

**Study Population:**

It was expected that up to 320 subjects were to be randomized to one of two treatment groups, with each center enrolling approximately 8 subjects.

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**Inclusion and Exclusion Criteria:**

**Medical Officer's Comment:** *The criteria were the same as those used in study 154-113. For MO comment, please see page 394 of the MOR.*

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**Randomization and Blinding:**

**Medical Officer's Comment:** *Please see MOR page 394. This study was unblinded.*

**Dosage Form and Administration (Copied from pages 21 and 22 of the study report):**

Study drug medication was not blinded. Intravenous alatrofloxacin (equivalent to 300 mg trovafloxacin) for intravenous administration was provided in vials of 5 mg/mL (100 mg/20 mL) to be diluted to 1.5 mg/mL with 5% dextrose (D5W). Intravenous ceftazidime was provided in vials containing 2 g to be diluted in 50 mL sodium chloride intravenous infusion.

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Subjects received one of the following intravenous treatment regimens:

Alatrofloxacin 300 mg in 200 mL of D5W administered as a 60-minute infusion once daily in the morning (3 x 100 mg vials).

Ceftazidime 2 g in 50 mL sodium chloride for intravenous infusion administered twice daily as a 30-minute infusion.

Subjects unable to tolerate oral medication (e.g., ventilated subjects) or subjects with severe nosocomial pneumonias at baseline, defined as bacteremia or requiring mechanical ventilation or high fractional O<sub>2</sub> (>35% to maintain PO<sub>2</sub> at >60), may have received up to a total of 14 days of intravenous therapy.

When the investigator had determined a subject's resolution of fever with an improvement of symptoms and no new X-ray findings, the subject was switched from intravenous to oral therapy. Study drug for oral administration was in the form of trovafloxacin tablets and ciprofloxacin tablets and was packaged in blister packs. After 2 to 7 days of intravenous treatment with randomized study medication subjects received one of the following treatments orally:

Trovafloxacin 200 mg/day as a single active dose (2 x 100 mg tablet) administered in the morning.

Ciprofloxacin 1500 mg/day in two equally divided doses (1 x 750 mg tablet) once in the morning and once in the evening.

Subjects were to receive the appropriate oral therapy to complete a total maximum treatment duration of 10 to 14 days.

Subjects with *Pseudomonas* infection, methicillin-resistant *Staphylococcus aureus*, and/or anaerobic infection may have received optional antibiotic therapy, as follows:

**Optional gentamicin**

For subjects with documented *Pseudomonas* infection at baseline, treatment with open-label gentamicin, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in the ceftazidime/ciprofloxacin regimen. Treatment with gentamicin was to continue for a maximum of 14 days.

**Optional Vancomycin**

For subjects with documented methicillin-resistant *Staphylococcus aureus* infection at baseline, treatment with open-label vancomycin, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in either treatment regimen. Treatment with vancomycin was to continue for a maximum of 14 days.

**Optional Clindamycin / Metronidazole**

For subjects randomized to ceftazidime/ciprofloxacin who had suspected anaerobic nosocomial pneumonia at baseline, treatment with clindamycin or metronidazole, at medically appropriate and approved doses was to be initiated for a maximum of 14 days.

In renally impaired subjects (creatinine clearance  $\leq 50$  mL/min/1.73 m<sup>2</sup>) the dosages of both ceftazidime and ciprofloxacin required adjustment. If during the study the estimated creatinine clearance dropped below 5 mL/min/1.73 m<sup>2</sup> (Cockcroft-Gault equation; Appendix G - Protocol) the subject was to be withdrawn from treatment.

At intervals during treatment or at the time of premature discontinuation of study therapy, appropriate entries for tablets taken and returned were completed on the case report form (CRF) and the Pfizer Drug Inventory Record (PDIR). If doses were missed, the reason was to be recorded on the CRF.

**Medical Officer's Comment:** *With the exception that this study was unblinded, the overall design is the same as in study 154-113. The addition of concomitant antimicrobials was pathogen driven and was allowed only when a culture result was available.*

**Compliance:** Please see the MOR page 395.

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**Microbiologic Methods:**

Criteria for determining susceptibility to the study drugs are summarized below:  
(Copied from page 24 of the study report)

Criteria	Trovafoxacin		Ciprofloxacin		Ceftazidime	
	MIC ( $\mu\text{g/mL}$ )	Zone Diameter (mm) (5 $\mu\text{g}$ Disk)	MIC ( $\mu\text{g/mL}$ )	Zone Diameter (mm) 5 $\mu\text{g}$ Disk	MIC ( $\mu\text{g/mL}$ )	Zone Diameter (mm) 30 $\mu\text{g}$ Disk
Susceptible	$\leq 2$	$\geq 15$	$\leq 2$	$\geq 15$	$\leq 8$	$\geq 18$
Intermediate	4		4			
Resistant	$\geq 8$	$\leq 10$	$\geq 8$	$\leq 10$	$\geq 32$	$\leq 14$

Note: Trovafoxacin 5  $\mu\text{g}$  disks were never approved for clinical trial use and were subsequently replaced with 10  $\mu\text{g}$  disks. Results using the 10  $\mu\text{g}$  disks were not available during the study report period.

Susceptibility breakpoints for trovafoxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and zone diameter (mm) for ciprofloxacin and ceftazidime are based on NCCLS criteria.

**Clinical and Bacteriological Response:**

Please see the MOR page 396.

**Safety Assessments, Adverse Events, Clinical Laboratory Tests:**

Please the MOR page 397.

**Data Analysis:**

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Please see the introduction to the MOR, page 382 for an overview of the sponsor's subsets.

**Clinical Evaluability Criteria:**

See the introduction to the MOR, page 383, for a review of the sponsor's criteria and the MO's comments.

**Criteria for Bacteriological Evaluability:**

See the introduction to the MOR, page 383, for a review of the sponsor's criteria and the MO's comments.

**Primary and Secondary Endpoints for Efficacy:**

See the introduction to the MOR, page 383, for a review of the sponsor's endpoints and the MO's comments.

**Definitions of Response:**

See the introduction to the MOR, page 383, for a review of the sponsor's definitions and the MO's comments.

**Interim Analyses:**

No interim analyses were performed.

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**Demographics:**

As per the sponsor, 275 patients signed consent, 2 of these however, were withdrawn prior to randomization because they did not meet the study entry criteria. Thus 272 subjects were randomized and treated (135/274 (49.2%) to receive alatrofloxacin/trovafloxacin and 140/272 (51.8%) to receive ceftazidime/ciprofloxacin). All randomized subjects received treatment. (Total treated = 272).

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

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**Table 137.1  
Subject Disposition, All Enrolled Patients (As per the Sponsor)**

	274	Alatro/Trovafloxacin 300 mg → 200 mg	Ceftazidime/Ciprofloxacin 2 gm bid → 750 mg bid
Subjects with Signed Consent	274		
Withdrawn Prior to Randomization	2		
Randomized		135	140
Randomized, But Not Treated		0	0
All Treated Subjects		135 (100%)	140 (100%)
Withdrawn During Treatment		47 (35%)	39 (28%)
Completed Treatment		88 (65%)	101 (72%)
Withdrawn During Follow-up		17 (13%)	22 (16%)
Completed Study		86 (64%)	89 (64%)
Completed Treatment and Study		71 (53%)	79 (56%)
Withdrawn During Treatment and Study		32 (24%)	29 (21%)

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**Medical Officer's Comment:**

The MO realized that 135 + 140 = 275 randomized patients instead of 272 as stated by the sponsor. The MO queried the sponsor as to this discrepancy on 10/9/97. The sponsor provided a written response on 10/24/97. They stated that there were 274 subjects with signed consent of which 2 were withdrawn. Therefore there were 272 subjects randomized with signed consent but there were also 3 subjects randomized who did not sign consent. Thus there were 275 randomized subjects.

