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 2 trovafloxacin-treated and 3 ciprofloxacin-treated patients were not evaluable. Of those patients who were evaluable per the MO, there was no disagreement between the MO's and the sponsor's determinations of outcome.*

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Sponsor's Conclusion:
(Copied from page 77 of the study report and modified by the MO (in Times New Roman font)

Alatrofloxacin/trovafloxacin was comparable to ciprofloxacin for clinical success rate in subjects with nosocomial pneumonia.

One hundred twenty-nine (129) subjects were randomized to treatment with alatrofloxacin/trovafloxacin and 138 subjects were randomized to treatment with ciprofloxacin.

Of the randomized subjects, 127 subjects in the alatrofloxacin/trovafloxacin group and 137 subjects in the ciprofloxacin group received treatment; two randomized subjects in the alatrofloxacin/trovafloxacin group and one randomized subject in the ciprofloxacin group did not receive 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 pneumonia.

Eighty-eight (88) subjects in the alatrofloxacin/trovafloxacin group and 103 subjects in the ciprofloxacin group were clinically evaluable; 47 subjects in the alatrofloxacin/trovafloxacin group and 52 subjects in the ciprofloxacin group were bacteriologically evaluable. All treated subjects were included in analysis of adverse events.

Sponsor-defined clinical success rates (cure + improvement) supported equivalence of the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups at the end of treatment for both clinically evaluable and intent-to-treat subjects. Success rates were comparable between the two treatment groups at the end of study. Success rates among clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups were 77% (68/88) and 78% (79/101), respectively, at the end of treatment and 69% (50/72) and 68% (54/79), respectively, at the end of study and those among clinically intent-to-treat subjects were 63% (80/127) and 70% (94/135), respectively, at the end of treatment and 61% (77/127) and 67% (91/135), respectively, at the end of study. These findings were supported by marked decreases from baseline to the end of treatment and to the end of study in the presence of clinical and radiologic signs and symptoms of pneumonia in both treatment groups.

Among clinically evaluable subjects, 12 (14%) subjects in the alatrofloxacin/trovafloxacin group and 17 (17%) subjects in the ciprofloxacin group died within 45 days of initiation of study therapy. Among clinically intent-to-treat subjects, 30 (24%) subjects in the alatrofloxacin/trovafloxacin group and 34 (25%) subjects died within 45 days of initiation of study therapy.

Sponsor-defined pathogen eradication rates for the most commonly isolated pathogens were comparable among bacteriologically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups at the end of treatment and end of study.

Of the 15 evaluable alatrofloxacin/trovafloxacin subjects and 11 ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, six alatrofloxacin/trovafloxacin (40%) and four ciprofloxacin (36%) received optional aztreonam therapy (dual therapy). There appeared to be no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy in sponsor-defined clinical response at end of treatment or end of study. Subjects in

both treatment groups who received dual therapy had a lower rate of persistence and presumed persistence for *Pseudomonas aeruginosa* at the end of treatment, however, due to the small number of subjects no definitive conclusions could be drawn.

Of the subjects with an unfavorable clinical or bacteriological response who had baseline isolates with susceptibility testing performed both prior to and following treatment, none had pathogens that became resistant to trovafloxacin, ciprofloxacin, or aztreonam.

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Medical Officer's Efficacy Analysis:

In accordance with the previously described MO evaluability criteria, the MO excluded 40 additional patients from the clinically evaluable population because they had no EOS visit. Additionally, 4 patients were excluded because they received < 80% of the prescribed therapeutic regimen. This information has been presented in MO table 113.14, below:

Table 113.14
Clinically Evaluable Population (as per the MO)

Reason for exclusion	Trovafloxacin	Ciprofloxacin
Total Treated	127	137
Sponsor Evaluable	88	103
MO Excluded	18	26
No EOS Visit	16	24
< 80% Of regimen	2	2
Total Evaluated at EOS	**70**	**77**

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In the MO's analysis, the number of clinically evaluable patients at the EOT and the EOS were the same. The 70 clinically evaluable trovafloxacin patients represented 26.5% of the treated patients and the 77 ciprofloxacin patients represented 29.1%.

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 113.15:

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Table 113.15
Clinically Evaluable Population by Center (as per MO)

