Bacteriologic Outcome
51750163	*Staphylococcus aureus (sputum)*	15	Failure	Presumed Persistent (MO agreed. Patient was unable to produce a specimen and clindamycin was instituted).
51750717	*Klebsiella pneumoniae* *Streptococcus anginosus* (sputum)	10	Failure	Presumed Persistent (MO agreed. Patient was unable to produce a specimen and multiple antimicrobials were instituted).
51880191	*Haemophilus influenzae* *Streptococcus pneumoniae* (sputum)	3	Failure	Eradication (MO agreed that pathogens were eradicated at the time of the institution of Unasyn® for inadequate response. No further specimens were obtained).
53860201	*Enterococcus faecalis* *Klebsiella pneumoniae* *Staphylococcus aureus* (sputum)	9	Failure	Presumed Persistent (MO agreed. Patient was unable to produce a specimen and oxacillin and rifampin were instituted).
53950338	*Enterobacter cloacae* (sputum, blood) *Acinetobacter calcoaceticus* (sputum)	7	Failure	Persistent (MO agreed. Patient was unable to produce a specimen and alternative antimicrobials were instituted).
54090357	*Enterobacter aerogenes* *Escherichia coli* *Pseudomonas aeruginosa* (sputum)	10	Failure	Eradication of *Enterobacter* and *Escherichia coli* but persistence of *Pseudomonas* requiring gentamicin. MO agreed.
54090359	*Pseudomonas aeruginosa* (sputum)	10	Failure	Persistent (MO agreed. Patient required ticarcillin).
54670138	*Pseudomonas aeruginosa* (sputum)	9	Failure	Presumed Persistent (MO agreed in face of no repeat cultures and Primaxin® therapy).
55460092	*Klebsiella pneumoniae* (sputum)	10	Failure	Presumed Persistent (MO agreed)
56230309	*Haemophilus parainfluenzae* (LRT)	3	Failure	Presumed Persistent (MO agreed)
59030541	*Moraxella catarrhalis* *Citrobacter diversus* (not specified)	7	Failure	Eradication (MO agreed that the EOT specimen was negative. Patient then received cefotaxime for 8 days.)
63670745	*Pseudomonas aeruginosa* (lung, sputum)	14	Failure	Persistent (MO agreed. Patient received gentamicin and an anti-pseudomonal penicillin).
65430810	*Klebsiella pneumoniae* *Pseudomonas aeruginosa* (sputum)	12	Failure	Presumed Persistence of both isolates (MO agreed).

51750020	*Pseudomonas aeruginosa* (LRT, sputum)	10	Cure Relapse	Persistent at EOT and EOS (MO agreed)

The MO agreed with the sponsor's determination of bacteriologic outcome in all cases. On the trovafloxacin arm, there were 3 patients with Pseudomonas aeruginosa who were clinical failures despite the eradication of this organism. During the PID review, the MO found that the sponsor determined this outcome based on an EOT culture. If it was negative on the day of stopping therapy or within a day, then the organism was "eradicated". The MO could not disagree with this approach as there was objective evidence of eradication at the EOT timepoint and a further EOS determination could not be made as these patients were then treated with other antimicrobials. On the trovafloxacin arm , this also occurred in a patient with Proteus mirabilis.

On the ciprofloxacin arm, there were 2 patient only who had documented eradication at the EOT in the face of clinical failure and prior to the institution of alternative therapies. In one case the patient had Haemophilus influenzae and Streptococcus pneumoniae, and in the other, Moraxella catarrhalis and Citrobacter diversus.

None of the baseline pathogens from patients that failed therapy were resistant to the study drugs, either at baseline or if re-cultured.

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

Among the bacteriologically evaluable subjects, sponsor-defined clinical response was consistent with sponsor-defined pathogen outcome at the end of treatment except for 12 alatrofloxacin/trovafloxacin subjects and seven ciprofloxacin subjects. The MO has copied and modified sponsor table E from page 68 of the study report below:

Table 113.13
Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor: Table E) and the EOS (in Times New Roman font as per the MO)

Table E. Summary of Inconsistencies Between Sponsor-Defined Clinical Response and Pathogen Outcome at the End of Treatment Bacteriologically Evaluable Subjects			
Subject Number	**Baseline Pathogen**	**Clinical Response**	**Pathogen Bacteriological Response**
Alatrofloxacin/Trovafloxacin EOT/EOS		**EOT/EOS**	
5030-0265	*Klebsiella pneumoniae*	Improvement/Failed	Persistent/Persistent
5106-0050	*Pseudomonas aeruginosa*	Failure/ Failure	Eradicated/Eradicated
5111-0108	*Acinetobacter calcoaceticus*	Improvement/Cure	Persistent/Presumed Eradicated
5121-0230	*Escherichia coli*	Failure/ Failure	Eradicated/ Eradicated
5174-0016	*Pseudomonas aeruginosa* *Serratia marcescens*	Improvement/ Not Eval, no EOS	Persistent/ Not Eval., no EOS Persistent/ Not Eval., no EOS
5175-0154	*Proteus mirabilis*	Failure/ Failure	Eradicated/ Eradicated
5211-0136	*Pseudomonas aeruginosa* *Staphylococcus aureus*	Improvement/Improvement	Persistent/Persistent Persistent/ Persistent
5396-0335	*Escherichia coli*	Improvement/Cure	Persistent/ Eradicated
5409-0346	*Pseudomonas aeruginosa*	Cure/ Not Eval, no EOS	Persistent/ Not Eval., no EOS
5409-0358	*Pseudomonas aeruginosa*	Improvement/Cure	Persistent/Eradicated
5623-0323	*Pseudomonas aeruginosa*	Failure/Failure	Eradicated/ Eradicated
5623-0682	*Pseudomonas aeruginosa*	Failure/ Failure	Eradicated/ Eradicated
Ciprofloxacin			
5175-0020	*Pseudomonas aeruginosa*	Cure/Failure	Persistent/Persistent
5188-0191	*Haemophilus influenzae* *Streptococcus pneumoniae*	Failure/Failure	Eradicated/ Eradicated Eradicated/ Eradicated
5191-0040	*Pseudomonas aeruginosa*	Improvement/ Not Eval, no EOS	Persistent/ Not Eval., no EOS
5386-0252	*Pseudomonas aeruginosa*	Improvement/ Not Eval, no EOS	Persistent/ Not Eval., no EOS
5409-0357	*Enterobacter aerogenes* *Escherichia coli*	Failure/Failure	Eradicated/ Eradicated Eradicated/ Eradicated
5483-0125	*Staphylococcus aureus*[a]	Improvement/Not Eval, no EOS	Persistent/Not Eval., no EOS
5903-0541	*Moraxella catarrhalis* *Citrobacter diversus*	Failure/Failure	Eradicated/ Eradicated Eradicated/ Eradicated
a Resistant to study drug at baseline			