*There were a larger number of patients withdrawn during treatment on the trovafloxacin arm as compared to the ciprofloxacin arm. 19/47 (14%) of the discontinuation on the trovafloxacin arm were considered related to the study drug and included 7 withdrawals (5%) for an AE, 11 for an insufficient response (8%), and 1 because of a laboratory abnormality. 28/47 discontinuations on this arm were considered unrelated to the study drug and included 8 withdrawals because of an AE, 9 deaths, 5 "other", 1 protocol violation, 1 did not meet randomization criteria, and 4 laboratory abnormalities.*

*On the ceftazidime/ciprofloxacin arm, 16/39 discontinuations from treatment (11%) were considered related to the study drug. 15 of these were due to insufficient response and 1 to an adverse event. Of the 23/39 discontinuations unrelated to ceftazidime/ciprofloxacin therapy, 4 were due to an AE, 2 patients did not meet randomization criteria, 3 "other," 12 deaths, and 2 laboratory abnormalities.*

*Of the 53 trovafloxacin patients withdrawn from treatment, 15/47 completed the study as compared to 10/39 of the ceftazidime/ciprofloxacin patients.*

*Discontinuation from 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:

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**Table 137.2**  
**Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)**

	Alatro/Trovafloxacin	Ceftazidime/Ciprofloxacin
All Randomized Subjects	135 (100%)	140 (100%)
All Treated Subjects	135 (100%)	140 (100%)
Subjects with Inappropriate Baseline Diagnosis	3 (2%)	1 (<1%)
Clinically Intent- to- Treat Subjects	132 (98%)	139 (>99%)
Subjects with Negative Baseline Culture	66 (49%)	58 (41%)
Bacteriologically ITT Subjects	66 (49%)	81 (58%)
Clinically Evaluable Subjects	103 (76%)	109 (78%)
Clinically evaluable with baseline pathogen	53 (39%)	66 (47%)
Clinically Not Evaluable Subjects	29 (21%)	30 (21%)
Insufficient Therapy	21 (16%)	11 (8%)
No post-baseline clinical assessment	18 (13%)	16 (11%)
Prior Antibiotic therapy	0	0
Concomitant Antibiotic therapy	3 (2%)	7 (5%)
No post-baseline clinical assessment in evaluable analysis window	18 (13%)	16 (11%)
Other	3 (2%)	6 (4%)
Clinically evaluable at EOS	85 (63%)	89 (64%)
Clinically evaluable at EOS with baseline pathogen	42 (31%)	56 (40%)
Bacteriologically Evaluable Subjects	52 (39%)	66 (47%)
Bacteriologically Not Evaluable Subjects	51 (38%)	43 (31%)
No Baseline Pathogen	50 (37%)	43 (31%)
No post-baseline cultures or outside window	1 (<1%)	2 (1%)
Bacteriologically Evaluable at EOS	41 (30%)	55 (39%)
Baseline Blood Cultures Performed	126 (93%)	132 (94%)
Analyzed for Safety		
Adverse Events	135 (100%)	140 (100%)
Laboratory Data	119 (88%)	124 (89%)

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

**Medical Officer's Comment:** From table 137.2, it can be appreciated that on the alatrofloxacin/trovafloxacin arm there were 29/132 (21.9%) randomized and treated subjects with an appropriate baseline diagnosis who were clinically unevaluable at the EOT and an additional 18/132 (13.6%) clinically unevaluable at the EOS, thus there were a total of 47/132 (35.6%) that were clinically unevaluable.

On the ceftazidime/ciprofloxacin arm, there were 30/139(21.5%) randomized and treated subjects with an appropriate baseline diagnosis, who were clinically unevaluable at the EOT and an additional 20/139 (14.3%) subjects clinically unevaluable at the EOS. Thus, on the ceftazidime/ciprofloxacin arm there were 50/139 (35.9%) subjects who were clinically unevaluable.

Additionally, the bacteriologically evaluable population was a subset of the clinically evaluable and the bacteriological ITT population, which are 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.

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**Table 137.3**  
**Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)**

Center	Total Randomized N = 275 (100%)		Alatrofloxacin/Trovafloxacin				Ceftazidime/Ciprofloxacin			
			Randomized and Treated N = 135 (100%)		N = 135 (100%)		Randomized and Treated N = 140 (100%)		N = 140 (100%)	
5414	12	4.3	6	4.4	6	4.4	6	4.9	6	4.9
5437	1	0.3	0	-	0	-	1	0.7	1	0.7
5439	5	1.8	2	1.9	2	1.9	3	2.5	3	2.5
5795	1	0.3	1	0.7	1	0.7	0	-	0	-
5800	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5869	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5871	40	14.5	20	14.8	20	14.8	20	14.9	20	14.9
5877	14	5.0	8	5.9	8	5.9	6	4.9	6	4.9
5924	12	4.3	6	4.4	6	4.4	6	4.9	6	4.9
5926	21	7.6	11	8.1	11	8.1	10	7.5	10	7.5
5930	1	0.3	0	-	0	-	1	0.7	1	0.7
5935	6	2.4	2	1.9	2	1.9	4	2.8	4	2.8
5936	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5937	2	0.7	0	-	0	-	2	1.4	2	1.4
5940	1	0.3	1	0.7	1	0.7	0	-	0	-
5942	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5945	5	1.8	2	1.9	2	1.9	3	2.5	3	2.5
5948	3	1.0	2	1.9	2	1.9	1	0.7	1	0.7
5952	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5953	12	4.3	6	4.4	6	4.4	6	4.9	6	4.9
5955	27	9.8	13	9.6	13	9.6	14	5.1	14	5.1
5956	5	1.8	3	2.2	3	2.2	2	1.4	2	1.4
5957	6	2.9	3	2.2	3	2.2	3	2.5	3	2.5
5958	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5961	1	0.3	1	0.7	1	0.7	0	-	0	-
5962	1	0.3	0	-	0	-	1	0.7	1	0.7
5963	2	0.7	0	-	0	-	2	1.4	2	1.4
5964	1	0.3	1	0.7	1	0.7	0	-	0	-
5966	9	3.2	5	3.7	5	3.7	4	2.8	4	2.8
5972	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5973	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5975	11	4.0	6	4.4	6	4.4	5	3.6	5	3.6
5977	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5978	14	5.0	7	5.9	7	5.9	7	5.0	7	5.0
5979	6	2.4	2	1.9	2	1.9	4	2.8	4	2.8
5996	1	0.3	1	0.7	1	0.7	0	-	0	-
6072	3	1.0	2	1.9	2	1.9	1	0.7	1	0.7
6073	6	2.4	3	2.2	3	2.2	3	2.5	3	2.5
6075	5	1.8	3	2.2	3	2.2	2	1.4	2	1.4
6342	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
6357	4	1.6	2	2.2	2	2.2	2	1.4	2	1.4
6557	1	0.3	0	-	0	-	1	0.7	1	0.7
6569	1	0.3	1	0.7	1	0.7	0	-	0	-

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**Medical Officer's Comment:** *It can be appreciated from table 137.3, that no center had > 10% of the except for one center, #5871, which had approximately 15%. That center was in Greece and the MO elected to review those patients separately as well as in conjunction with the other patients. Otherwise, patients were well distributed over the 43 centers listed.*

*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.*

**Alatrofloxacin/Trovafloxacin (N = 17):**

- #57950577: 72 YO female, smoker, who was neither clinically nor bacteriologically evaluable. The patient died on the second study day of her underlying COPD, aggravated by NP. No organisms were isolated from the blood or the sputum, and the CxR revealed probable fluid overload. The Reviewer agreed that this patient was not evaluable because of the lack of confirmatory evidence of a NP.
- 58710073: 57 YO female, never smoked, clinically evaluable only. The patient received a 14 day course of therapy for a new left lower lobe infiltrate. The initial sputum sample had no growth and the patient was unable to produce a sample at the EOT and EOS. The patient was assessed as a cure at the EOT and at the EOS. The Reviewer agreed.
- #58710422: 61 YO male, smoker, who was clinically and bacteriologically evaluable. The patient received 7 days of therapy. The initial CxR revealed right lower lobe consolidation. The initial sputum sample as well as those obtained at the time of withdrawal revealed *Pseudomonas aeruginosa*. The patient was changed to imipenem, and was classified as a failure with persistence. Reviewer agreed.
- #59260083: 74 YO female, never smoked, neither clinically nor bacteriologically evaluable. This patient received 2 days of therapy. Initial sputum was induced but had no growth and the CxR was normal. Blood cultures were negative and sepsis was ruled out. The patient died on day 3 of her underlying disease processes which included a CVA and renal failure. Reviewer agreed that this patient was unevaluable because of lack of radiographic evidence of NP.
- #59450133: 73 YO male, smoker, clinically evaluable only. This patient received 12 days of therapy and was classified as a cure at both the EOT and EOS. The CxR revealed bilateral new atelectasis, and the initial sputum as well as blood cultures were negative. Reviewer agreed.
- #59520095: 72 YO male never smoked, clinically evaluable only after 14 days of study drug. Sputum cultures at the start of the study as well as at the EOT were notable for the absence of a bacterial pathogen and positive only for *Candida albicans*. Initial CxR revealed bibasilar new infiltrates. No other antimicrobial was utilized either prior to the study or concomitantly. The Reviewer agreed with the evaluability of this patient as well as with the outcome of cure at the EOS.
- #59550221: 18 YO male, never smoked, clinically and bacteriologically evaluable after 12 days of therapy. Initial CxR revealed "pneumonia". Initial specimens for culture were obtained bronchoscopically and revealed *Staphylococcus aureus*, *Haemophilus influenzae*, and *Bacteroides melaninogenicus*. Blood cultures were negative. Sputum obtained at day 7 revealed eradication of all isolates and at the EOS the patient was unable to produce a specimen. The patient was classified as a cure at the EOT and EOS with eradication of all pathogens. Reviewer agreed.
- #59550227: 70 YO female, never smoked, clinically and bacteriologically evaluable after 3 days of therapy as a failure with persistence of the original isolate, *Pseudomonas aeruginosa*. Notable is that the isolate had a MIC of 1 mcg/mL which was determined to be resistant to the study drug. The patient was treated with ceftazidime and fosfomycin through day 14. CxR revealed patchy bilateral lower lobe