Center	Total Treated N = 264	(100%)	Trovafloxacin N = 70	100%	Ciprofloxacin N = 77	100 %
5423	1	0.4	0	-	0	-
5467*	3	1.1	0	-	1	1.3
5483*	15	5.6	3	4.3	3	3.9
5508	1	0.4	1	1.4	0	-
5510	3	1.1	2	2.9	1	1.3
5511	3	1.1	2	2.9	0	-
5513	2	0.7	0	-	1	1.3
5515	1	0.4	0	-	1	1.3
5516	1	0.4	0	-	1	1.3
5541*	2	0.7	0	-	1	1.3
5546*	4	1.4	1	1.4	2	2.6
5623	18	6.7	7	10	5	6.5
5627	4	1.5	0	-	1	1.3
5628*	1	0.4	0	-	0	-
5834	3	1.1	2	2.9	0	-
5835	7	2.6	2	2.9	4	5.2
5837*	1	0.4	0	-	0	-
5903	2	0.7	1	1.4	1	1.3
5970*	1	0.4	0	-	0	-
5984*	1	0.4	0	-	0	-
5985*	3	1.1	0	-	1	1.3
5987*	2	0.7	0	-	0	-
6111	1	0.4	1	1.4	0	-
6112	1	0.4	1	1.4	0	-
6127*	7	2.6	1	1.4	2	2.6
6367*	3	1.1	0	-	2	2.6
6376*	1	0.4	0	-	0	-
5030	2	0.7	2	2.9	0	-
5034	3	1.1	0	-	1	1.3
5079*	5	1.8	3	4.3	2	2.6
5106*	4	1.5	1	1.4	0	-
5111*	8	3.0	2	2.9	1	1.3
5112*	14	5.2	3	4.3	4	5.2
5115*	2	0.7	0	-	1	1.3
5117*	1	0.4	0	-	0	-
5118*	2	0.7	0	-	1	1.3
5119*	8	3.0	3	4.3	3	3.9
5121*	5	1.8	3	4.3	2	2.6
5173*	5	1.8	1	1.4	3	3.9
5174*	6	2.2	2	2.9	2	2.6
5175*	19	7.1	8	11.4	6	7.8
5181*	1	0.4	0	-	1	1.3
5188*	11	4.1	2	2.9	3	3.9
5191*	8	3.0	1	1.4	2	2.6
5193*	1	0.4	0	-	0	-

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5211*	7	2.6	2	2.9	2	2.6
5249*	3	1.1	1	1.4	0	-
5384*	1	0.4	0	-	0	-
5386*	20	7.5	5	7.1	5	6.5
5395	1	0.4	0	-	1	1.3
5396	2	0.7	1	1.4	0	-
5407	2	0.7	0	-	1	1.3
5409	8	3.0	2	2.9	2	2.6
5410	7	2.6	0	-	1	1.3
6404	11	4.1	1	1.4	4	5.2
6455*	1	0.4	0	-	0	-
6543	7	2.6	3	4.3	2	2.6

*Designates US centers

As appreciated from the above table, no center had greater than 10% of the evaluable patients and most centers were able to provide only 1 or 2 evaluable patients. As in all indications, as the primary efficacy variable of clinical outcome was determined by the sponsor, the data were pooled for the analyses.

The demographic make-up of the FDA evaluable population can be seen in Table 113.16:

Table 113.16
Demographic Characteristics of the FDA Evaluable Population:

		Trovafloxacin	Ciprofloxacin
Characteristics		N = 70	N = 77
Sex (Female)		32	35
(Male)		38	42
Age (years)	16 –44	9	6
	45 – 64	11	11
	≥ 65	50	60
	Mean	69.8	72.1
Race:			
	Black	4	3
	White	60	68
	Hispanic	6	5
	Indian	0	1
Body weight (kg)	Mean	71.8	67.7
Smoking Status	Ex Smoker	27	29
	Never	31	29
	Smoker	12	27
	Missing	0	2
Mechanical Ventilation	Yes	18	16
	No	52	61
Compromised Respiration	Yes	15	24
	No	55	53
Severity if Illness			
	Mild/Moderate	50	52
	Severe	20	35
APACHE Score	Mean	13.1	13.4

The MO's evaluable populations are very similar in terms of the demographic variables of age, weight, sex, and race.

Both groups had a similar number of patients requiring ventilator assistance and presumably more severely ill. Specifically, 18/70 (25.7%) trovafloxacin-treated, MO evaluable patients received ventilator support as compared to 16/77 (20.7%) ciprofloxacin-treated, MO evaluable patients. The number of evaluable patients was small in this study and the difference of 1 or 2 patients leads to a large percentage point difference. The MO provided a separate efficacy analysis for this subgroup as well as for the subgroups of patients with mild/moderate disease, severe disease, and those that were both clinically and bacteriologically evaluable..

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EFFICACY:

Table 113.17
Clinical Response by Patient (as per the MO):

	Trovafloxacin			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	70	50	71.4	76	54	70.1
EOS	70	48	68.6	77	52	67.5

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

EOT: Trovafloxacin versus Ciprofloxacin: -15.7%, 16.4% ($\Delta = 20$).

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EOS: Trovafloxacin versus Ciprofloxacin: -15.4%, 17.5% ($\Delta = 20$).

Thus the MO's results mirrored those of the sponsor (EOS: trovafloxacin 50/72 (69%) and 54/79 (68%) ciprofloxacin) and showed equivalence between trovafloxacin and the approved comparator agent at the MO TOC, the EOS.

Based on the MO's analysis, there were 22 failures at the EOS on the trovafloxacin arm (22/70{31.4%}) as compared to 25 on the ciprofloxacin arm (25/77 {32.5%}). Once again, these numbers are comparable to the sponsor's 22 failures at the EOS on the trovafloxacin arm and 25 on the ciprofloxacin arm. The patients who failed as per the MO include failures and relapses.

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Clinical Response by Disease Severity Status:

Table 113.18
Clinical Response at EOS for Patients with Mild/Moderate Disease (as per MO):

	Trovafloxacin			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	50	40	80	51	41	78.8
EOS	50	38	76	52	39	75

EOT: Trovafloxacin versus Ciprofloxacin: -17.9%, 17.1% ($\Delta = 20$).

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EOS: Trovafloxacin versus Ciprofloxacin: -17.7%, 19.7% ($\Delta = 20$).

