Medical Officer's Comment: *The MO agreed with the sponsor's analysis of the data as it pertained to their evaluable population. Interestingly, in this open trial, alatrofloxacin/trovafloxacin's activity versus Pseudomonas aeruginosa was much lower than expected and as compared with study 154-113 where there was an eradication rate of 77% at the EOT and 63.6% at the EOS. Additionally, the activity against Staphylococcus aureus was much higher (113: 55% EOT, 38% EOS).*

Overall eradication rates were not comparable to clinical response rate and additionally, were opposite to those seen in study 154-113. Eradication rates increased at the EOS on both arms, potentially because of the exclusion from the EOS from the evaluable population of most of the patients that the MO considered unevaluable either because of no EOS visit or because of concomitant antimicrobials. Please note that as in previous studies, the sponsor's evaluable population is not the same at the EOT and the EOS.

The overall eradication rate for the alatrofloxacin/trovafloxacin arm of this study was similar to that seen at the EOS in study 154-113 (72.1%), however the ceftazidime/ciprofloxacin rate was lower at the EOT and higher at the EOS (72.2%EOT, 55.3% EOS).

The eradication rates only for the requested pathogens can be seen below:

Table 137.12

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

		Trovafloxacin			Ceftazidime/Ciprofloxacin		
Pathogen		N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	7	6	86	7	6	86
	EOS	5	4	80	6	5	83
Escherichia coli	EOT	6	6	100	11	9	82
	EOS	6	6	100	9	9	100
Klebsiella pneumoniae	EOT	4	2	50	4	2	50
	EOS	4	2	50	2	1	50
Staphylococcus aureus	EOT	16	12	75	20	12	60
	EOS	12	11	92	12	6	50
Pseudomonas aeruginosa	EOT	8	2	25	17	9	53
	EOS	5	1	20	13	7	54
Total	**EOT**	**41**	**28**	**68.2**	**59**	**38**	**64.4**
	EOS	**32**	**24**	**75**	**42**	**28**	**66.6**

Medical Officer's Comment: *These rates are comparable to those seen in table 137.11 and the EOT results are comparable to those seen in study 154-113 (EOT: trovafloxacin 63.6% and ciprofloxacin 63.4%). However, the alatrofloxacin/trovafloxacin EOS eradication rate is approximately 10 percentage points higher than that of ceftazidime/ciprofloxacin, and to the trovafloxacin overall eradication rate seen in study 154-113(EOS: trovafloxacin 65.7% and ciprofloxacin 63.5%).*

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

Of the eight evaluable alatrofloxacin/trovafloxacin subjects and 17 ceftazidime/ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, five alatrofloxacin/trovafloxacin subjects (63%) and ten ceftazidime/ciprofloxacin (59%) subjects received optional gentamicin therapy (dual therapy).

There was no difference in clinical outcomes between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy; however, due to the small number of subjects no definitive conclusions could be drawn.

Medical Officer's Comment: *The MO independently audited the 8 alatrofloxacin/trovafloxacin and 17 ceftazidime/ciprofloxacin subjects who had Pseudomonas aeruginosa isolated at baseline. The MO found that 7/8(87.5%) trovafloxacin patients with Pseudomonas aeruginosa at baseline received an aminoglycoside, either per protocol gentamicin or amikacin as compared to 12/17 (70.5%) ceftazidime/ciprofloxacin patients.*

Please note that the MO counted any evaluable patient ho received any aminoglycoside at any time during the study.

Of the 7 patients who received gentamicin or amikacin (1) on the trovafloxacin arm, only 4 were followed to the EOS and at that point, 3 were clinical failures with persistence of the Pseudomonas, and 1 was a clinical cure with presumed eradication (persistence at EOT). The EOT results revealed failure with persistence in the same 3 patients as well as 2 clinical cures with eradication and 2 improvement s with persistence. The 1 patient who received NO aminoglycoside, was a clinical failure at the EOT, with persistence, and was carried forward as such.

On the ceftazidime/ciprofloxacin arm, of the 12 patients who received an aminoglycoside, 9 were followed through to the EOS. Of these patients, 5 were clinical failures with persistence, 1 was a failure with eradication, 2 were clinical improvements with eradication, and 1 was clinically cured with eradication.

Of the remaining 3 patients on this arm, who received an aminoglycoside but who were not followed through to the EOS, 2 were clinical cures with eradication at the EOT and 1 was a clinical improvement with eradication at the EOT.

Of the 5 patients who received no adjunctive aminoglycoside therpy, 2 were failures with eradication and 1 was a failure with persistence at the EOS. The remaining 2 patients were cures with eradication.

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. The MO was sufficiently impressed by the very poor activity of trovafloxacin versus Pseudomonas aeruginosa seen in this open trial, to suggest rewording of the above statement to reflect the definite need for the addition of a second ant-pseudomonal agent when treating a NP secondary to this organism.*

The overall eradication rate from both trials for the trovafloxacin arm, was 11/18 (sponsor evaluable, EOS: 61.1%) as compared to the ciprofloxacin eradication rate of 9/21(42.8%), which is very low considering the lack of the development of resistance in these trials. The MO could not explain these very disparate results.

Bacteriologic Response in Subjects with *Staphylococcus aureus* at Baseline:

The MO requested that the sponsor provide a separate listing of patients with this organism at baseline, the source, and if it was a sole pathogen or not. From these listings, the MO found that 17 alatrofloxacin/trovafloxacin patients had *Staphylococcus aureus* at baseline as compared to 20 ceftazidime/ciprofloxacin patients.

13/17 (76.4%) of the alatrofloxacin/trovafloxacin patients and 15/20 (75%) of the ceftazidime/ciprofloxacin patients were followed through the EOS (MO TOC).

On the alatrofloxacin/trovafloxacin arm, 3 of the 13 were clinical failures, 2 with eradication, and one with persistence. The remaining 10 patients were clinical cures and the pathogen was eradicated in all cases.

On the ciprofloxacin arm, 8 of the 15 were clinical failures with persistence in all 8. One patient was a relapse with persistence and in all the remaining cases there was clinical cure with eradication.

The conclusion drawn from the above is that alatrofloxacin/trovafloxacin was more effective in eradicating *Staphylococcus aureus* than ceftazidime/ciprofloxacin and that there was general consistency between a clinical outcome of cure and a bacteriologic outcome of eradication.

Of the 4 patients on the trovafloxacin arm who were not seen at the EOS but only at the EOT, 2 were cures with persistence and 2 were improvements with eradication.

Of the 5 ciprofloxacin patients who were not seen at the EOS but only at the EOT, 3 were clinical cures with eradication and 2 were clinical improvements, one with eradication, and 1 with persistence.

Superinfecting Pathogens and Colonizing Organisms:

As per the sponsor, 5 patients on the alatrofloxacin/trovafloxacin arm and 8 subjects on the ceftazidime/ciprofloxacin arm had superinfecting pathogens at the EOS requiring further therapy. 30 (29%) trovafloxacin-treated subjects were found to have colonizing organisms not requiring treatment as compared to 29 (27%) ciprofloxacin subjects. The sponsor's text has been copied from page 56 of the study report. Please note that patients with *Pseudomonas aeruginosa* were already reviewed in the previous section.