*infiltrates, The Reviewer agreed that this patient was an evaluable failure and that the patient was carried forward appropriately.*

- *#59550245: 50 YO male, never smoked, clinically and bacteriologically evaluable after 3 days of therapy as a failure with presumed persistence of the original sputum isolate, Enterobacter aerogenes. CxR revealed left lower lobe infiltrate. The patient received a 10 day course of ceftriaxone and netilmicin for inadequate response and had resolution of the pneumonia. Reviewer agreed with the evaluability of this patient and determined that he was carried forward as a failure.*
- *#59559246: 71 YO female, smoker, clinically evaluable only, after 14 days of therapy as a cure. Sputum revealed only Neisseria meningitidis and the CxR revealed questionable lower lobe interstitial infiltrates. These early infiltrates improved with antimicrobial therapy and therefore the Reviewer agreed with the evaluability of this patient based on the initial CxR and with the outcome assessment.*
- *#59550268: 28 YO male, smoker, clinically and bacteriologically evaluable after 12 days of therapy. Initial specimens for culture were obtained bronchoscopically and revealed Morganella morganii and Staphylococcus aureus. An EOT sputum specimen revealed eradication of both organisms and the patient was unable to produce a specimen at the EOS. The CxR revealed left upper lobe infiltrate and early lower lobe infiltration. Reviewer agreed with the evaluability and outcome assessment of this patient.*
- *#59550290: 57 YO male, ex-smoker, clinically evaluable only as a cure at the EOT and EOS. The patient received 12 days of study drug for new left and right lower lobe infiltrates, without bacteriologic confirmation, which completely resolved by the EOT without any other antimicrobial coverage. Reviewer agreed.*
- *#59550291: 49 YO male, smoker, clinically and bacteriologically evaluable after 11 days of study drug as a cure at the EOT. The patient did not have an EOS visit. CxR revealed a right lower and a left upper lobe infiltrate. Initial bronchoscopic specimen revealed Haemophilus influenzae, which was eradicated, in follow-up specimens. The reviewer excluded this patient because there was no EOS visit.\**
- *#59560229: 92 YO male, ex-smoker, clinically evaluable only after 16 days of therapy as a cure at the EOS. This patient had a right middle lobe pneumonia which resolved by the EOS. There was no EOT visit and all sputum specimens were negative. Reviewer agreed with the evaluability and outcome assessments of the sponsor.*
- *#60750459: 89 YO female, ex-smoker, clinically and bacteriologically evaluable after 12 days of study drug. Initial blood cultures were notable for the growth of Escherichia coli and the initial sputum culture was negative. CxR revealed bilateral lower lobe patchy infiltrates. Reviewer agreed with evaluability and outcome assessments in this patient because of the initial CxR and the lack of additional antimicrobial therapy.*
- *#63570484: 67 YO female, ex-smoker, clinically and bacteriologically evaluable after 11 days of therapy. Initial CxR revealed consolidation of the right upper and middle lobes. Initial specimen for culture was obtained bronchoscopically, and revealed Pseudomonas aeruginosa which was persistent at the EOT. The patient was classified as a cure at the EOT with presumed eradication of the baseline pathogen, There was no EOS visit. Reviewer excluded the patient because of the lack of an EOS visit (transferred to nursing home), and therefore no appropriate follow-up. \**
- *#65690509: 89 YO female never smoked, clinically evaluable only after 12 days of therapy. CxR revealed left upper lobe consolidation. Initial sputum well as all follow-up specimens were negative as were the blood cultures. The patient was classified as a cure at the EOT and EOS. Reviewer agreed.*

\* Denotes patients excluded by MO for other reasons.

**Ceftazidime/Ciprofloxacin (N = 11):**

- #54390220: 60 YO male, smoker, neither clinically nor bacteriologically evaluable after 13 days of therapy. CxR revealed ARDS without a bacterial isolate. The patient did not receive alternative antimicrobials. The Reviewer agreed with the unevaluability of this patient because of the lack of confirmatory evidence of a NP.
- #58000582: 42 YO male, smoker, clinically and bacteriologically evaluable after 15 days of therapy as an improvement at the EOT and a failure at the EOS. The patient presented with a left lower lobe infiltrate on initial CxR, which improved and had growth of *Escherichia coli* in the initial culture obtained bronchoscopically. The isolate was eradicated in the face of clinical improvement at the EOT and no further specimens were obtainable. The patient received an additional 5 days of ciprofloxacin from days 15 – 19. Reviewer agreed that this patient was a clinical failure with eradication of the baseline pathogen.
- #58710080: 83 YO male, ex-smoker, clinically evaluable only after 11 days of therapy for a new right middle lobe infiltrate that resolved. The patient was assessed as a cure at both the EOT and EOS. Reviewer agreed.
- #58710433: 53 YO male, never smoked, clinically and bacteriologically evaluable after 6 days of therapy for a new left lower lobe infiltrate. Initial sputum revealed *Enterobacter aerogenes* which was persistent. The patient received aztreonam and Primaxin® after discontinuation of the study drugs. Classified as a failure with persistence. Reviewer agreed.
- #59240046: 72 YO male, never smoked, neither clinically nor bacteriologically evaluable after 2 days of study drug for diffuse bilateral interstitial pneumonia by CxR (ARDS). Initial sputum revealed both *Haemophilus influenzae* and *Streptococcus pneumoniae*. The *Haemophilus* was resistant to ceftazidime and the study drugs were stopped. The patient was changed to benzylpenicillin and he died at day 5 of multiorgan failure. Reviewer agreed that this patient was unevaluable because of lack of radiographic evidence of NP.
- #59530249: 71 YO male ex-smoker, neither clinically nor bacteriologically evaluable after 2 days of therapy. Initial CxR was read, as compatible with NP and *Pseudomonas aeruginosa* and *Candida albicans* were isolated bronchoscopically. The patient died of respiratory failure and septic shock on the day of withdrawal. Reviewer agreed that this patient was unevaluable because he did not receive the minimum duration of therapy necessary to be evaluable as a failure and there was no way of independently verifying the CxR.
- #59560231: 82 YO female, ex-smoker, clinically evaluable only after 12 days of therapy as an EOS cure. The patient was treated for a new left upper infiltrate without a bacterial pathogen. Reviewer agreed with evaluability and outcome assessments as per the sponsor.
- #59570280: 81 YO male, never smoked, clinically and bacteriologically evaluable after 13 days of therapy as a cure at the EOT and EOS with presumed eradication of the baseline bronchoscopically obtained isolate, *Proteus vulgaris*. Had new left lower lobe consolidation at onset which completely resolved. Reviewer agreed.
- #59570281: 30 YO male, never smoked, neither clinically nor bacteriologically evaluable after 1 day of therapy. CxR revealed left lower lobe infiltrate and bronchoscopically obtained specimen revealed *Staphylococcus aureus* and *Streptococcus pneumoniae*. Reviewer agreed because of absence of confirmatory evidence of NP.
- #59730318: 83 YO male, ex-smoker, clinically and bacteriologically evaluable after 12 days of therapy as a failure with presumed persistence of the baseline sputum isolates (*Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*). CxR revealed basilar consolidation of the

right lower lobe. The patient was changed to cefuroxime and aztreonam on day 12, but die during the post-study period of multiorgan failure.