As noted previously, in the sponsor's analysis, the overall success rate was higher in this less severely ill population. (sponsor EOS: 39/51 (76%) trovafloxacin versus 40/53 (75%).

Table 113.19
Clinical Response at EOS for Patients with Severe Disease (as per MO):

	Trovafloxacin			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	20	10	50	25	13	52
EOS	**20**	**10**	**50**	**25**	**13**	**52**

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Table 113.20

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

	Trovafloxacin			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	18	10	55.6	16	8	50
EOS	**18**	**10**	**55.6**	**16**	**8**	**50**

CIs were not applied to these smaller groups of patients; that is in the patients with severe disease and in those requiring ventilatory support. However, trovafloxacin appeared slightly numerically superior to ciprofloxacin in this more severely ill subgroup, that is those patients on ventilators. Once again, these results were consistent with those of the sponsor.

Specifically, in patients with severe disease the sponsor found an EOS success rate of 11/21 (52%) trovafloxacin versus 14/26 (54%) ciprofloxacin.

As noted previously, in the sponsor's analysis, the overall success rate was higher in the less severely ill population (sponsor EOS: 39/51 (76%) trovafloxacin versus 40/53 (75%). The results between the arms were comparable in both the MO's and the sponsor's analyses and indicate a 20 percentage point difference in success rates depending on disease severity and ventilatory status.

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Table 113.21
Clinical Response at EOS for Clinically and Bacteriologically Evaluable Patients (as per MO):

	Trovafloxacin			Ciprofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	37	24	64.9	36	24	66.7
EOS	**37**	**23**	**62.2**	**36**	**23**	**63.9**

EOT: Trovafloxacin versus Ciprofloxacin: - 26.3%, 22.7% ($\Delta = 20$).

EOS: Trovafloxacin versus Ciprofloxacin: - 26.6%, 23.2% ($\Delta = 20$).

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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.

Table 113.22
Clinical Response by Baseline Pathogen at the EOS (as per MO)

Pathogen	Trovafloxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	6	5	83	7	6	86
Moraxella catarrhalis	1	0	0	2	1	50
Streptococcus pneumoniae	4	2	50	4	3	75
Stenotrophomonas maltophilia	2	2	100	-	-	-
Haemophilus parainfluenzae	4	4	100	2	1	50
Klebsiella pneumoniae	4	2	50	5	1	20
Pseudomonas aeruginosa	13	8	62	7	1	14.3
Klebsiella oxytoca	3	2	67	-	-	-
Escherichia coli	6	3	50	5	4	80
Proteus mirabilis	2	1	50	1	1	100
Morganella morganii	1	1	100	1	1	100
Acinetobacter spp.	1	1	100	2	2	100
Staphylococcus aureus	8	4	50	6	4	67
Serratia marcescens	1	1	100	1	1	100
Enterococcus faecalis	2	1	50	1	0	0
Enterobacter cloace	1	1	100	2	1	50
Enterobacter aerogenes	-	-	-	1	0	0
Neisseria meningitidis	1	1	100	-	-	-
Providencia spp.	1	1	100	-	-	-
Aerococcus spp.	-	-	-	1	1	100
Citrobacter diversus	-	-	-	1	0	0
Corynebacterium spp.	-	-	-	-	-	-
Haemophilus parahemolyticus	-	-	-	1	1	100
Legionella pneumophilia	1	1	100	-	-	-
Streptococcus anginosus	-	-	-	1	0	0
Total	**62**	**41**	**66.1**	**51**	**29**	**56.8**

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The MO's results differed from those of the sponsor (EOS 59.4% trovafloxacin versus 54.8% ciprofloxacin) for this variable in that clinical response was slightly better for the trovafloxacin-treated patients as compared to the ciprofloxacin-treated group. Once again there was a much higher rate of clinical failure in patients with *Pseudomonas aeruginosa* as the baseline pathogen on the ciprofloxacin arm. A CI was not applied as this was not an individual variable.

Below, in MO table 113.23 is clinical response by baseline pathogen only for the requested pathogens:

Table 113.23
Clinical Response by Baseline Pathogen at the EOS (Clinically Evaluable Population/Requested Pathogens Only: as per MO)

Pathogen	Trovafloxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	6	5	83	7	6	86
Escherichia coli	6	3	50	5	4	80
Klebsiella pneumoniae	4	2	50	5	1	20
Staphylococcus aureus	8	4	50	6	4	67
Pseudomonas aeruginosa	13	8	62	7	1	14.3
Total	**37**	**22**	**59.4**	**30**	**16**	**53.5**

Thus indicating that when only the requested pathogens were evaluated, the clinical response of the trovafloxacin-treated patients was higher than that of the 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 ciprofloxacin versus *Pseudomonas aeruginosa.*

Mortality:

The MO found that there were 8 deaths on the trovafloxacin arm (8/70 {11.6%) as compared to 9 on the ciprofloxacin arm (9/77 {11.7%). 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.