Eleven (11) superinfecting pathogens (one isolate of *Pseudomonas putida* from the bronchi; three isolates of *Pseudomonas aeruginosa* and one isolate of *Klebsiella pneumoniae* from the lung; and one isolate each of *Escherichia coli* and *Klebsiella pneumoniae*; and four isolates of *Pseudomonas aeruginosa* from sputum or induced sputum) were isolated from five subjects (5%) in the alatrofloxacin/trovafloxacin group and 14 superinfecting pathogens (one isolate of *Streptococcus pneumoniae* isolate from the bronchi; one isolate each of *Staphylococcus aureus* and *Acinetobacter baumanii*, and one isolate of *Pseudomonas aeruginosa* (via transtracheal aspiration) from the lung; three isolates each of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and one isolate each of *Streptococcus pneumoniae*, *Acinetobacter baumanii*, *Enterococcus faecalis*, and *Candida* species from sputum) were isolated from eight subjects (7%) in the ceftazidime/ciprofloxacin group.

Medical Officer's Comment: *The MO verified the above information and agreed that the sponsor's statement was accurate.*

Subjects with Positive Blood Cultures at Baseline (copied from page 58 of the study report):

Among bacteriologically intent-to-treat subjects, seven subjects in the alatrofloxacin/trovafloxacin group and nine subjects in the ceftazidime/ciprofloxacin group had a positive blood culture at baseline and at least one follow-up blood culture during the study. With the exception of one isolate of *Staphylococcus aureus* in the ceftazidime/ciprofloxacin treatment group, which was persistent, all follow-up blood cultures in both treatment groups showed eradication of baseline blood pathogens, as presented in the following table.

Table D. Summary of Sponsor-Defined Pathogen Eradication Rates For Baseline Pathogens Isolated from Blood (Bacteriologically Intent-to-Treat Subjects)[a]		
	Alatrofloxacin ↓ Trovafloxacin	Ceftazidime ↓ Ciprofloxacin
	Number of Pathogens [b]	
Staphylococcus aureus	0/0	3/4
Pseudomonas aeruginosa	0/0	1/1
Escherichia coli	2/2	0/0
Streptococcus pneumoniae	1/1	0/0
Enterobacter cloacae	0/0	1/1
Klebsiella pneumoniae	0/0	1/1
Enterococcus faecalis	1/1	0/0
Serratia marcescens	1/1	0/0
Morganella morganii	1/1	0/0
Klebsiella sp	0/0	1/1
Streptococcus mitis	1/1	0/0
Bacteroides sp	0/0	1/1
Enterobacter sp	0/0	1/1

a Subjects with a positive baseline blood culture and at least one follow-up blood culture during study.

b Percents displayed only when denominator is ≥15.

Ref.: Table 5.4.4

In addition, three bacteriologically intent-to-treat subjects in the alatrofloxacin/trovafloxacin group and three subjects in the ceftazidime/ciprofloxacin group had positive baseline blood cultures and no follow-up blood cultures. Two subjects in the alatrofloxacin/trovafloxacin group were clinically cured and one subject died after 5 days of treatment. One subject in the ceftazidime/ciprofloxacin group was clinically improved, one subject was discontinued from treatment after receiving two days of treatment due to *Haemophilus influenzae* isolated in sputum, and one subject received additional antibiotics due to insufficient response.

Medical Officer's Comment: *The MO agreed with the sponsor's statements and tables.*

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Mortality:

The sponsor stated that amongst the clinically evaluable alatrofloxacin/trovafloxacin patents, there were 15 (15%) deaths within 45 days of the initiation of study therapy as compared to 14 (13%) on the ceftazidime/ciprofloxacin arm.

Amongst the clinically ITT subjects, there were 32 (24%) deaths on the alatrofloxacin/trovafloxacin arm and 29 (21%) on the ceftazidime/ciprofloxacin arm. Copied below is sponsor's table E (page 59 of the study report):

Table E. Summary of Subject Mortality

	Clinically Evaluable Subjects	
	Alatrofloxacin ↓ Trovafloxacin (N=103)	Ceftazidime ↓ Ciprofloxacin (N=109)
Number of Deaths[a]	17 (17%)	15 (14%)
≤48 Hours	0	0
Day 3 to 7	3 (3%)	1 (<1%)
Day 8 to 15	7 (7%)	4 (4%)
Day 16 to 45	5 (5%)	9 (8%)
Day 46 to 60	2 (2%)	1 (<1%)

	Clinically Intent-to-Treat Subjects	
	Alatrofloxacin ↓ Trovafloxacin (N=132)	Ceftazidime ↓ Ciprofloxacin (N=139)
Number of Deaths[a]	35 (27%)	30 (22%)
≤48 Hours	5 (4%)	2 (1%)
Day 3 to 7	7 (5%)	10 (7%)
Day 8 to 15	12 (9%)	7 (5%)
Day 16 to 45	8 (6%)	10 (7%)
Day 45 to 60	2 (2%)	1 (<1%)
Missing	1 (<1%)	0

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 is that most of the deaths on the alatrofloxacin/trovafloxacin arm occurred during active therapy as compared to the ceftazidime/ciprofloxacin arm where they 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 26 alatrofloxacin/trovafloxacin and 32 ceftazidime/ciprofloxacin-treated subjects who were clinical failures at the EOT and carried forward as such to the EOS. In addition, the MO copied the sponsor's analysis of relapses because these patients were considered failures by the MO. This analysis has been copied from page 59 of the study report:

Ten (10) of the 26 alatrofloxacin/trovafloxacin subjects designated as clinical failures were discontinued from treatment between Days 2 and 10 due to inadequate response. Of the subjects designated as clinical failures, four received optional treatment with vancomycin and two (Subjects 5871-0422 and 5961-0285) received gentamicin in violation of the protocol (See Section 7). Twenty-three (23) subjects received additional antibiotics for inadequate response. Four (4) subjects were re-hospitalized or had hospitalization prolonged due to worsening of condition. Five (5) subjects who were clinical failures died due to the disease under study.

Fifteen (15) of the 32 ceftazidime/ciprofloxacin subjects designated as clinical failures were discontinued from treatment between Days 3 and 13 due to inadequate response. Of the subjects designated as clinical failures, four received optional vancomycin, five received optional gentamicin, and one received optional gentamicin and vancomycin. Twenty-five (25) ceftazidime/ciprofloxacin subjects received additional antibiotics for inadequate response. Two (2) subjects, who were clinical failures and died, had their cause of death attributed to the disease under study.

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In addition to the clinically evaluable subjects discussed above, 21 alatrofloxacin/trovafloxacin subjects and 16 ceftazidime/ciprofloxacin subjects who were not clinically evaluable were designated as clinical failures in the intent-to-treat analysis.

Clinical Relapse. Among clinically evaluable subjects who were clinical successes at the end of treatment, three subjects in the alatrofloxacin/trovafloxacin group and five subjects in the ceftazidime/ciprofloxacin group were designated as clinical relapses at the end of study.

All three subjects in the alatrofloxacin/trovafloxacin group who were designated as clinical relapse received additional antibiotics for inadequate response. None were re-hospitalized or had hospitalization prolonged due to worsening of condition.

All five subjects in the ceftazidime/ciprofloxacin group who were designated as clinical relapses received additional antibiotics for inadequate response. One subject was re-hospitalized or had hospitalization prolonged due to worsening of condition, and one subject (Subject 5942-0145) received optional vancomycin.