- #60750457: 84 YO male, never smoked, neither clinically nor bacteriologically evaluable after 1 day of therapy for a "severe" right upper lobe pneumonia. No bacterial pathogens were isolated from blood or sputum and the patient died on study day 1 of respiratory failure secondary to pneumonia. Reviewer agreed that this patient was unevaluable because he did not receive enough therapy to be evaluable as a failure.

**Medical Officer's Comment:** As can be appreciated from the synopses of the above 28 patients, there was general concordance between the MO and the sponsor both in terms of evaluability and outcome assessments. The only exception was in 2 trovafloxacin-treated patients who would have been excluded from the MO's evaluable population because they had no EOS visit.

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. Additionally, the MO verified that the recordation of data from the CRFs to the PIDs was appropriate. Specifically, there was concurrence in all CxR and culture reports. 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 18 alatrofloxacin/trovafloxacin and 20 ceftazidime/ciprofloxacin patients who did not have an EOS visit and therefore did not meet the MO's evaluability criteria. An additional 3 alatrofloxacin/trovafloxacin and 2 ceftazidime/ciprofloxacin patients were excluded from the sponsor's EOT analysis because they had no EOT visit. These patients were included in the sponsor's EOS analysis and were also included in the MO's evaluable population.

2 patients were excluded from the MO's population because they were classified as cures after 6 and 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 (#59360110: alatrofloxacin/trovafloxacin and #59750407: ceftazidime/ciprofloxacin).

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

Alatrofloxacin/Trovafloxacin (N = 18):

- #58710078: improvement
- #58770360: cure
- #59260041: improvement
- #59360111: cure
- #59530250: cure
- #59550275: cure
- #59550291: cure
- #59550350: cure
- #59560230: cure
- #59570277: cure
- #59570237: cure
- #59580277: cure
- #59570278: cure
- #59580237: cure
- #59640321: improvement
- #59660311: improvement
- #60730474: cure
- #63420382: cure
- #63570484: cure

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*Ceftazidime/Ciprofloxacin (N = 20)*

- #58690026: *improvement*
- #58710079: *improvement*
- #58710425: *improvement*
- #58710438: *improvement*
- #58770358: *cure*
- #59240013: *cure*
- #59240015: *cure*
- #59240038: *cure*
- #59260042: *cure*
- #59260081: *cure*
- #59260084: *cure*
- #59350161: *cure*
- #59410148: *cure*
- #59560232: *improvement*
- #59580239: *improvement*
- #59660338: *cure*
- #59660340: *cure*
- #59790361: *cure*
- #60750458: *cure*
- #63570482: *cure*

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*The 5 additional patients who did not have an EOT visit are listed below:*

*Alatrofloxacin/Trovafloxacin (N=5)*

- #59450136: *cure*
- #59560229: *cure*
- #59750386: *cure*
- #58690025: *cure*
- #59340016: *cure*

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*Ceftazidime/Ciprofloxacin (N = 3)*

- #59560231: *cure*
- #63420381: *cure*
- #54390241: *cure*

**Sponsor's Evaluable Population:** As per the sponsor, of the 135 alatrofloxacin/trovafloxacin and 140 ceftazidime/ciprofloxacin subjects who were randomized, 3 alatrofloxacin/trovafloxacin and 1 ceftazidime/ciprofloxacin subjects had an inappropriate baseline diagnosis and were excluded from the ITT and evaluable analyses.

Of the 132 alatrofloxacin/trovafloxacin and 139 ceftazidime/ciprofloxacin clinical ITT patients, 29 alatrofloxacin/trovafloxacin and 30 ceftazidime/ciprofloxacin patients were not clinically evaluable at the EOT therefore, 103 alatrofloxacin/trovafloxacin-treated subjects and 109 ceftazidime/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.

66/132 alatrofloxacin/trovafloxacin ITT subjects and 81/109 ceftazidime/ciprofloxacin ITT subjects were included in the bacteriological ITT analysis. The remaining patients (66 and 58 per arm respectively), had negative baseline cultures.

Of the 88 clinically evaluable as per the sponsor, alatrofloxacin/trovafoxacin patients, and the 103 ceftazidime/ciprofloxacin patients, 51 and 43 per arm respectively, were not included in the bacteriologically evaluable analysis. Therefore, 52 alatrofloxacin/trovafoxacin-treated subjects and 66 ceftazidime/ciprofloxacin subjects were bacteriologically evaluable.

**Baseline Characteristics:**

88/135 alatrofloxacin/trovafoxacin-treated subjects (65%) were male and 497(35%) were female and 99/140 ceftazidime/ciprofloxacin-treated subjects (71%) were male and 41 (29%) were female. Treated subjects in the alatrofloxacin/trovafoxacin and ceftazidime/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/trovafoxacin and ceftazidime/ciprofloxacin treatment groups (28% and 36% ex-smoker, 37% and 35% never smoked, and 34% and 29% smoker, respectively.

The primary diagnosis for clinically-intent-to-treat subjects was nosocomial-acquired pneumonia. The median duration (range) since onset of pneumonia was 2 days (0 – 12 days) for subjects in the alatrofloxacin/trovafoxacin group and 2 days (1-19 days) for subjects in the ceftazidime/ciprofloxacin group.

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

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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)				
Baseline Characteristic	Alatrofloxacin ↓ Trovafoxacin (N=135)		Ceftazidime ↓ Ciprofloxacin (N=140)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	61.7		63.6	
Minimum				
Maximum				
16-44	25	(19%)	20	(14%)
45-64	43	(23%)	42	(30%)
≥65	67	(50%)	78	(56%)
Smokers	46	(34%)	41	(29%)
Asthma	4	(3%)	7	(5%)
Chronic Obstructive Lung Disease	25	(19%)	26	(19%)
Congestive Heart Failure	17	(13%)	28	(20%)
Diabetes Mellitus	16	(12%)	21	(15%)
Hepatic Disease	6	(4%)	5	(4%)
Impaired Renal Function	16	(12%)	22	(16%)
Ref.: Tables 2.1.1 and Appendix I, Table 1				

Of the clinically evaluable subjects in the alatrofloxacin/trovafoxacin treatment group, 28 (27%) had post-surgical pneumonia as compared to 33 (30%) of the subjects in the ceftazidime/ciprofloxacin group. Additionally, 31 (30%) and 24 (22%) subjects, respectively, had nosocomial pneumonia resulting from suspected aspiration, 21 (20%) and 28 (26%) subjects, respectively, had nosocomial pneumonia resulting

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from mechanical ventilation, and 23 (22%) and 24 (22%) 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 56/103 (54%) alatrofloxacin/trovafloxacin-treated subjects and 60/109 (55%) of the ceftazidime/ciprofloxacin treated subjects had severe disease. 48/103 (47%) and 54/109 (50%) respectively, had compromised respiratory function (included all subjects who were mechanically ventilated or required a fractional oxygen concentration of  $\geq 0.35$  to maintain an arterial oxygen tension of  $\geq 60$  mm Hg.).

41/103 (40%) of the alatrofloxacin/trovafloxacin-treated subjects and 37/109 (34%) of the ceftazidime/ciprofloxacin-treated subjects required mechanical ventilation.

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The mean APACHE score at baseline for both the alatrofloxacin/trovafloxacin-treated patients was 12.66 at baseline as compared to 13.59 for the ceftazidime/ciprofloxacin-treated group.

#### Duration of Treatment:

On the alatrofloxacin/trovafloxacin arm, the subjects were treated for a median number of 6 days with alatrofloxacin and 6 days with trovafloxacin. The total median number of days of treatment was 10 (range 1 – 23). On the ceftazidime/ciprofloxacin arm, the subjects were treated with a median number of 7 days intravenously and 7 days orally. The total median number of days of therapy was 12 on this arm (range 1 – 19).

***Medical Officer's Comment:** It appeared as if the ceftazidime/ciprofloxacin-treated subjects were marginally more severely ill at baseline and that they received 1 – 2 day longer courses of therapy.*

#### Concomitant Medications:

Protocol-specified Antimicrobials:  
(Copied from page 36 of the study report):

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Among treated subjects, 12 alatrofloxacin/trovafloxacin and 32 ceftazidime/ciprofloxacin subjects received additional protocol-specified therapy with gentamicin (for documented baseline *Pseudomonas* infection), vancomycin (for documented baseline methicillin-resistant *Staphylococcus aureus*), clindamycin, and/or metronidazole (for suspected anaerobic infections). (Subjects in the alatrofloxacin/trovafloxacin group may have received vancomycin; subjects in the ceftazidime/ciprofloxacin group may have received gentamicin, vancomycin, clindamycin, and/or metronidazole.) The use of these protocol-specified adjunctive antibiotics did not impact subject evaluability or clinical or bacteriologic outcome as long as they were used appropriately for the indicated baseline pathogen or had no impact on the baseline pathogen.