Bacteriologic Response:

Table 113.24
Pathogen Eradication Rates at the EOS (Bacteriologically Evaluable Population, as per MO)

Pathogen	Trovafloxacin			Ciprofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	6	5	83	7	7	100
Moraxella catarrhalis	1	0	0	2	2	100
Streptococcus pneumoniae	4	2	50	4	4	100
Stenotrophomonas maltophiliä	2	2	100	-	-	-
Haemophilus parainfluenzae	4	4	100	2	1	50
Klebsiella pneumoniae	4	2	50	4	1	25
Pseudomonas aeruginosa	13	10	76.9	7	1	14.3
Klebsiella oxytoca	3	2	67	-	-	-
Escherichia coli	4	3	75	5	5	100
Proteus mirabilis	2	2	100	1	1	100
Morganella morganii	1	1	100	1	1	100
Acinetobacter spp.	1	1	100	1	0	0
Staphylococcus aureus	8	3	37.5	6	4	67
Serratia marcescens	1	1	100	1	1	100
Enterococcus faecalis	1	0	0	1	0	0
Enterobacter cloace	1	1	100	2	1	50
Enterobacter aerogenes	-	-	-	1	1	100
Neisseria meningitidis	1	1	100	-	-	-
Providencia spp.	1	1	100	-	-	-
Aerococcus spp.	-	-	-	1	1	100
Citrobacter diversus	-	-	-	1	0	0
Corynebacterium spp.	-	-	-	1	1	100
Haemophilus parahemolyticus	-	-	-	1	1	100
Legionella pneumophilia	1	1	100	-	-	-
Streptococcus anginosus	-	-	-	1	0	0
Total	**59**	**42**	**71.2**	**50**	**33**	**66**

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Based on the MO's analysis, the overall pathogen eradication rate of trovafloxacin was numerically superior to that of 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.

Although the MO determined that not all the organisms found in table 113.24 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 MO's results were similar to those of the sponsor to the degree that the pathogen eradication rate of trovafloxacin was superior to that of ciprofloxacin at the EOS. As noted in table 113.11, the sponsor's rates were EOS: trovafloxacin 44/61 (72.1%) as compared to ciprofloxacin 34/52 (55.3%). Thus the MO's results narrowed the numerical difference between the 2 arms.

The lower eradication rate of ciprofloxacin appeared to be attributable to the lower eradication rate of *Pseudomonas aeruginosa.*

Pathogen eradication rates for the requested pathogens only, can be seen below in table 113.25:

Table 113.25
Pathogen Eradication Rates at the EOS (Bacteriologically Evaluable Population/Requested Pathogens Only: as per MO)

Pathogen	Trovafloxacin			Ciprofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	6	5	83	7	7	100
Escherichia coli	4	3	75	5	5	100
Klebsiella pneumoniae	4	2	50	4	1	25
Staphylococcus aureus	8	3	37.5	6	4	67
Pseudomonas aeruginosa	13	10	76.9	7	1	14.3
Total	35	23	65.7	29	18	62

The MO's results are the same as the sponsor's on the trovafloxacin arm and only 1 percentage point different on the ciprofloxacin arm. Overall, the 2 agents appeared numerically comparable in the eradication of *Haemophilus influenzae*. The number of *Escherichia coli* and *Klebsiella pneumoniae* isolates was too small to be able to draw any valid conclusions. The activity of trovafloxacin versus *Staphylococcus aureus* was marginal, whereas the activity of ciprofloxacin against *Pseudomonas aeruginosa* was very poor.

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

There were 13 trovafloxacin and 7 ciprofloxacin subjects in the MO evaluable population that had *Pseudomonas aeruginosa* as the baseline pathogen.

6/13 trovafloxacin patients received concurrent anti-pseudomonal coverage (5 aztreonam and 1 amikacin). 3 of the 6 were clinical failures with eradication of the baseline pathogen. Of the 3 patients who were clinical successes, there was persistence of the baseline pathogen in only 1 patient. Thus in 5 of the 6 patient on the trovafloxacin arm who received additional anti-pseudomonal coverage, eradication was seen in 80%.

Of the remaining 7 trovafloxacin patients, 2 patients were clinical failures with persistence of the baseline pathogen and 5 were clinical successes with persistence in only 1. Thus 3/7 (43%) patients who received monotherapy had persistence.

Based on the above, the sponsor's claim that additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population appeared to be accurate.

On the ciprofloxacin arm, 4/7 subjects received additional anti-pseudomonal coverage (1 aztreonam and 3 aminoglycosides). 2/4 (50%) were clinical failures with persistence and persistence was also noted in 1 of 2 cures. Thus of the 4 patients with additional anti-pseudomonal coverage, 3 of 4 (75%) had persistence.

Of the remaining 3 patients, all were failures with persistence (100%). Thus on this arm of the study, the addition of an additional anti-pseudomonal agent did not appear to affect bacteriologic outcome. Resistance was not documented in these patients and the poor activity of ciprofloxacin versus *Pseudomonas aeruginosa* cannot be explained.

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

8 MO evaluable trovafloxacin subjects and 6 evaluable ciprofloxacin subjects had *Staphylococcus aureus* at baseline.

The patients are listed below with source, commensual pathogens, and outcome:

Trovafloxacin (N= 8)

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- #51120053: Orotracheal aspirate: *Staphylococcus aureus*: Cure with eradication.
- #51190064: Sputum: *Staphylococcus aureus*: Failure with persistence.
- #51880192: Orotracheal aspirate: *Staphylococcus aureus*: Failure with persistence.
- #51910039: Bronchial lavage: *Staphylococcus aureus*: Failure with persistence.
- #52110136: Nasotracheal aspirate: *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa.* Improvement with persistence.
- #53860249: Sputum: *Staphylococcus aureus, Klebsiella oxytoca*: Cure with eradication.
- #55110618: Bronchial lavage: *Staphylococcus aureus, Klebsiella oxytoca*, and *Pseudomonas aeruginosa.* Failure with persistence.
- #56230318: Orotracheal aspirate: *Staphylococcus aureus*: Cure with eradication. Also had sputum with *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*, both eradicated.