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Medical Officer's Comment: *The MO reviewed all failures, and found that on the alatrofloxacin/trovafloxacin arm, 16 of the 26 patients who were designated as clinical failures and two of the three subjects who were designated as clinical relapses had pathogens isolated at baseline (18 total). Eight (8) of the 16 subjects with a baseline pathogen and a clinical response of failure and one of the two with a baseline pathogen and a clinical response of relapse had repeat cultures that showed persistence of Acinetobacter baumanii, Haemophilus influenzae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Proteus mirabilis, and Staphylococcus aureus.*

On the ceftazidime/ciprofloxacin arm, 25 of the 32 patients who were designated as clinical failures and four of the five subjects who were designated as clinical relapses had pathogens isolated at baseline (29 total). Six (6) of the 25 subjects with a baseline pathogen and a clinical response of failure and two of the four subjects with a baseline pathogen and a clinical response of relapse had repeat cultures that showed persistence of Enterobacter aerogenes, Pseudomonas aeruginosa, Acinetobacter calcoaceticus, and Staphylococcus aureus.

Of the subjects with an unfavorable clinical and/or bacteriological response who had baseline pathogens isolated with susceptibility testing performed both prior to and following treatment, none had pathogens that became resistant to trovafloxacin (≥8 μg/mL), ceftazidime (≥ 32 μg/mL), or ciprofloxacin (≥8 μg/mL).

Subjects with Resistant Organisms at Baseline (copied from pages 61 and 62 of the study report):

A number of subjects in both treatment groups isolated resistant organisms at baseline, which are listed in the following table (the table includes all pathogens isolated at baseline that were resistant to the study drug used as judged by sensitivities performed by the central laboratory). For subjects with baseline pathogens resistant to the study drug the clinical success rate at the end of treatment was 1/5(20%) for alatrofloxacin/trovafloxacin compared with 7/12(58%) with ceftazidime/ciprofloxacin.

Table F. Summary of Sponsor-Defined Clinical Response (ITT) and Bacteriological Response (ITT) at the End of Treatment for Those Subjects [a] with a Resistant Baseline Isolate

Subject Number	Organism (Source)	MIC (µg/mL)	Bacteriologic al Response	Clinical Response
Alatrofloxacin/trovafloxacin (MICs stated are to trovafloxacin with resistance being ≥8µg/mL)				
5871-0071	*Acinetobacter baumanii* (Sputum)	16	PP	Failure
5871-0548	*Acinetobacter baumanii* (Sputum)	8	E	Failure
5871-0552	*Acinetobacter baumanii* (Sputum)	8	P	Failure
5955-0245	*Enterobacter aerogenes* (Sputum)	32	PP	Failure
5978-0365	*Escherichia Coli* (Blood)	>64	E	Cure
Ceftazidime/ciprofloxacin (MICs stated are to ceftazidime with resistance being ≥32µg/mL)				
5871-0427[v]	*Staphylococcus aureus* (Sputum)	>128	P	Failure
5871-0433	*Enterobacter aerogenes* (Sputum)	>128	P	Failure
5871-0439[v]	*Enterobacter aerogenes* (Sputum)	>128	P	Failure
5871-0439[v]	*Pseudomonas aeruginosa* (Sputum)	32	E	Failure
5871-0439[v]	*Staphylococcus aureus* (Blood)	>128	E	Failure
5877-0389	*Acinetobacter* sp (Sputum)	32	PE	Improvement
5877-0389	*Enterococcus faecalis* (Sputum)	>128	PE	Improvement
5926-0066	*Staphylococcus aureus* (Sputum)	>128	PE	Cure
5936-0112[v]	*Staphylococcus aureus* (Sputum)	>128	PE	Cure
5942-0145[v]	*Acinetobacter calcoaceticus* (Sputum)	>128	P	Cure
5942-0148	*Enterococcus faecalis* (Sputum)	64	PE	Cure
5948-0126[v]	*Staphylococcus aureus* (Sputum)	>128	PE	Cure
5953-0253	*Enterobacter cloacae* (Sputum)	128	PE	Cure
5966-0309	*Enterococcus faecalis* (Sputum)	32	E	Failure
6357-0481[v]	*Enterobacter aerogenes* (Sputum)	>128	PP	Failure

MIC = Minimum Inhibitory Concentration; P = Persistent; E = Eradicated; PP = Presumed Persistent; PE = Presumed Eradicated

a One subject (Subject 5955-0349) does not appear in this table because the pathogen was resistant at baseline to ciprofloxacin but not to ceftazidime.

v Received optional therapy with vancomycin.

Medical Officer's Comment: *Interestingly, there were a higher number of bacterial isolates with baseline resistance in this trial as compared to study 154-113 where there were none. The higher number of patients with ciprofloxacin resistance probably is representative of the fact that this is an approved agent that is widely used in all the participating countries.*

Of concern to the MO were the isolates of Staphylococcus aureus that there MR and that developed during the trial. The MO requested a separate listing of these patients on 10/14/97. This listing had not been provided at the time of approval.

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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 14 alatrofloxacin/trovafloxacin subjects and 15 ciprofloxacin subjects. The MO has copied and modified sponsor table G from page 68 of the study report below:

Table 137.13

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

Table G. 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**
5414-0269	*Haemophilus parainfluenzae* *Staphylococcus aureus* *Streptococcus pneumoniae* *Serratia marcescens*	Failure/Failure	Eradication/Eradicated Eradication/ Eradicated Eradication/ Eradicated Eradication/ Eradicated
5871-0440[v]	*Klebsiella pneumoniae* *Staphylococcus aureus*	Failure/Failure	Eradication/ Eradicated Eradication/Eradicated
5871-0548	*Acinetobacter baumanii*[a]	Failure/Failure	Eradication/Eradicated
5871-0552	*Enterobacter cloacae*	Failure/ Failure	Eradication/Eradicated
5926-0041	*Pseudomonas aeruginosa*	Improvement/Not Eval., no EOS	Persistent/ Not Eval., no EOS
5953-0216	*Enterobacter cloacae*	Cure/ Cure	Persistent/Pres. Eradicated
5953-0254[9]	*Pseudomonas aeruginosa*	Improvement/ Cure	Persistent/ Pres. Eradicated
5955-0224	*Haemophilus influenzae* *Proteus mirabilis*	Improvement/ Failure	Persistent/Persistent Persistent/ Persistent
5955-0267	*Staphylococcus aureus*	Cure/Cure	Persistent/ Eradicated
5955-0274	*Staphylococcus aureus*	Cure/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5957-0278	*Staphylococcus aureus*	Cure/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5966-0311	*Serratia marcescens*	Improvement/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5975-0401	*B. streptococcus* Group C	Cure/ Cure	Persistent/ Pres. Eradicated
5978-0365	*Klebsiella pneumoniae*	Cure/ Cure	Persistent/ Persistent
Ceftazidime/Ciprofloxacin			
5414-0270	*Pseudomonas*	Improvement/Relapse	Persistent/Persistent