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#### • Additional Therapy with Gentamicin

Eight (8) subjects in the alatrofloxacin/trovafloxacin group and 17 subjects in the ceftazidime/ciprofloxacin group received additional therapy with gentamicin. Of the clinically evaluable subjects with a baseline pathogen of *Pseudomonas aeruginosa*, 5/8 subjects in the alatrofloxacin/trovafloxacin group and 10/17 subjects in the ceftazidime/ciprofloxacin group received gentamicin as adjunctive therapy. The alatrofloxacin/trovafloxacin subjects were assessed as fully evaluable despite this deviation from protocol. The median number of days that subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups were treated with gentamicin was 5 and 6 days, respectively.

**Medical Officer's Comment:** *The MO agreed that the use of adjunctive gentamicin therapy for patients with documented Pseudomonas aeruginosa infections was allowable since it was specified in a protocol amendment a priori. The use of other anti-pseudomonal agents was not specified, however, the MO elected to consider these patients as evaluable because the use of one or another aminoglycoside is clearly dependent upon regional differences in hospital sensitivity patterns.*

- Additional Therapy with Vancomycin  
Five (5) subjects in the alatrofloxacin/trovafloxacin group and 17 subjects in the ceftazidime/ciprofloxacin group received additional therapy with vancomycin. The median number of days that subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups were treated with vancomycin was 11 and 9 days, respectively.
- Additional Therapy with Clindamycin and/or Metronidazole  
One subject in the ceftazidime/ciprofloxacin group received additional therapy with metronidazole for 9 days.

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**Medical Officer's Comment:** *From the sponsor's submission, it was apparent that more patients in the ceftazidime/ciprofloxacin treatment group received protocol-specified concomitant antimicrobials. This increased usage should have created a "worst case" scenario in favor of that arm.*

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**Other Medications:**

135/135 (100%) subjects in the alatrofloxacin/trovafloxacin group and 140/140 (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.

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**Concomitant Antimicrobials:**

During the study, 69 subjects in the alatrofloxacin/trovafloxacin group and 84 subjects in the ceftazidime/ciprofloxacin group received antibiotics or other anti-microbials other than study drug for the following reasons:

- inadequate response (23, alatrofloxacin/ trovafloxacin; 28, ceftazidime/ciprofloxacin),
- early discontinuation of study drug due to an adverse event (3, alatrofloxacin/trovafloxacin; 1, ciprofloxacin)
- other reasons (43, alatrofloxacin/trovafloxacin; 55, ceftazidime/ciprofloxacin).

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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 alatrofloxacin/ trovafloxacin patients treated for other reasons were not clinically evaluable. Of the alatrofloxacin/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 ceftazidime/ciprofloxacin arm, 21 subjects were not 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" was carried forward as failures. Additionally, all of the "other" category of patients who received antimicrobials for a pulmonic process were carried forward as failures.*

*From the audit of all patients who received concomitant antimicrobial therapy, the MO disagreed with the sponsor's assessment of evaluability or outcome in the following patient:*

*Alatrofloxacin/Trovafloxacin (N=1):*

- #58770392: *Evaluable cure with presumed eradication of one of the presumed baseline pathogens, Streptococcus pneumoniae (as per the sponsor). The patient also had Staphylococcus aureus isolated from the baseline specimen. The patient received 14 days of study drug as well as vancomycin between days 6-14 for the development of MRSA. The sponsor has not provided MIC results. The sponsor determined that as the patient had radiographic resolution in conjunction with sterilization that an outcome of clinical cure was appropriate. However, the MO determined that this patient was unevaluable. This decision was mad because of the known activity of vancomycin versus Streptococcus pneumoniae. Additionally, the vancomycin was started on study day 6 even though, as per protocol, it may be utilized within the first 3 days of the documentation of MRSA. As no MIC information was provided, the appropriateness of the institution at this time cannot be determined.*

*(Note: additional 9 alatrofloxacin/trovafloxacin patients and 7 ceftazidime/ciprofloxacin patients with outcomes of cure or improvement would have been excluded by the MO because of concomitant antimicrobial usage. However, all patients were excluded previously because of the absence of an EOS visit or in the case of 1 ceftazidime/ciprofloxacin patient because of the assignment of an assessment of cure prior to the allowed minimum duration of therapy.)*

*Based on the above, the MO excluded an additional patient from the clinically evaluable population on the alatrofloxacin/trovafloxacin arm of the study and added 2 patients. Thus, the MO found that there were 85 clinically evaluable patients at the EOS.*

*On the ceftazidime/ciprofloxacin arm, the MO excluded 20 patients because of "no EOS visit." The MO found that there were 89 clinically evaluable patients at the EOS.*

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**Protocol Deviations:**

(Copied from page 38 of the study report)

Deviations from protocol were noted for 37 subjects, two of whom had more than one deviation, during the study. These deviations were categorized as follows.

- Inclusion criteria deviations included three subjects who did not give written informed consent, two subjects who did not have radiological evidence of nosocomial pneumonia at baseline, one subject who had a baseline chest x-ray performed on Day 2, one subject who had a pulmonary embolism rather than nosocomial pneumonia, one subject with no signs and symptoms consistent with nosocomial pneumonia, and one subject who was admitted to the hospital with nosocomial pneumonia but had been in the hospital for 4 days with an infective exacerbation of chronic obstructive pulmonary disease 3 days earlier.
- Exclusion criteria deviations included one subject with known hypersensitivity to study drugs, two subjects with known hypersensitivity to penicillin, one subject who received an investigational drug within 4 weeks of enrollment, two subjects who had evidence of drug or alcohol abuse or dependence, and two subjects who had a history of epilepsy.
- Study drug administration deviations included five subjects with *Pseudomonas* in the alatrofloxacin/trovafloxacin arm who received gentamicin, five subjects who received concomitant gentamicin without evidence of *Pseudomonas* infection, ten subjects who received concomitant vancomycin without having evidence of methicillin-resistant *Staphylococcus aureus* infection, one subject who received ceftazidime for 18 days, and one subject who received alatrofloxacin/trovafloxacin for 23 days.

With the exception of subjects who were not evaluable due to inappropriate baseline diagnosis and subjects who were not evaluable due to inappropriate use of optional antibiotics, none of the protocol deviations discussed above affected subject evaluability.

Subjects with protocol deviations are listed in the following table.

Inclusion Criteria	5439-0218 <sup>a</sup> ; 5926-0083; 5942-0145; 5956-0232; 5962-0261; 5966-0309; 5966-0339; 6075-0461; 6357-0482
Exclusion Criteria	5924-0047; 5926-0059; 5957-0281; 5979-0361; 5926-0010; 5930-0049; 5953-0256; 5439-0218 <sup>a</sup>
Study Drug Administration	5871-0422; 5439-0217; 5439-0219; 5439-0220; 5439-0241; 5800-0581; 5924-0037; 5926-0057; 5935-0143; 5945-0136; 5953-0251; 5953-0254; 5955-0248; 5955-0292; 5955-0349; 5958-0237; 5958-0239; 5961-0285 <sup>b</sup> ; 5966-0338; 6357-0481; 6357-0484
<p>a Subject 5439-0218 had an inclusion and an exclusion criteria deviation.</p> <p>b Subject 5961-0285 had two study drug administration deviations.</p>	

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*Medical Officer's Comment: The MO agreed with the exclusion of the patients as described by the sponsor with the exception of the patients listed previously who received concomitant antimicrobial therapy.*

**Sponsor's Efficacy Analysis:**

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**Sponsor-Defined Clinical Response:**

**Table 137.4**

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

Timepoint	Alatrofloxacin/Trovafloxacin N= 103	Ceftazidime/Ciprofloxacin N = 109
Number of patients evaluated at EOT	100 (100%)	107 (100%)
Cure	54 (54%)	52 (49%)
Improvement	20 (20%)	23 (21%)
Failure	26 (26%)	32 (30%)
<b>Success (Cure + Improvement)</b>	<b>74 (74%)</b>	<b>75 (70%)</b>
Number of patients evaluated at EOS	85 (100%)	89 (100%)
Cure	54 (64%)	48 (67%)
Improvement	2 (2%)	4 (1%)
Failure	26 (31%)	32 (28%)
Relapse	3 (4%)	5 (4%)
<b>Success (Cure + Improvement)</b>	<b>56 (66%)</b>	<b>52 (58%)</b>

The sponsor provided the following CIs without continuity correction factor:

EOT: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 8.3%, 16.1% ( $\Delta = 20$ )  
 EOS: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 5.9%, 21.8% ( $\Delta = 20$ )

The sponsor stated that: sponsor-defined clinical success rates (cure + improvement) supported equivalence between the 2 treatment arms at the EOT (74% and 70%, respectively) and were comparable between the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin treatment groups at the end of study (66% and 58%, respectively).