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Ciprofloxacin (N=6):

- #51190225: Nasotracheal aspirate: *Staphylococcus aureus*: Cure with eradication.
- #51730152: Blood: *Staphylococcus aureus:* Cure with eradication.
- #51740013: Sputum: *Staphylococcus aureus* and *Haemophilus parainfluenzae*: Cure with eradication.
- #51750163: Sputum: *Staphylococcus aureus*: Failure with persistence.
- #53860201: Sputum: *Staphylococcus aureus* and *Enterococcus faecalis*: Failure with persistence.
- #65430537: Sputum: *Staphylococcus aureus:* Cure with eradication.

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Failure with persistence was seen in 4/8 (50%) of the trovafloxacin patients. Additionally, 1 of 4 (25%) of the clinical cures was assosciated with persistence. Thus 5/8 (62.5%) of isolates were assosciated with persistence. Once again the development of resistance was not an issue and the MO could not explain the higher clinical failure rate assosciated with the high rate of bacteriologic persistence seen on this arm.

Staphylococcus aureus was the sole isolate in 4 specimens, none of which were obtained from the lower respiratory tree. In 3 of the 4 of these cases, there was failure with persistence. If one excluded all specimens except lavage specimens then the eradication rate would be 1/8, if however, one only accepted specimens where *Staphylococcus aureus* was the sole pathogen, independent of the source, the eradication rate changed to 3 of 4 or 75%.

On the ciprofloxacin arm, 4/6 subjects were clinical cures with eradication (100%). There were 2 failures and in both there was persistence. Thus, eradication was seen in 67% of the cases and always assosciated with clinical success.

Staphylococcus aureus was the sole isolate in 4 specimens, none of which were obtained from the lower respiratory tree. In 3 of the 4 of these cases, there was cure with eradication. If one excluded all specimens except lavage specimens then no isolates would have been considered evaluable. If however, one only accepted specimens where *Staphylococcus aureus* was the sole pathogen, independent of the source, the eradication rate changed to 3 of 4 or 75%.

There appeared to be a good clinical correlation between eradication rates and clinical outcome in this subgroup of patients.

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

There were few cases of incompatibility between clinical response and pathogen outcome in this trial. Specifically, there were 6 cases of clinical failure with bacteriologic eradication on the ciprofloxacin arm and 2 cases on the trovafloxacin arm. There were no cases of success with persistence on the ciprofloxacin arm and 2 cases on the trovafloxacin arm.

In all cases, there was no more than 1 bacterial isolate assosciated with the incongruity.

On the ciprofloxacin arm, the 6 failures were assosciated with 1 each of *Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae.*

On the trovafloxacin arm, the 2 failures were assosciated with 1 each of *Proteus mirabilis* and *Escherichia coli.* The 2 successes were assosciated with 1 each of *Pseudomonas aeruginosa* and *Staphylococcus aureus.*

No meaningful conclusions could be drawn from this data.

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Safety Review:

121/127 (95%: 458 events) trovafloxacin-treated subjects and 111/137 (81%: 405 events) ciprofloxacin-treated subjects had at least one AE, (all causality). This study included the intravenous administration of study drug for at least 3 days and therefore there appeared to be a large number of events associated with the intravenous insertion site. Specifically, 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 22% (28/127: 42 events), on the trovafloxacin arm, and 17% (23/137: 30 events), on the ciprofloxacin arm.

The most commonly reported adverse events on the trovafloxacin arm were related to the gastrointestinal system with nausea being reported most frequently.

On the ciprofloxacin arm, the system most affected was the respiratory tract.

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.

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Table 113.26
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin	Ciprofloxacin
Number of Subjects Treated	127 (100%)	137 (100%)
Subject-Days of Exposure	1100	1364
Subjects With At Least One Event	121 (95%)	111 (81%)
Number of Adverse Events	485	405
Subjects with Serious Adverse Events	46 (36%)	38 (28%)
Subjects with Severe Adverse Events	46 (36%(	40 (29%)
Subjects Discontinued Due to Adverse Events	19 (15%)	10 (7%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	4 (3%)	1 (<1%)
Subjects Discontinued Due to Objective Test Findings	3 (2%)	2 (1%)
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

Table 113.27
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	127 (100%)	137 (100%)
Subjects With At Least One Event	121 (95%)	111 (81%)
Subjects Discontinued due to Adverse Event	19 (15%)	10 (7%)
ADVERSE EVENTS BY BODY SYSTEM:		
Appl./Inj./Incision/Insertion Site	29 (23%)	24 (18%)
Autonomic Nervous	5 (4%)	6 (4%)
Cardiovascular	47 (37%)	42 (31%)
Centr. & Periph. Nerv.	30 (24%)	25 (18%)
Endocrine	1 (< 1%)	2 (1%)
Gastrointestinal	61 (48%)	47 (34%)
General	30 (24%)	32 (23%)
Hematopoietic	8 (6%)	2 (1%)
Liver/Biliary	3 (2%)	0
Metabolic/Nutritional	6 (5%)	3 (2%)
Musculoskeletal	7 (6%)	5 (4%)
Neoplasms	3 (2%)	1 (<1%)
Other Adverse Events	9 (7%)	8 (6%)
Psychiatric	26 (20%)	20 (15%)
Reproductive	2 (2%)	2 (1%)
Respiratory	43 (34%)	47 (34%)
Skin/Appendages	26 (20%)	30 (22%)
Special Senses	1 (<1%)	6 (4%)
Urinary System	19 (15%)	13 (9%)