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	aeruginosa		
5414-0294	*H. parainfluenzae* *S. marcescens*	Failure/Failure	Eradication/ Eradicated Eradication/ Eradicated
5800-0582	*Escherichia coli*	Failure/ Failure	Eradication/ Eradicated
5871-0079	*Staphylococcus aureus*	Improvement/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5871-0439 [v]	*Pseudomonas aeruginosa* *Staphylococcus aureus*	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
5926-0011	*Staphylococcus aureus*	Failure/ Failure	Eradication/ Eradicated
5935-0143 [g,v]	*Escherichia coli*	Failure/Failure	Eradication/ Eradicated
5942-0145 [v]	*Acinetobacter calcoaceticus* [a]	Cure/ Failure	Persistent/Pres. Persistent
5953-0251 [g,v]	*Pseudomonas aeruginosa* *Staphylococcus aureus*	Improvement/Cure	Persistent/ Eradicated Persistent/ Eradicated
5955-0222 [g]	*Pseudomonas aeruginosa*	Cure/Improvement	Persistent/ Eradicated
5955-0223	*Haemophilus influenzae*	Failure/ Failure	Eradication/ Eradicated
5957-0279 [g]	*Escherichia coli* *Pseudomonas aeruginosa*	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
5966-0309	*Enterobacter cloacae* *Enterococcus faecalis*	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
5972-0325	*Enterobacter cloacae* *Citrobacter diversus*	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
6073-0475	*Enterobacter cloacae* *Escherichia coli* *Pseudomonas aeruginosa*	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated Eradication/ Eradicated

a Resistant to study drug at baseline
v Received optional therapy with vancomycin.
g Received optional therapy with gentamicin.
Ref.: Table 5.7.1 and Appendix I, Tables 8 and 8a

Medical Officer's Comment: *All failures were reviewed previously. As stated on the previous page a determination of eradication in the face of failure could only have been made based on an objective culture report at the EOT. The MO determined that 4 trovafloxacin-treated and 1 ceftazidime/ ciprofloxacin-treated patients were not evaluable. Of those patient who were evaluable per the MO, there was no disagreement between the MO's and the sponsor's determinations of outcome. On the alatrofloxacin/trovafloxacin arm there were 4 EOS failures with eradication as compared to 10 on the ceftazidime/ciprofloxacin arm. There was 1 cure with persistence on the alatrofloxacin/trovafloxacin arm as compared to 0 EOS inconsistencies in this group on the ceftazidime/ciprofloxacin arm.*

Sponsor's Conclusion:
(Copied from page 71 of the study report and modified by the MO (in Times New Roman font)

Alatrofloxacin/trovafloxacin was clinically effective in the treatment of subjects with nosocomial pneumonia and statistically equivalent to ceftazidime/ciprofloxacin for sponsor-defined clinical success rates.

One hundred thirty-five (135) subjects were randomized to treatment with alatrofloxacin/trovafloxacin and 140 subjects were randomized to treatment with ceftazidime/ciprofloxacin. All of the randomized subjects in both treatment groups received

treatment. The two treatment groups were generally comparable with respect to characteristics at baseline, including medical history, use of prior and concomitant medications, severity factors (compromised respiratory function and need for mechanical ventilation), APACHE II score, and severity of nosocomial pneumonia.

One hundred three (103) subjects in the alatrofloxacin/trovafloxacin group and 109 subjects in the ceftazidime/ciprofloxacin group were clinically evaluable; 52 subjects in the alatrofloxacin/trovafloxacin group and 66 subjects in the ceftazidime/ciprofloxacin group were bacteriologically evaluable. All treated subjects were included in analysis of adverse events.

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

Success rates among clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups were 74% (74/100) and 70% (75/107) (CI: -8.3, 16.1), respectively, at the end of treatment and 66% (56/85)and 58% (52/89), respectively, at the end of study and those among clinically intent-to-treat subjects were 64% (82/129)and 65% (88/136) (CI: -12.7, 10.4), respectively, at the end of treatment and 61% (80/132) and 60% (84/139), respectively, at the end of study. The clinical success in the subgroup of subjects both clinically and bacteriologically evaluable also supported equivalence of the two treatment regimens.

When sponsor-defined clinical success rates were evaluated by baseline pathogen, higher clinical success rates were observed among clinically evaluable subjects at both the end of treatment and the end of study among subjects in the alatrofloxacin/trovafloxacin group with baseline isolates of *Staphylococcus aureus* compared to subjects in the ceftazidime/ciprofloxacin group (end of treatment: 82% (14/17) and 60% (12/20), respectively; end of study: 77% (10/13) and 40% (6/15), respectively).

Sponsor-defined clinical success rates among clinically evaluable subjects were comparable at the end of treatment and end of study among subjects with baseline isolates of *Pseudomonas aeruginosa* (end of treatment: 50% (4/8) and 53% (9/17), respectively; end of study: 20% (1/5) and 36% (5/14), respectively). Similar results were noted among clinical intent-to-treat subjects.

Absolute eradication rates were higher for *Staphylococcus aureus* and *Streptococcus pneumoniae*, lower for *Pseudomonas aeruginosa* and *Enterobacter cloacae*, and comparable for *Escherichia coli* and *Haemophilus influenzae* in the alatrofloxacin/trovafloxacin compared with the ceftazidime/ciprofloxacin groups, respectively. For *Staphylococcus aureus*, the end of treatment eradication rates were 75% (12/16) and 60% (12/20) in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups, respectively. All *Streptococcus pneumoniae* isolates were eradicated in the alatrofloxacin/trovafloxacin compared with none in the ceftazidime/ciprofloxacin group. The eradication rate of *Pseudomonas aeruginosa* at the end of treatment was 25% (2/8) and 53% (9/17) in the alatrofloxacin/trovafloxacin compared with the ceftazidime/ciprofloxacin groups, respectively. However, sponsor-defined clinical response was comparable at end of treatment at 50% (4/8) and 53% (9/17) in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups, respectively. In those subjects receiving adjunctive therapy with gentamicin for *Pseudomonas aeruginosa*, the eradication rate was comparable at 40% (2/5) and 40% (4/10) for the alatrofloxacin/trovafloxacin group compared with the ceftazidime/ciprofloxacin group, respectively. There was no evidence of the development of resistance in any persistent isolate of *Pseudomonas aeruginosa*.

Of the eight evaluable alatrofloxacin/trovafloxacin subjects and 17 ceftazidime/ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, five alatrofloxacin/trovafloxacin subjects (63%) and ten ceftazidime/ciprofloxacin (59%) subjects received optional gentamicin therapy (dual therapy). There was no difference in clinical outcomes between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy; however, due to the small number of subjects no definitive conclusions could be drawn.

In bacteriological intent-to-treat subjects, the eradication rates among the most frequently isolated pathogens at baseline were similar to those of the clinically evaluable subset. Of note were two subjects with penicillin-resistant *Streptococcus pneumoniae* in the alatrofloxacin/trovafloxacin group who were clinically cured with eradication. There were seven and nine subjects with baseline septicemia and a post-baseline blood culture in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups, respectively. All were eradicated except for one isolate of *Staphylococcus aureus* in the ceftazidime/ciprofloxacin treatment group, which was persistent.

Among clinically evaluable subjects, 15 (15%) subjects in the alatrofloxacin/ trovafloxacin group and 14 (13%) subjects in the ceftazidime/ciprofloxacin group died within 45 days of initiation of study therapy. Among clinically intent-to-treat subjects, 32 (24%) subjects in the alatrofloxacin/trovafloxacin group and 29 (21%) subjects died within 45 days of initiation of study therapy. The date of death was missing but had occurred after the end of study following discharge from hospital for one subject (Subject 5926-0065) in the alatrofloxacin/trovafloxacin group.