Of note, the results for center #5871, which enrolled 15% of the patients, were as follows: Trovafloxacin EOT: 11/18 (61%) and EOS: 10/17 (59%); Ceftazidime/ciprofloxacin: EOT: 10/16 (63%) and EOS 7/13 (54%). These results are consistent with those of the general population and support the pooling of the centers.

**Medical Officer's Comment:** *The MO agreed with the sponsor's determination that the 2 agents were equivalent at the EOT but the ceftazidime/ciprofloxacin combination appeared numerically less effective at the EOS. CIs with continuity correction factor, were provided by the FDA statistician, Dr. Nancy Silliman:*

EOT: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 9.3%, 17.1% ( $\Delta = 20$ )  
 EOS: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 8.1%, 23% ( $\Delta = 20$ )

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*Based on the FDA CI, the alatrofloxacin/trovafloxacin combination was superior to the ceftazidime/ciprofloxacin combination at the EOS (MO TOC).*

*The results seen in the ITT population were relatively similar, with an overall success rate at the EOT of 82/129 (64%) for the trovafloxacin-treated patients as compared to 88/136 (65%) for the ceftazidime/ciprofloxacin-treated patients (CI: -13.5%, 11.2% with continuity correction factor ( $\Delta = 20$ ). Thus indicating equivalence of ciprofloxacin at this early timepoint.*

*At the EOS, the overall success rate was 80/132 (61%) trovafloxacin versus 84/139 (60%) ciprofloxacin, (CI: -12.2%, 12.5% with continuity correction factor ( $\Delta = 20$ ). It therefore appeared as if trovafloxacin was equivalent to ciprofloxacin in this broader population at the MO TOC, the EOS.*

*The MO noted that the results from this trial were similar to those seen in the US study, 154-113, where the trovafloxacin EOT clinical response rate was 68/88 (78%) and the ciprofloxacin clinical response rate was 79/101 (78%). Thus the 2 agents were also equivalent at this early timepoint in that study. Clinical response was marginally lower in the current study.*

*At the EOS in 154-113, the trovafloxacin clinical response rate was 50/72 (69%) as compared to the ciprofloxacin arm, 54/79 (68%). In this study the response rate of both arms was lower, by 7 percentage points on the alatrofloxacin/trovafloxacin arm and by 10 percentage points on the ceftazidime/ciprofloxacin arm. The MO was unable to explain the lower rates in this trial especially for the ceftazidime/ciprofloxacin arm, except to postulate that the population on that arm was marginally more severely ill, and that the use of ceftazidime as the intravenous comparator agent had an effect. Although, the 2 populations appeared similar demographically, the overall number of severely ill patients on both arms was higher in this study (50%)*

*Although clinical response by severity of illness can be found below, the MO found that patients on ceftazidime/ciprofloxacin with mild/moderate disease had a lower response rate as compared to the alatrofloxacin/trovafloxacin-treated patients and that the clinical response rates in the more severely ill population were very similar. This as compared to study 154-113 where ciprofloxacin-treated patients had a higher clinical response rate in patients with mild/moderate disease and a similar response rate in patients with severe disease.*

**Clinical Response by Baseline Severity:**

**Table 137.5**

**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	Alatrofloxacin/Trovafloxacin N= 47	Ceftazidime/Ciprofloxacin N = 49
Number of patients evaluated at EOT	44 (100%)	47 (100%)
Cure	29 (66%)	26 (59%)
Improvement	10 (23%)	9 (26%)
Failure	5 (11%)	12 (15%)
<b>Success (Cure + Improvement)</b>	<b>39 (89%)</b>	<b>35 (74%)</b>
Number of patients evaluated at EOS	40 (100%)	42 (100%)
Cure	33 (83%)	29 (69%)
Improvement	1 ( 3%)	1 (2%)
Failure	5 (13%)	12 (29%)
Relapse	1 ( 3%)	0
<b>Success (Cure + Improvement)</b>	<b>34 (85%)</b>	<b>30 (71%)</b>

*Medical Officer's Comment:* 95% CI with continuity correction factor for the EOT was - 3.6%, 32% and for the EOS, it was - 6.5%, 33.6% ( $\Delta = 20$ ). Thus equivalence was not supported in this subgroup, but rather trovafloxacin was more effective. The clinical success rates were approximately the same at the EOT and the EOS on both arms of this study and the alatrofloxacin/trovafloxacin combination was numerically superior to the ceftazidime/ciprofloxacin at both timepoints. This did not occur in study 154-113 where the 2 arms were comparable for this subgroup of patients, and the comparators success rate was numerically superior to trovafloxacin's at the EOT (83% trovafloxacin versus 85% ciprofloxacin). At the EOS in study 154-113 the 2 arms were approximately equivalent (EOS trovafloxacin 76% versus 75% ciprofloxacin).

The superior success rate on the trovafloxacin arm in this trial can be explained by the open nature of this study. The much lower rate on the ceftazidime/ciprofloxacin arm can potentially be explained only by the inclusion of a more severely ill population as well as by the use of ceftazidime as a comparator agent.

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 a fractional inspired oxygen concentration of  $\geq 0.35$  to maintain an arterial oxygen tension of 60 mmHg.

**Table 137.6**

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

Timepoint	Alatrofloxacin/Trovafloxacin N= 56	Ceftazidime/Ciprofloxacin N = 60
Number of patients evaluated at EOT	56 (100%)	60 (100%)
Cure	25 (45%)	26 (43%)
Improvement	10 (18%)	14 (23%)
Failure	21 (38%)	20 (33%)
<b>Success (Cure + Improvement)</b>	<b>35 (63%)</b>	<b>40 (67%)</b>
Number of patients evaluated at EOS	45 (100%)	47 (100%)
Cure	21 (47%)	19 (40%)
Improvement	1 (2%)	3 (6%)
Failure	21 (47%)	20 (46%)
Relapse	2 (4%)	5 (11%)
<b>Success (Cure + Improvement)</b>	<b>22 (49%)</b>	<b>22 (47%)</b>

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**Medical Officer's Comment:** 95 % CI with continuity correction factor at the EOT was – 23.3%, 15% and at the EOS, - 20.5%, 25 % ( $\Delta = 20$ ). The validity of the CIs is suspect given the small numbers involved. From this table, it can be appreciated that the 2 treatment arms were numerically similar for this subgroup of patients and that overall response was approximately 20 percentage points less at both the EOT and the EOS. Similar results were found in study 154-113 where the EOT response was 66% for both arms and the EOS clinical response rate was 52% for the trovafloxacin arm and 54% for the ciprofloxacin.

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

**Table 137.7**  
**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= 52	Ciprofloxacin N = 66
Number of patients evaluated at EOT	50 (100%)	66 (100%)
Cure	21 (42%)	25 (38%)
Improvement	13 (26%)	16 (24%)
Failure	16(32%)	25(38%)
<b>Success (Cure + Improvement)</b>	<b>34 (68%)</b>	<b>41 (62%)</b>
Number of patients evaluated at EOS	41 (100%)	56 (100%)
Cure	23 (56%)	23 (41%)
Improvement	0	4 (7%)
Failure	16 (39%)	25 (45%)
Relapse	2( 5%)	4 ( 7%)
<b>Success (Cure + Improvement)</b>	<b>23 (56%)</b>	<b>27 (48%)</b>

**Medical Officer's Comment:** 95% CI with continuity correction factor at the EOT was –15.3%, 25%, and at the EOS was – 14.3%, 30% ( $\Delta = 20$ ). It appeared, as if in this subpopulation, that there was a numerical superiority of trovafloxacin to ceftazidime/ciprofloxacin at both timepoints, as compared to study 154-113 where 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 were about 10 percentage points lower than those for all clinically evaluable patients.