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Table 113.28
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	127 (100%)	137 (100%)
Subjects With At Least One Event	28 (22%)	23 (17%)
Subjects Discontinued due to Adverse Event	5 (4%)	0
ADVERSE EVENTS BY BODY SYSTEM:		
Appl//Inj./Insertion/Incision/Site	6 (5%)	7 (5%)
Cardiovascular	5 (4%)	2 (1%)
Centr. & Periph. Nerv.	4 (3%)	2 (1%)
Gastrointestinal	11 (9%)	6 (4%)
General	4 (3%)	3 (2%)
Psychiatric	2 (2%)	0
Reproductive	1 (< 1%)	0
Respiratory	0	6 (4%)
Skin/ Appendages	3 (2%)	3 (2%)
Special Senses	0	1 (<1%)

Further breakdown of the treatment-related events, indicated that 3 (7%) of the events on the trovafloxacin arm were severe in nature, as compared to 0 on the ciprofloxacin arm. The 3 severe events on the trovafloxacin arm, were from the central and peripheral nervous systems (2), one event each confusion and involuntary muscle contraction and one from the gastrointestinal tract, diarrhea.

Table 113.29

Most Common AEs/Treatment-Related All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin N = 127 28 (22%)		Ciprofloxacin N = 137 23 (17%)	
Nervous system	4	(3%)	2	(1%)
Headache	2	(2%)	1	(< 1%)
GI System	11	(9%)	6	(4%)
Nausea	6	(5%)	1	(< 1%)
Diarrhea	2	(2%)	2	(1%)
Vomiting	2	(2%)	1	(< 1%)
Appl./Inj./Incision/Insertion Site	6	(5%)	7	(5%)
Site Reaction	4	(3%)	3	(2%)
Site Complication	2	(2%)	1	(<1%)
Cardiovascular	5	(4%)	2	(1%)
Phlebitis	5	(4%)	2	(1%)
General	4	(3%)	3	(2%)
Moniliasis	3	(2%)	3	(2%)
Reproductive	1	(<1%)	0	0
Vaginitis	1	(<1%)	0	0
Respiratory	0	0	6	(4%)
Respiratory Tract Infection	0	0	4	(3%)

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Deaths:

Overall (ITT population), there were 35 deaths on the trovafloxacin arm and 38 on the ciprofloxacin arm during the study. 6 deaths on each arm occurred while receiving therapy and were considered unrelated to the study drug by the investigator. 25 deaths on the trovafloxacin arm and 29 on the ciprofloxacin arm occurred after therapy but during the study period and were also considered unrelated to the study drugs. An additional 4 subjects on the trovafloxacin arm and 3 on the ciprofloxacin arm died > 30 days after the last dose of the study drug and these deaths were also considered unrelated to the study drugs.

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The subjects who died during the study are reviewed below:

Trovafloxacin (N = 35):

- # 51060050: 85 YO male died on study day 57 of renal failure, metabolic acidosis, respiratory failure, and cardiopulmonary arrest. This death was not attributed to the study drug.
- #51190227: 79 YO male died on study day 25 of cardiomyopathy, COPD, and congestive heart failure. This death was not attributed to the study drug.
- #50300265: 91 YO male with a history of tongue cancer, died on study day 31 of progression of his disease. This death was not attributed to the study drug
- #51060049: 72 YO male died on study day 2 of Gram (-) sepsis and respiratory failure. This death was not attributed to the study drug
- #51120224: 89 YO died of respiratory failure on study day 8. Death was attributed to a pulmonary embolism.
- #51180070: 95 YO female died on study day 8 of respiratory failure attributed to natural causes.
- #51190064: 78 YO male died on study day 6 of pulmonary edema and congestive heart failure. This death was not attributed to the study drug.
- #51730151: 69 YO male died on study day 2 of pneumonia and respiratory failure. This death was not attributed to the study drug.
- #51740016: 61 YO male died approximately 3 months after the completion of the study, of cardio-pulmonary arrest secondary to underlying atrial fibrillation.
- #51740241: 93 YO female died on study day 34 of cardio-pulmonary arrest secondary to pneumonia. This death was not attributed to the study drug.
- #51750017: 85 YO male died on study day 5 of ventricular tachycardia and cardiopulmonary arrest secondary to nosocomial pneumonia. This death was not attributed to the study drug.
- #51750154: 90 YO female died on study day 15 of pneumonia. This death was not attributed to the study drug.
- #51750719: 95 YO female died on study day 12 of pneumonia. This death was not attributed to the study drug.
- #51880004: 41 YO male died on study day 3 secondary to complications of a fatal head injury.