Medical Officer's Efficacy Analysis:

In accordance with the previously described MO evaluability criteria, the MO excluded 38 additional patients from the clinically evaluable population because they had no EOS visit. Additionally, 2 patients were excluded because they received < 80% of the prescribed therapeutic regimen. However, the MO changed the evaluability status on an additional 3 patients, thus the total number of MO evaluable patients, approximated that of the sponsor at the EOS. This information has been presented in MO table 137.14, below:

Table 137.14
Clinically Evaluable Population (as per the MO)

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
Total Treated	135	140
Sponsor Evaluable EOT	103	109
Sponsor Evaluable EOS	85	89
MO Evaluable at EOT	80	86
MO Evaluable at EOS	85	89
MO Excluded at EOS	18	20
No EOS Visit	18	20
< 80% Of regimen	1	1
Concomitant Antimicrobials	1	1
Re-included in Analysis	2	1
Total Evaluable at EOS	**85**	**89**

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* 5 Alatrofloxacin/trovafloxacin patients and 3 ceftazidime/ciprofloxacin patients had no EOT but are included in the EOS analysis thus justifying the increase in evaluable patients at the EOS.

The 85 clinically evaluable alatrofloxacin/trovafloxacin patients represented 63% of the randomized patients and the 89 ceftazidime/ciprofloxacin patients represented 63.6%. The total MO evaluable population of 174 patients represented 63.3% of the total randomized.

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

A by-center breakdown of the MO's evaluable population, is presented below in table 137.15:

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Table 137.15
Clinically Evaluable Population at EOS by Center (as per MO)

Center	Total Randomized N = 275	(100%)	Alatrofloxacin/Trovafloxacin N = 85	100 %	Ceftazidime/Ciprofloxacin N = 89	100 %
5414	12	4.3	5	5.9	6	6.7
5437	1	0.3	0	-	1	1.1
5439	5	1.8	0	-	1	1.1
5795	1	0.3	0	-	0	-
5800	3	1.0	1	1.2	2	2.2
5869	4	1.6	2	2.4	0	-
5871	40	14.5	17	20	13	14.6
5877	14	5.0	5	5.9	4	4.5
5924	12	4.3	4	3.5	0	-
5926	21	7.6	7	8.2	5	6.7
5930	1	0.3	0	-	0	-
5935	6	2.4	1	1.2	3	3.4
5936	4	1.6	0	-	1	1.1
5937	2	0.7	0	-	2	2.2
5940	1	0.3	0	-	0	-
5942	4	1.6	0	-	1	1.1
5945	5	1.8	2	2.4	2	2.2
5948	3	1.0	1	1.2	1	1.1
5952	3	1.0	1	1.2	2	2.2
5953	12	4.3	5	5.9	5	5.6
5955	27	9.8	9	10.6	10	11.2
5956	5	1.8	2	2.4	1	1.1
5957	6	2.9	0	-	2	2.2
5958	3	1.0	0	-	0	-
5961	1	0.3	1	1.2	0	-
5962	1	0.3	0	-	0	-
5963	2	0.7	0	-	2	2.2
5964	1	0.3	0	-	0	-
5966	9	3.2	2	2.4	2	2.2
5972	4	1.6	0	-	1	1.1
5973	3	1.0	1	1.2	1	1.1
5975	11	4.0	5	5.9	4	4.4
5977	4	1.6	1	1.2	2	2.2
5978	14	5.0	6	7.1	7	7.9
5979	6	2.4	1	1.2	1	1.1
5996	1	0.3	1	1.2	0	-
6072	3	1.0	1	1.2	1	1.1
6073	6	2.4	1	1.2	2	2.2
6075	5	1.8	2	2.4	0	-
6342	3	1.0	0	-	2	2.2
6357	4	1.6	1	1.2	0	-
6557	1	0.3	0	-	1	1.1
6569	1	0.3	1	1.2	0	-

The demographic make-up of the FDA evaluable population can be seen in Table 137.16:

Table 137.16
Demographic Characteristics of the FDA Evaluable EOS Population:

Characteristics		Alatrofloxacin/Trovafloxacin N = 85	Ceftazidime/Ciprofloxacin N = 89
Sex (Female)		27	28
(Male)		58	61
Age (years)	16 –44	23	13
	45 – 64	27	34
	≥ 65	35	42
	Mean	58.3	62.4
Race:			
	Arab	1	0
	White	82	86
	Asian	2	0
	East Indian	0	1
	Chinese	0	1
	Fijian	1	1
Body weight (kg)	Mean	70.8	62.4
Smoking Status	Ex Smoker	20	33
	Never	33	29
	Smoker	31	27
	Missing	1	0
Mechanical Ventilation	Yes	33	31
	No	52	56
Compromised Respiration	Yes	40	43
	No	42	45
	Missing	2	1
Severity if Illness			
	Mild/Moderate	39	41
	Severe	46	48
APACHE Score	Mean	12.3	13.6

The MO's evaluable populations were very similar in terms of the demographic variables of age, weight, sex, and race. However, and as pointed out previously in the sponsor's efficacy analysis, the ceftazidime/ciprofloxacin population appeared to be more severely ill as compared to the trovafloxacin population. This can be appreciated from the higher APACHE score, although the numbers of patients requiring mechanical ventilation or with respiratory compromise are similar. The MO requested that the sponsor determine if there was statistical significance in the difference between APACHE scores between the treatment arms. The sponsor responded that the above values were representative of 75 and 72 of the patients per arm respectively, and that the difference was not statistically significant.

As in study 154-113, the MO provided a separate efficacy analysis for the subgroups of patients who were mechanically ventilated and for those with compromised respiration, as well as for patients with mild/moderate disease, severe disease, and those that were both clinically and bacteriologically evaluable.

EFFICACY:

Table 137.17
Clinical Response by Patient (as per the MO):

	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	80	54	67.5	86	54	62.8
EOS	**85**	**54**	**63.5**	**89**	**51**	**57.3**

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

EOT: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: -11%, 20.4% ($\Delta = 20$).

EOS: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 9.4%, 21.8% ($\Delta = 20$).

Thus the MO's results differed from those of the sponsor. In the MO's analysis, trovafloxacin appeared to have superior efficacy at the EOT and at the EOS. In the sponsor's analysis, there was equivalence at the EOT timepoint.

Based on the MO's analysis, there were 32 failures at the EOS on the alatrofloxacin/trovafloxacin arm (32/85 {37.6%}) as compared to 38 on the ceftazidime/ciprofloxacin arm (38/89 {42.6%}). The patients who failed as per the MO include failures and relapses. The number of failures in the MO's analysis was comparable to the number in the sponsor's analysis (EOS: 29 and 37 per arm respectively) and the slight increase on both arms was caused by the MO's change in outcome on 3 patients and 1 patient per arm respectively.

Clinical Response by Disease Severity Status:

Table 137.18
Clinical Response at EOS for Patients with Mild/Moderate Disease (as per MO):

	alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	36	31	86.1	39	27	69.2
EOS	**39**	**33**	**84.6**	**41**	**29**	**70.7**

As noted previously, in the sponsor's analysis, the overall success rate was higher in this less severely ill population. The MO's and the sponsor's results were comparable (EOS: 85% versus 71% per arm respectively), and were also comparable to the sponsor's results in study 154-113 (EOS: 39/51 (76%) trovafloxacin versus 40/53 (75%). CIs were not applied to any of these analyses because of the small numbers of patients; however, the results were consistent between the studies and between the sponsor and the MO. Overall, alatrofloxacin/trovafloxacin appeared numerically superior to the comparator arms in both studies.