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Clinical Response by Baseline Pathogen:

Table 137.8

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

Pathogen		Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	7	7	100	7	5	71
	EOS	5	4	80	6	4	67
<i>Moraxella catarrhalis</i>	EOT	1	0	0	2	2	100
	EOS	1	0	0	2	1	50
<i>Streptococcus pneumoniae</i>	EOT	6	5	83	3	0	0
	EOS	4	3	75	3	0	0
<i>Stenotrophomonas maltophilia</i>	EOT	1	0	0	-	-	-
	EOS	1	0	0	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	1	0	0	3	2	67
	EOS	1	0	0	3	2	67
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	3	1	33
<i>Pseudomonas aeruginosa</i>	EOT	8	4	50	17	9	53
	EOS	5	1	20	14	5	36
<i>Klebsiella oxytoca</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Escherichia coli</i>	EOT	6	6	100	11	5	45
	EOS	6	5	83	11	5	45
<i>Proteus mirabilis</i>	EOT	1	1	100	-	-	-
	EOS	1	0	0	-	-	-
<i>Morganella morganii</i>	EOT	2	2	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Acinetobacter baumannii</i>	EOT	4	1	25	1	1	100
	EOS	4	1	25	1	1	100
<i>Staphylococcus aureus</i>	EOT	17	14	82	20	12	60
	EOS	13	10	77	15	6	40
<i>Serratia marcescens</i>	EOT	3	2	67	3	1	33
	EOS	2	1	50	3	1	33
<i>Enterococcus faecalis</i>	EOT	2	1	50	3	2	67
	EOS	1	0	0	2	1	50
<i>Enterobacter cloacae</i>	EOT	4	1	25	6	3	50
	EOS	4	1	25	6	3	50
<i>Enterobacter aerogenes</i>	EOT	1	0	0	3	0	0
	EOS	1	0	0	3	0	0
<i>Neisseria meningitidis</i>	EOT	2	2	100	3	1	33
	EOS	2	2	100	3	1	33
<i>Bacteroides melaninogenicus</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter diversus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Hafnia alvei</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter freundii</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Legionella pneumophila</i>	EOT	2	2	100	2	2	100
	EOS	3	2	67	2	2	100
<i>Proteus vulgaris</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Acinetobacter calcoaceticus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	0	0
<i>Streptococcus mitis</i>	EOT	1	1	100	-	-	-
	EOS	-	-	-	-	-	-
<i>Streptococcus agalactiae</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	0	0
<b>Total</b>	EOT	76	56	73.6	94	53	56.3
	EOS	61	49	80.3	73	45	47.9

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\* The MO omitted all non-specified isolates from this table.

**Medical Officer's Comment:** The results in table 137.8 were very different from those in table 137.4, with a clinical response in the 70% range at the EOT which increased by the EOS to 80.3% for the alatrofloxacin/trovafloxacin-treated patients as compared to a much lower 56.3% at the EOT and 47.9% at the EOS for the ceftazidime/ciprofloxacin-treated patients.

The MO elected to evaluate the requested pathogens separately to see if any difference in results was obtained.

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

**Table 137.9**  
**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		Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	7	7	100	7	5	71
	EOS	5	4	80	6	4	67
<i>Escherichia coli</i>	EOT	6	6	100	11	5	45
	EOS	6	5	83	11	5	45
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	3	1	33
<i>Staphylococcus aureus</i>	EOT	17	14	82	20	12	60
	EOS	13	10	77	15	6	40
<i>Pseudomonas aeruginosa</i>	EOT	8	4	50	17	9	53
	EOS	5	1	20	14	5	36
<b>Total</b>	EOT	<b>42</b>	<b>33</b>	<b>78.5</b>	<b>59</b>	<b>33</b>	<b>56</b>
	EOS	<b>33</b>	<b>22</b>	<b>66.6</b>	<b>49</b>	<b>21</b>	<b>42.8</b>

**Medical Officer's Comment:** When only clinical response by requested pathogen was assessed, the clinical response rates are essentially unchanged at the EOT although slightly lower. At the EOS however, the clinical response rates on both arms decreased proportionately and as expected. In this study, it appeared as if both agents had similar and relatively low clinical response rates in patients with *Pseudomonas aeruginosa* as compared to study 154-113 where trovafloxacin had better activity in a similar subgroup (EOS 62% clinical success trovafloxacin versus 25% ciprofloxacin), and that trovafloxacin also had a higher success rate in patients with *Staphylococcus aureus*, as compared to study 154-113 where ciprofloxacin had a higher clinical response rate in patients with this organism (EOS 50% trovafloxacin versus 67% ciprofloxacin).

The sponsor stated that (copied from page 47 of the study report):

When sponsor-defined clinical success rates were evaluated by baseline pathogen, higher clinical success rates were observed at both the end of treatment and the end of study among subjects in the alatrofloxacin/trovafloxacin group with baseline isolates of *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pneumoniae* compared to subjects in the ceftazidime/ciprofloxacin group.

Sponsor-defined clinical success rates were comparable at both the end of treatment and the end of study among subjects with baseline isolates of *Haemophilus influenzae* and *Pseudomonas aeruginosa*. A comparable percentage of subjects in both the alatrofloxacin/trovafloxacin (62%, 5/8) and ceftazidime/ciprofloxacin (59%, 10/17) treatment groups received adjunctive gentamicin for the treatment of baseline *Pseudomonas aeruginosa*. Of those subjects with clinical success for *Pseudomonas aeruginosa*, 3/4 alatrofloxacin/trovafloxacin subjects and 5/10 ceftazidime/ciprofloxacin subjects received adjunctive gentamicin. Of these four subjects receiving alatrofloxacin/trovafloxacin with clinical success for *Pseudomonas aeruginosa* at end of treatment, three were not evaluable at the end of study (2 subjects [Subjects 5926-0041 and 5958-0254] due to concomitant use of antibiotics for

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reasons other than nosocomial pneumonia and 1 subject [Subject 6357-0484] died of a cardiac arrest). One subject (Subject 5414-0270) in the ceftazidime/ciprofloxacin subgroup relapsed with *Pseudomonas aeruginosa* nosocomial pneumonia. There was no evidence of the development of resistance in any of the failures in either subgroup.

*C<sub>s</sub>* were not applied to this variable as each patient could have had more than 1 bacterial isolate.

**Clinical Response by Ventilator Status:**

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

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**Table 137.10**

**Sponsor-Defined Clinical Response/Clinically Evaluable Population requiring Mechanical Ventilation at EOT and EOS**

Timepoint	Alatrofloxacin/Trovafloxacin N= 41	Ceftazidime/Ciprofloxacin N = 37
Number of patients evaluated at EOT	41 (100%)	37 (100%)
Cure	20 (50%)	15 (36.4%)
Improvement	6 (31.2%)	8 (27.3%)
Failure	15 (18.8%)	14 (36.4%)
<b>Success (Cure + Improvement)</b>	<b>26 (63.4%)</b>	<b>23 (62.2%)</b>
Number of patients evaluated at EOS	32 (100%)	30 (100%)
Cure	16 (50%)	13 (50%)
Improvement	-	1 (3.3%)
Failure	15 (46.9%)	14 (46.7%)
Relapse	1 (3.1%)	2 (6.7%)
<b>Success (Cure + Improvement)</b>	<b>16 (50%)</b>	<b>14 (46.7%)</b>

*Medical Officer's Comment: As expected, clinical response was worse overall in this apparently more ill population by about 20 percentage points at both the EOT and the EOS. Alatrofloxacin/trovafloxacin appeared numerically superior to ceftazidime/ciprofloxacin at the MO TOC, the EOS. These results are comparable to those in study 154-113, where the clinical response rates at the EOT were 66.7% trovafloxacin versus 63.6% ciprofloxacin and at the EOS, 55.6% and 50% per arm respectively.*

**Signs and Symptoms:**

(Copied from page 50 of the study report)