- #51910038: 78 YO male died on study day 4 of pneumonia. This death was not attributed to the study drug.
- #51910194: 76 YO male died on study day 3 of complications related to underlying interstitial lung disease
- #52110781: 90 YO male died on study day 6 of aspiration pneumonia. This death was not attributed to the study drug.
- #52490159: 80 YO male died on study day 2 of pulmonary edema. This death was not attributed to the study drug.
- #54070351: 75 YO male died on study day 21 of CHF. This death was not attributed to the study drug.
- #54090346: 66 YO female died on study day 17 of complications of peritonitis.
- #54100341: 51 YO female died on study day 7 of complications of an underlying intraperitoneal malignancy.
- #54100363: 49 YO female died on study day 22 of complications related to esophageal cancer.
- #54830113: 84 YO male died on study day 6 of respiratory failure related to underlying COPD.
- #55110618: 76 YO female died on study day 5 of septic shock. This death was not attributed to the study drug.
- #55460090: 98 YO male died on study day 8 of pneumonia. This death was not attributed to the study drug.
- #56230322: 76 YO male died on study day 29 of a gastrointestinal hemorrhage.
- #56230323: 74 YO female died on study day 37 of valvular cardiomyopathy and multisystem failure.
- #56230682: 64 YO male died on study day 51 of respiratory arrest and hemorrhage.
- #56270301: 75 YO male died on study day 7 of complications related to an underlying malignancy.
- #58350319: 64 YO male died on study day 47 of multiorgan failure secondary to surgical intervention.
- #59840281: 77 YO female died on study day 12 of sepsis secondary to an abdominal abscess.
- #61270209: 74 YO male died on study day 8 of ARDS. This death was not attributed to the study drug.
- #61270785: 45 YO male died on study day 8 of complications of an underlying brain tumor.
- #64010534: 81 YO female died on study day 3 of CHF secondary to underlying coronary artery disease.
- #64040804: 80 YO female died on study day 6 of acute heart failure.

Medical Officer's Comment: *The MO detected no clear pattern in the deaths above that could be attributed to the alatrofloxacin/trovafloxacin regimen. Approximately 8 patients died of complications related to the disease under study, nosocomial pneumonia, and therefore could be classified as therapeutic failures. This number however, was not unexpected.*

Ciprofloxacin (N = 38):

- #50340165: 91 YO male died on study day 6 of septic shock associated with underlying rectal carcinoma.
- #51060051: 70 YO male died on study day 2 of respiratory arrest secondary to pneumonia. This death was not attributed to the study drug.
- #51110081: 48 YO male died on study day 69 of CHF.
- #51120055: 78 YO male died on study day 6 of respiratory arrest. This death was not attributed to the study drug but to underlying Shy-Drager syndrome.
- #51750014: 87 YO female died on study day 25 of pneumonia (aspiration). This death was not attributed to the study drug.
- #51740242: 85 YO male died on study day 13 of cardiopulmonary arrest secondary to the disease under study. This death was not attributed to the study drug.
- #51750046: 94 YO female died on study day 5 of pneumonia. This death was not attributed to the study drug.
- #51750163: 78 YO female died on study day 62 of cardiac arrest.
- #51880190: 57 YO female died on study day 26 of nercotizing fascititis.
- #51910040: 71 YO female died on study day 21 of complications related to a pulmonary embolism.
- #51910193: 73 YO male died on study day 9 of heart failure.
- #51930029: 37 YO female died on study day 19 of respiratory arrest secondary to underlying metastatic cancer.
- #52110134: 73 YO male died on study day 3 of complications related to septic shock and anoxic brain damage.
- #52110782: 71 YO male died on study day 3 of complications related to a pneumothorax, related to underlying pneumonia. This death was not attributed to the study drug.
- #53860246: 74 YO male died on study day 2 of respiratory arrest. This death was not attributed to the study drug.
- #53860250: 86 YO female died on study day 16 of cardiac arrest secondary to a CVA.
- #54070349: 42 YO female died on study day 11 of ARDS. This death was not attributed to the study drug.
- #54090345: 72 YO male died on study day 17 of respiratory failure secondary to COPD.
- #54090347: 54 YO female died on study day 6 secondary to sepsis and pneumonia. This death was not attributed to the study drug.
- #54090359: 77 YO male died on study day 29 of complications of bladder carcinoma.

- #54100362: 77 YO female died on study day 20 of pneumonia. This death was not attributed to the study drug.
- #54100364: 87 YO male died on study day 11 of CHF.
- #54830256: 81 YO female died on study day 23 of urospesis.
- #55110619: 59 YO male died on study day 15 of septic shock. Secondary to *Staphylococcus aureus.*
- #55460092: 78 YO male died on study day 16 of aspiration pneumonia. This death was not attributed to the study drug.
- #56230317: 74 YO male died on study day 18 of bilateral pneumonia. This death was not attributed to the study drug.
- #56230324: 74 YO male died on study day 33 of sepsis.
- #58350330: 73 YO male died on study day 37 of peritoneal carcinomatosis.
- #59030541: 79 YO male died on study day 57 of COPD.
- #59879258: 73 YO female died on study day 32 of CHF.
- #61270211: 66 YO male died on study day 27 of lymphoma.
- #61270786: 66 YO female died on study day 15 of ARDS and pneumonia. This death was not attributed to the study drug.
- #63670745: 79 YO male died on study day 25 of multisystem organ failure.
- #63670746: 63 YO female died on study day 4 of pneumonia. This death was not attributed to the study drug.
- #63760709: 83 YO female died on study day 8 of pneumonia. This death was not attributed to the study drug.
- #64040803: 85 YO female died on study day 2 of acute heart failure.
- #64550789: 89 YO male died on study day 6 of pneumonia. This death was not attributed to the study drug.
- #65430810: 75 YO male died on study day 18 of acute heart failure.