Table 137.19
Clinical Response at EOS for Patients with Severe Disease (as per MO):

	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	44	23	52.3	47	27	57.4
EOS	**46**	**21**	**45.7**	**48**	**22**	**45.8**

The MO's results were again comparable to those of the sponsor (49% versus 47%) in this more severely ill population. As in the previously reviewed study (154-113), there was a significant drop in efficacy in this subgroup. However, the 2 arms appeared to be numerically comparable.

Table 137.20
Clinical Response at EOS for Patients requiring Mechanical Ventilation Only (as per MO):

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	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	31	16	51.6	30	16	53.3
EOS	**33**	**15**	**45.5**	**31**	**14**	**45.2**

CIs were not applied to this smaller group of patients; that is in the patients requiring ventilatory support. However, trovafloxacin appeared numerically comparable to ciprofloxacin in both of these more severely ill subgroups. Once again, these results were consistent with those of the sponsor at the EOS (EOS: 50% versus 46.7% per arm respectively). Additionally, these results were consistent with those of the sponsor in study 154-113 (EOS: 15/31 (48.3%) trovafloxacin versus 18/33 (54.6%) ciprofloxacin).

As noted previously, in the sponsor's analysis, the overall success rate was higher in the less severely ill population. (sponsor EOS: 84.6%) trovafloxacin versus 70.7%). The results between the arms were comparable in both the MO's and the sponsor's analyses and indicate at least a 20 percentage point difference in success rates depending on disease severity and ventilatory status.

Table 137.21
Clinical Response at EOS for Clinically and Bacteriologically Evaluable Patients (as per MO):

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	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	37	21	56.8	50	30	60
EOS	**39**	**21**	**53.8**	**58**	**26**	**51**

As noted from the above the treatment arms appeared relatively equal at the EOS with a slight numerical superiority of trovafloxacin. Additionally, these results differed moderately from those of the sponsor, where the alatrofloxacin/trovafloxacin arm was superior to the ceftazidime/ciprofloxacin arm at both the EOT and EOS (EOT: 68% versus 62% and EOS: 56% and 48% per arm respectively), whereas in the MO's analysis ciprofloxacin evidenced a moderate numerical superiority at the EOT and a moderate numerical inferiority at the EOS.

Clinical Response by Baseline Pathogen:

The MO elected to present clinical response by baseline pathogen as well as pathogen eradication rates for the EOS only. As stated in the introduction, the determination of bacteriologic outcome was based on either culture results or in the absence of a culture, the outcome was extrapolated from the clinical outcome. Neither variable was an individual, by-patient variable because there were patients who had more than 1 organism isolated from predominantly bronchoscopy samples.

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Table 137.20
Clinical Response by Baseline Pathogen at the EOS (as per MO)

	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Pathogen	N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	5	4	80	6	4	66.7
Moraxella catarrhalis	-	-	-	2	1	50
Streptococcus pneumoniae	3	2	66.7	3	0	0
Stenotrophomonas maltophilia	1	0	0	-	-	-
Haemophilus parainfluenzae	1	0	0	3	2	66.7
Klebsiella pneumoniae	4	2	50	3	1	33.3
Pseudomonas aeruginosa	5	1	20	14	5	35.7
Klebsiella oxytoca	-	-	-	1	1	100
Escherichia coli	6	5	83.3	12	5	41.7
Proteus mirabilis	1	0	0	-	-	-
Morganella morganii	1	1	100	-	-	-
Acinetobacter baumanii.	4	1	25	1	1	100
Staphylococcus aureus	11	8	72.7	15	6	40
Serratia marcescens	2	1	50	3	1	33.3
Enterococcus faecalis	1	0	0	2	1	50
Enterobacter cloace	4	1	25	6	3	50
Enterobacter aerogenes	1	0	0	3	0	0
Neisseria meningitidis	2	2	100	-	-	-
Bacteroides melaninogenicus	1	1	100	-	-	-
Acinetobacter calcoaceticus	-	-	-	1	0	0
Citrobacter diversus	-	-	-	1	0	0
Citrobacter freundii	-	-	-	2	1	50
Proteus vulgaris	-	-	-	2	1	50
Legionella pneumophilia	3	2	66.7	2	2	100
Streptococcus mitis	1	1	100	-	-	-
Streptococcus agalactiae	1	1	100	-	-	-
Hafnia alvei	1	1	100	-	-	-
Pseudomonas fluorescens	-	-	-	1	0	0
Total	55	34	61.8	75	33	44

The MO's results differed from those of the sponsor (EOS: alatrofloxacin/trovafloxacin 80.3% versus ceftazidime/ciprofloxacin: 47.9%) although proportionately the clinical response rates were similar. In study 154-113, the clinical response rates for this subgroup were: EOS 59.4% trovafloxacin versus 54.8% ciprofloxacin. There was a much higher rate of clinical failure in patients with *Staphylococcus aureus* as the baseline pathogen on the ciprofloxacin arm. A CI was not applied as this was not an individual variable.

Below, in MO table 137.21 is clinical response by baseline pathogen only for the requested pathogens:

Table 137.21
Clinical Response by Baseline Pathogen at the EOS (Clinically evaluable Population/Requested Pathogens Only: as per MO)

	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Pathogen	N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	5	4	80	6	4	66.7
Escherichia coli	6	5	83.3	12	5	41.7
Klebsiella pneumoniae	4	2	50	3	1	33.3
Staphylococcus aureus	11	8	72.7	15	6	40
Pseudomonas aeruginosa	5	1	20	14	5	35.7
Total	31	20	64.5	50	21	42

Thus indicating that when only the requested pathogens were evaluated, the clinical response of the alatrofloxacin/trovafloxacin-treated patients was superior to that of the ceftazidime/ciprofloxacin-treated

patients. This result was similar to that seen in the sponsor's analysis and once again appears to be in part due to the numerically inferior activity of ceftazidime/ciprofloxacin versus *Staphylococcus aureus.*

Mortality:

The MO found that there were 11 deaths on the trovafloxacin arm (11/85 {12.9%) as compared to 10 on the ciprofloxacin arm (10/89 {11.22%). These were deaths that occurred within 45 days of the study. As stated previously, the MO elected to evaluate these patients in the safety portion of this review. The number of deaths was comparable between the 2 studies.