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The percentage of clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups with moderate or severe signs and symptoms of nosocomial pneumonia at baseline was as follows: dyspnea (48% and 51%, respectively), cough (52% and 48%, respectively), pleuritic chest pain (3% and 9%, respectively), chills/rigor (14% and 17%, respectively), and increased sputum volume (64% and 68%, respectively). In both treatment groups, the percentage of subjects with these signs and symptoms of nosocomial 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 ceftazidime/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 (72% in each group), FAAF (83% and 80%, respectively), and DAAF (44% 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 ( $\pm$  standard deviation) time to afebrile was 6.30 days ( $\pm$  5.85) and 6.29 days ( $\pm$  6.03) for subjects in the alatrofloxacin/trovafoxacin (n=70) and ceftazidime/ciprofloxacin (n=73) groups, respectively. Among the clinically intent-to-treat subjects, the mean ( $\pm$  standard deviation) time to afebrile was 6.08 days ( $\pm$  5.58) and 6.60 days ( $\pm$  6.11) for subjects in the alatrofloxacin/trovafoxacin (n=79) and ceftazidime/ciprofloxacin (n=87) groups, respectively. A summary of the percentage of subjects with mild, moderate, or severe clinical signs and symptoms of nosocomial 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 ↓ Trovafoxacin			Ceftazidime ↓ Ciprofloxacin		
	Baseline	EOT	EOS	Baseline	EOT	EOS
	<b>Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms</b>					
<b>Sign/Symptom<sup>a</sup></b>						
Dyspnea	68%	30%	17%	69%	25%	20%
Cough	75%	33%	18%	72%	39%	20%
PCP	16%	7%	1%	19%	6%	1%
Chills/Rigors	23%	3%	1%	29%	<1%	2%
ISV	83%	40%	20%	88%	36%	22%
Fever	72%	13%	9%	72%	10%	11%
FAAF	83%	22%	10%	80%	15%	8%
DAAF	44%	16%	9%	50%	24%	11%
	Baseline	EOT	EOS	Baseline	EOT	EOS
	<b>Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms</b>					
<b>Sign/Symptom<sup>a</sup></b>						
Dyspnea	68%	33%	16%	70%	30%	20%
Cough	74%	39%	17%	73%	40%	23%
PCP	14%	5%	1%	17%	6%	1%
Chills/Rigors	22%	3%	1%	24%	3%	2%
ISV	83%	44%	20%	90%	39%	26%
Fever	67%	16%	8%	70%	13%	11%
FAAF	82%	28%	10%	80%	19%	8%
DAAF	48%	26%	8%	51%	26%	15%

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

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*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.

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

Four clinically evaluable subjects in the alatrofloxacin/trovafoxacin group and three clinically evaluable subjects in the ceftazidime/ciprofloxacin group had a chest x-ray that was not obtained within the evaluable window at baseline (Day -1 to Day 1). All other clinically evaluable subjects (alatrofloxacin/trovafoxacin, 99 and ceftazidime/ciprofloxacin, 106) had x-rays obtained within the appropriate window at baseline. Of these, 58 (56%) alatrofloxacin/trovafoxacin subjects and 67 (61%) ceftazidime/ciprofloxacin subjects had unilateral abnormalities and 41 (40%) alatrofloxacin/trovafoxacin subjects and 39 (36%) ceftazidime/ciprofloxacin subjects had bilateral abnormalities. Ten (10) subjects (10%) in the alatrofloxacin/trovafoxacin group and 12 subjects (11%) in the ceftazidime/ciprofloxacin group had abnormalities in  $\geq 3$  lobes at baseline. The mean number of lobes involved at baseline was 1.5 for subjects in both treatment groups. 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 (84%, alatrofloxacin/trovafoxacin; 80%, ceftazidime/ciprofloxacin) and to the end of study (87%, alatrofloxacin/trovafoxacin; 88%, ceftazidime/ciprofloxacin).

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

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#### **Bacteriological Response:**

As per the sponsor, 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. The sponsor stated that (copied from page 51 of the study report):

The pathogens isolated at baseline were those expected in a population of subjects with nosocomial pneumonia. Among the bacteriological evaluable subjects, sponsor-defined pathogen eradication rates for the most frequently isolated baseline pathogens were compared between the two treatment groups both at the end of treatment and study.

Higher eradication rates for the baseline pathogens *Staphylococcus aureus* and *Streptococcus pneumoniae* were seen both at the end of treatment and end of study in the alatrofloxacin/trovafoxacin compared with the ceftazidime/ciprofloxacin groups.

For *Staphylococcus aureus*, the higher eradication rate at the end of treatment (75%, 12/16 versus 60%, 12/20) became more pronounced at the end of study (92%, 11/12 versus 50%, 6/12) in the alatrofloxacin/trovafoxacin group compared with the ceftazidime/ciprofloxacin group.

For *Streptococcus pneumoniae*, all isolates in the alatrofloxacin/trovafoxacin group were either eradicated or presumed eradicated (end of treatment 3/3, end of study 1/1) compared with the presumed persistence of all isolates (end of treatment and end of study 0/3 eradicated) in the ceftazidime/ciprofloxacin group.

Lower eradication rates for the baseline pathogens *Pseudomonas aeruginosa* and *Enterobacter cloacae* were seen both at the end of treatment and end of study in the alatrofloxacin/trovafoxacin compared with the ceftazidime/ciprofloxacin groups.

For *Pseudomonas aeruginosa*, the eradication rate at the end of treatment (25%, 2/8 versus 53%, 9/17) and end of study (20%, 2/5 versus 54%, 7/13) was lower in the alatrofloxacin/trovafoxacin compared to the ceftazidime/ciprofloxacin group, respectively. This is in contrast to the comparable clinical success rate for *Pseudomonas aeruginosa* in both treatment groups (Table I). Adjunctive use of gentamicin as specified in the protocol occurred in 5/8 and 10/17 of the subjects in the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin groups, respectively. Of those subjects receiving gentamicin, the eradication rate of *Pseudomonas aeruginosa* was 2/5 (40%) and 4/10 (40%) for the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin groups,

respectively, at the end of treatment. There was no evidence of the development of resistance in any of the persistent *Pseudomonas aeruginosa* pathogens in either treatment group.

For *Enterobacter cloacae*, the eradication rate at the end of treatment (25%, 1/4 versus 100%, 6/6) and end of study (50%, 2/4 versus 100%, 5/5) was lower in the alatrofloxacin/trovafoxacin group compared to the ceftazidime/ciprofloxacin group, respectively. In the alatrofloxacin/trovafoxacin group, 2/4 isolates were persistent at the end of treatment compared with 0/4 at end of study (2/4 were presumed persistent). Comparable eradication rates were seen for *Escherichia coli* and *Haemophilus influenzae* at the end of treatment and end of study in both the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin groups.

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**Table 137.11**  
**Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically Evaluable Population: Modified 5.4.1 by MO)**

Pathogen		Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	7	6	86	7	6	86
	EOS	5	4	80	6	5	83
<i>Moraxella catarrhalis</i>	EOT	-	-	-	2	2	100
	EOS	-	-	-	2	1	50
<i>Streptococcus pneumoniae</i>	EOT	5	5	100	3	0	0
	EOS	3	3	100	2	0	0
<i>Stenotrophomonas maltophilia</i>	EOT	1	0	0	-	-	-
	EOS	1	0	0	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	1	1	100	3	3	100
	EOS	1	1	100	3	3	100
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	2	1	50
<i>Pseudomonas aeruginosa</i>	EOT	8	2	25	17	9	53
	EOS	5	1	20	13	7	54
<i>Klebsiella oxytoca</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Escherichia coli</i>	EOT	6	6	100	11	9	82
	EOS	6	6	100	9	9	100
<i>Proteus mirabilis</i>	EOT	1	0	0	-	-	-
	EOS	1	0	0	-	-	-
<i>Morganella morganii</i>	EOT	2	2	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Acinetobacter baumannii</i>	EOT	4	2	50	1	1	100
	EOS	4	2	50	1	1	100
<i>Staphylococcus aureus</i>	EOT	16	12	75	20	12	60
	EOS	12	11	92	12	6	50
<i>Serratia marcescens</i>	EOT	3	2	67	3	2	67
	EOS	2	2	100	3	2	67
<i>Enterococcus faecalis</i>	EOT	2	1	50	2	2	100
	EOS	1	0	0	-	-	-
<i>Enterobacter cloacae</i>	EOT	4	1	25	6	6	100
	EOS	4	2	50	5	5	100
<i>Enterobacter aerogenes</i>	EOT	1	0	0	3	0	0
	EOS	1	0	0	2	0	0
<i>Neisseria meningitidis</i>	EOT	2	2	100	-	-	-
	EOS	2	2	100	-	-	-
<i>Bacteroides melaninogenicus</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter diversus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Hafnia alvei</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter freundii</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Legionella pneumophila</i>	EOT	2	2	100	2	2	100
	EOS	3	2	67	2	2	100
<i>Proteus vulgaris</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Acinetobacter calcoaceticus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Streptococcus mitis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Streptococcus agalactiae</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	0	0
<b>TOTAL</b>	EOT	<b>72</b>	<b>45</b>	<b>62.5</b>	<b>93</b>	<b>57</b>	<b>61.3</b>
	EOS	<b>58</b>	<b>42</b>	<b>72.4</b>	<b>71</b>	<b>46</b>	<b>64.7</b>

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