Bacteriologic Response:

Table 137.22
Pathogen Eradication Rates at the EOS (Bacteriologically evaluable Population, as per MO)

	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Pathogen	N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	5	4	80	6	5	83.3
Moraxella catarrhalis	-	-	-	2	1	50
Streptococcus pneumoniae	3	3	100	2	0	0
Stenotrophomonas maltophilia	1	0	0	-	-	-
Haemophilus parainfluenzae	1	1	100	3	3	100
Klebsiella pneumoniae	4	2	50	2	1	50
Pseudomonas aeruginosa	5	1	20	13	7	53.8
Klebsiella oxytoca	-	-	-	1	1	100
Escherichia coli	6	6	100	10	9	90
Proteus mirabilis	1	0	0	-	-	-
Morganella morganii	1	1	100	-	-	-
Acinetobacter baumanii.	4	2	50	1	1	100
Staphylococcus aureus	10	9	90	12	6	50
Serratia marcescens	2	2	100	3	2	66.7
Enterococcus faecalis	1	0	0	2	1	50
Enterobacter cloace	4	2	50	5	5	100
Enterobacter aerogenes	1	0	0	2	0	0
Neisseria meningitidis	2	2	100	-	-	-
Bacteroides melaninogenicus	1	1	100	-	-	-
Acinetobacter calcoaceticus	-	-	-	1	0	0
Citrobacter diversus	-	-	-	1	1	100
Citrobacter freundii	-	-	-	2	1	50
Proteus vulgaris	-	-	-	2	1	50
Legionella pneumophilia	3	2	66.7	2	2	100
Streptococcus mitis	1	1	100	-	-	-
Streptococcus agalactiae	-	-	-	1	0	0
Hafnia alvei	1	1	100	-	-	-
Pseudomonas fluorescens	-	-	-	1	0	0
Total	**51**	**36**	**70.5**	**68**	**47**	**69.1**

Based on the MO's analysis, the overall pathogen eradication rate of alatrofloxacin/trovafloxacin was marginally numerically superior to that of ceftazidime/ciprofloxacin at the EOS. As stated above, the MO's outcome assessment was based either on repeat culture data or, in the absence of a culture, outcome was extrapolated from the EOT data as well as the clinical status of the individual patient.

The MO noted however, that the results of this analysis were similar to those of the sponsor (EOS: alatrofloxacin/trovafloxacin: 72.4% versus ceftazidime/ciprofloxacin: 64.7%). These rates were comparable to the sponsor's EOS pathogen eradication rates in study 154-113 (EOS: trovafloxacin 44/61 (72.1%) as compared to ciprofloxacin 34/52 (55.3%).

Although the MO determined that not all the organisms found in table 137.22 were pathogens, for example, *Neisseria meningitidis*, the exclusion of a small number of organisms from each arm, would not ensure a major difference in outcome

The lower eradication rate of ciprofloxacin appeared to be attributable to the lower eradication rate of *Staphylococcus aureus*.

Pathogen eradication rates for the requested pathogens only, can be seen below in table 137.23:

Table 137.23
Pathogen Eradication Rates at the EOS (Bacteriologically Evaluable Population/Requested Pathogens Only: as per MO)

	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
Pathogen	N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	5	4	80	6	5	83.3
Escherichia coli	6	6	100	10	9	90
Klebsiella pneumoniae	4	2	50	2	1	50
Staphylococcus aureus	10	9	90	(14)	6	(42.8)
Pseudomonas aeruginosa	5	1	20	13	7	53.8
Total	30	22	73.3	43	28	65.1

The MO's results are the similar as the sponsor's (EOS: alatrofloxacin/trovafloxacin: 75% versus ceftazidime/ciprofloxacin: 66.6%).

Overall, the 2 agents appeared numerically comparable in the eradication of *Haemophilus influenzae*. *Escherichia coli,* and *Klebsiella pneumoniae*. The activity of alatrofloxacin/trovafloxacin versus *Staphylococcus aureus* was much higher than that of ceftazidime/ciprofloxacin. Additionally and as in the sponsor's analysis the activity of alatrofloxacin/trovafloxacin versus *Pseudomonas aeruginosa* was very poor as compared to that of ceftazidime/ciprofloxacin which was 50%.

Bacteriologic Response in Subjects with *Pseudomonas aeruginosa* at baseline:

There were 5 alatrofloxacin/trovafloxacin and 13 ceftazidime/ciprofloxacin subjects in the MO evaluable population that had *Pseudomonas aeruginosa* as the baseline pathogen.

4/5 trovafloxacin patients received concurrent anti-pseudomonal coverage (3 gentamicin and 1 amikacin) and 3 were clinical failures with persistence of the baseline pathogen. Only one of the 4 (25%) was a clinical cure with eradication. The 1 patient who received no concurrent aminoglycoside was also a failure with persistence. In study 154-113, 5 of the 6 patients on the trovafloxacin arm, who received additional anti-pseudomonal coverage, had eradication of the baseline isolate (83.3%). In that study, 3/7 (43%) patients who received monotherapy had persistence.

The total trovafloxacin versus *Pseudomonas aeruginosa* eradication rate for the 2 studies combined is 10/13 + 1/5 = 11/18 (61.1%). Concurrent anti-pseudomonal therapy was utilized in 6 of these cases with resultant eradication (33.3%), although 3 of these cases were clinical failures. Therefore, in 3 of 18 16.6%) clinically evaluable patients with baseline *Pseudomonas aeruginosa*, in whom additional coverage was used, both a clinical cure and pathogen eradication were obtained. The numbers between these 2 studies were too small and too inconsistent in order to be able to either verify or refute that sponsor's claim that additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population.

On the ceftazidime/ciprofloxacin arm of this study, 9/13 clinically evaluable patients with baseline *Pseudomonas aeruginosa,* received concurrent anti-pseudomonal coverage (6 gentamicin and 3 amikacin) and 6 were clinical failures with persistence of the baseline pathogen (66.6%). The remaining 3 patients were clinical cures with eradication (33.3%). Of the 4 patients who received no concurrent therapy, 2 were clinical cures with eradication, and 2 were clinical failures, one with eradication, and 1 with persistence. In study 154-113, 4/7 patients received additional anti-pseudomonal coverage, and persistence was seen in 3 of these cases, although clinical cure was seen in 4. The remaining 3 patients were failures with persistence (100%).

The total ciprofloxacin versus *Pseudomonas aeruginosa* eradication rate for the 2 studies combined is 7/13 + 1/7 = 8/20 (40%). Concurrent anti-pseudomonal therapy was utilized in 13 of these cases with resultant eradication in 4 cases (30.7%) although 9/13 of these cases were clinical failures. Therefore, in 4 of 13 clinically evaluable patients with baseline *Pseudomonas aeruginosa*, in whom additional coverage was used, both a clinical cure and pathogen eradication were obtained.

There is no doubt that the overall activity of trovafloxacin versus *Pseudomonas aeruginosa* appeared superior to that of ciprofloxacin, and that this result stemmed primarily from the controlled US study as opposed to this open study. Additionally, there were enough isolates from study 154-113, to meet the divisional requirements for approval by the "rule of 10".

Bacteriologic Response in Subjects with *Staphylococcus aureus* at baseline:

10 MO evaluable alatrofloxacin/trovafloxacin subjects and 15 evaluable ceftazidime/ciprofloxacin subjects had *Staphylococcus aureus* isolated at baseline. On the alatrofloxacin/trovafloxacin arm, eradication was seen in 9/10 cases. 2 of these 9 were clinical failures. Additionally, there was on patient who was a clinical failure with persistence.

The MO elected to list the patients with the specimen source and other isolates from the same specimen below:

- # 54140269: TTA: *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus parainfluenzae,* and *Serratia marcescens.* Failure with eradication of all isolates.
- #58710440: Lung biopsy: *Staphylococcus aureus* and *Klebsiella pneumoniae.* Failure with eradication of both isolates.

- #59260010: Sputum: *Staphylococcus aureus* only. Failure with persistence.
- #59480125: Sputum: *Staphylococcus aureus* and *Haemophilus influenzae.* Cure with eradication of both isolates.
- #59530216: Bronchial lavage: *Staphylococcus aureus* and *Hafnia alvei.* Cure with eradication of both isolates.
- #59530252: Bronchial lavage: *Staphylococcus aureus* and *Haemophilus influenzae.* Cure with eradication of both isolates.
- #59550221: Bronchial lavage: *Staphylococcus aureus, Haemophilus influenzae,* and *Bacteroides melaninogenicus.* Cure with eradication of all isolates.
- #59550267: Bronchial lavage: *Staphylococcus aureus.* Cure with eradication.
- #59550268: Bronchial lavage: *Staphylococcus aureus* and *Morganella morganii.* Cure with eradication of both isolates.
- #59660341: Orotracheal aspirate: *Staphylococcus aureus, Escherichia coli,* and *Acinetobacter baumanii.* Cure with eradication of all isolates.

Notable from this list is that *Staphylococcus aureus* was the sole isolate in 2 cases only. There was no discernible pattern from this listing as to the necessity of this isolate being the sole pathogen in order to be considered a true pathogen.

A similar listing follows for the ceftazidime/ciprofloxacin arm:

- #54140297: Bronchial lavage: *Staphylococcus aureus*. Failure with persistence.
- #54370329: Sputum: *Staphylococcus aureus, Klebsiella pneumoniae,* and *Streptococcus pneumoniae.* Failure with persistence of all isolates.
- #58710427: Lung biopsy: *Staphylococcus aureus*. Failure with persistence
- #58710439: Blood: *Staphylococcus aureus* and sputum: *Enterobacter aerogenes* and *Pseudomonas* aeruginosa. Failure with persistence of the blood isolate.
- #59260011: Sputum: *Staphylococcus aureus:* Failure with persistence.
- #59260060: Sputum: *Staphylococcus aureus:* cure with eradication.
- #59260066: Sputum: *Staphylococcus aureus* and *Haemophilus influenzae*. Cure with eradication of both isolates.
- #59450134: Sputum: *Staphylococcus aureus:* Failure with persistence.
- #59480126: Sputum: *Staphylococcus aureus* and *Klebsiella pneumoniae*. Cure with eradication of both isolates.
- #59520094: Orotracheal aspirate: *Staphylococcus aureus* and *Escherichia coli*: Failure with persistence of both isolates.
- #59530251: Bronchial lavage: *Staphylococcus aureus* and *Pseudomonas aeruginosa*: Cure with eradication of both isolates.
- #59550247: Bronchial lavage: *Staphylococcus aureus* and *Moraxella catarrhalis*: Failure with persistence of both isolates.
- #59720325: TTA: *Staphylococcus aureus* (persistent), and *Citrobacter freundii* (eradicated): failure.
- #59750404: Sputum: *Staphylococcus aureus:* Cure with eradication.
- #59780367: Bronchial lavage: *Staphylococcus aureus:* Cure with eradication.

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On this arm of the 15 evaluable isolates, 14 had the organism isolated from the respiratory tree. Not all isolates had an EOS outcome, as 2 were EOT failures with persistence. *Staphylococcus aureus* was the sole baseline isolate in 7 of the cases and was isolated from the sputum in 4 of these (2 cures/eradication and 2 failures/persistence). If these patients were eliminated from the analysis, the eradication rate would change to 5/11 (45.4%). If the same was done for the trovafloxacin arm (eliminate 1 failure with persistence), the eradication rate would be 9/9 (100%). Alternatively, if only those specimens where *Staphylococcus aureus* was the sole pathogen were considered evaluable, independent of the source, the eradication rates would be trovafloxacin ½ (50%) versus ciprofloxacin 3/7 (42.8%).

In study 154-113, 8 MO evaluable trovafloxacin subjects and 6 evaluable ciprofloxacin subjects had *Staphylococcus aureus* at baseline.

Failure with persistence was seen in 4/8 (50%) of the trovafloxacin patients. Additionally, ¼ (25%) of the clinical cures was assosciated with persistence. Thus 5/8 (62.5%) of isolates were assosciated with persistence. Therefore the cumulative eradication rate for all isolates would be 4/8 + 9/10 = 13/18 (72.2%).

On the ciprofloxacin arm, 4/6 subjects were clinical cures with eradication (100%). The cumulative eradication rate was 4/6 + 6/12 = 10/18 (57.8%). Or 6/14 (42.8%) if persistences carried forward from EOT = 10/20 (50%).

There appeared to be a good clinical correlation between eradication rates and clinical outcome in this subgroup of patients. The MO determined that trovafloxacin's activity against this isolate was better than that of the comparator. This is a requirement for approval, as the comparator is not approved for this isolate.

In terms of approval, if all specimens where *Staphylococcus aureus* as the sole isolate only were accepted, independent of source and in correlation with the Gram stain and clinical picture, then the cumulative eradication rate would be: ½ +0/3 = 1/5 (20%), as only 3 sputum specimens met these parameters in 113 and all were failures with persistence.

Cross-Tabulation of Clinical Response and Pathogen Outcome at the EOS:

There were 25 instances of incompatibility between clinical response and pathogen outcome in this trial. Specifically, there were 15 cases of clinical failure with bacteriologic eradication on the ceftazidime/ciprofloxacin arm and 9 cases on the alatrofloxacin/trovafloxacin arm. There were no cases of success with persistence on the ceftazidime/ciprofloxacin arm and 1 case on the alatrofloxacin/trovafloxacin arm.

On the ceftazidime/ciprofloxacin arm, the 15 failures were assosciated with *Citrobacter diversus (1), Enterobacter cloace (2), Escherichia coli (4), Haemophilus influenzae (1), Haemophilus parainfluenzae (1), Klebsiella oxytoca (1), Pseudomonas aeruginosa (2),* and *Serratia marsecens (1).*

On the alatrofloxacin/trovafloxacin arm, the 9 failures were assosciated with *Acinetobacter baumanii* (1), Enterobacter cloace (1), *Haemophilus parainfluenzae (1), Escherichia coli (1), Klebsiella pneumoniae (1), Serratia marsecens (1), staphylococcus aureus (1),* and *Streptococcus pneumoniae (1).* The 1 success was assosciated with *Klebsiella pneumoniae.*

No meaningful conclusions could be drawn from this data with regards to trovafloxacin. It appeared as if ceftazidime/ciprofloxacin was assosciated with more inconsistencies in cases where *Enterobactericiae* were considered pathogens.

Safety Review:

88/135 (65%: 176 events) alatrofloxacin/trovafloxacin-treated subjects and 79/140 (56%: 167 events) ceftazidime/ciprofloxacin-treated subjects had at least one AE, (all causality). In this study, which included the intravenous administration of study drug for at least 3 days, there did not appear to be a large number of events associated with the intravenous insertion site (2/135(1%) versus 8/140 (6%) per arm respectively, as compared to study 154-113 where this type of event was seen in 29/127 (23%) of the trovafloxacin-treated subjects and 24/137 (18%) of the ciprofloxacin-treated subjects.

The percentage of subjects reporting at least 1 treatment-related adverse event was 12% (16/135: 19 events), on the alatrofloxacin/trovafloxacin arm, and 4% (5/140: 5 events), on the ceftazidime/ciprofloxacin arm.

The most commonly reported adverse event on the alatrofloxacin/trovafloxacin arm was related to the gastrointestinal system (vomiting).

On the ceftazidime/ciprofloxacin arm, no system was more affected.

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