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***Medical Officer's Comment**: As on the trovafloxacin arm, the causes and number of deaths was not unexpected. Approximately 14 of the deaths appeared to be directly related to a pneumonia and occurred in the early days of the study.*

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Other Serious Adverse Events Related to the Study Drug:

2 patients from each treatment group had other serious adverse events which were related to the study drug. These are reviewed below:

Trovafloxacin (N = 2):

- #51110083: multifocal myoclonus in an 84 YO male with a history for renal failure, atrial fibrillation, CHF, and bilateral pleural effusions. The event occurred on study day 2 and resolved despite continuation of study drug.

- #53860208: respiratory failure in an 80 YO male on study day 4. This was 2 days after study drug was discontinued. Additionally, the patient developed recurrent pneumonia on study day 28 and this event was classified as being related to the study drug. The patient was hospitalized, and the event resolved.

Ciprofloxacin (N = 2)

- #51730150: atrial fibrillation on study day 6 requiring hospitalization. Event resolved and was attributed to underlying CHF. On study day 21, 9 days post-therapy, the patient developed worsening pneumonia attributed to the study drug. The patient was hospitalized, and the pneumonia resolved.

- #51750163: worsening pneumonia, possible deep vein thrombosis on day 29. Attributed by the investigator to the study drug. Both resolved with hospitalization. Also urospesis on day 43 with failure to thrive, attributed to the study drug and culminating in death.

***Medical Officer's Comment**: The MO did not find any untoward events that could be definitively attributed to either study drug. Interestingly, there were no complaints of dizziness in this non-ambulatory population.*

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Clinical Laboratory Abnormalities:

2 subjects, one on each arm, were discontinued from study drug due to laboratory abnormalities. The MO copied the sponsor's narratives of these patients below:

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Subject 5174-0241 Alatrofloxacin/Trovafloxacin

This subject, a 93 year-old white female with a history of congestive heart failure and impaired renal function and a primary diagnosis of nosocomial pneumonia, was treated with intravenous alatrofloxacin 300 mg for ten days. The subject had SGOT and SGPT values that were within the normal ranges at baseline. On Day 7, the subject was discontinued due to increased SGOT and SGPT values that were above the normal range. On Day 14, the subject's SGOT and SGPT values had decreased, however, the SGPT value was still above the normal range. On Day 30, both the SGOT and SGPT values were within the normal range.

	SGOT (U/L)	SGPT (U/L)
Baseline		
Day 7		
Day 14		
Day 30		
Normal Range		

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Medical Officer's Comment: *The MO agreed that there did not appear to be any other cause for this patient's increased LFTs. As noted in previous studies, these elevations do occur sporadically with shorter course of therapy, although consistently when the duration of therapy is prolonged (21 days).*

Subject 5386-0198 Ciprofloxacin

This subject, a 56 year-old white male with a history of coronary artery disease, hyperlipidemia, and hypertension and a primary diagnosis of nosocomial pneumonia, was treated with intravenous ciprofloxacin 400 mg for four days and oral ciprofloxacin 750 mg BID for three days. The subject had SGOT and SGPT values that were above the normal range at baseline. On Day 5, the subject's SGOT and SGPT values increased further above the normal range. On Day 17, the SGOT and SGPT values had decreased, however, the SGPT value was still above the normal range.

	SGOT (U/L)	SGPT (U/L)
Baseline		
Day 5		
Day 17		
Normal Range		

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Medical Officer's Comment: *Once again the MO determined no other cause for this increase.*

Other than the above, SGOT elevations were found in 7 (6%) of the trovafloxacin-treated subjects and 6 (5%) of the ciprofloxacin-treated subjects. SGPT elevations were found in 9 (8%) of the trovafloxacin-treated subjects and 7 (6%) of the ciprofloxacin treated subjects. All of these events resolved post-therapy.

Additionally, 9 (8%) of the trovafloxacin-treated subjects and 6 (5%) of the ciprofloxacin-treated subjects had increased serum creatinine values. The MO did not discern any patterns or find the above unusual for this much iller population that that seen in previous trials.

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Conclusions:

As per the Sponsor: Alatrofloxacin (300 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for a total treatment duration of 10 to 14 days and intravenous ciprofloxacin (400 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (750 mg twice daily) for a total treatment duration of 10 to 14 days were comparable for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable

subjects. (EOT: 68/88 (77%) trovafloxacin versus 79/101 (78%) ciprofloxacin and EOS: 50/72 (69%) trovafloxacin versus 54/79 (68% ciprofloxacin: clinically evaluable population).

Sponsor-defined pathogen eradication rates for many of the most commonly isolated pathogens were comparable among bacteriologically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups at the end of treatment and end of study isolated at baseline. Of the 15 evaluable alatrofloxacin/trovafloxacin subjects and 11 ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, six alatrofloxacin/trovafloxacin (40%) and four ciprofloxacin (36%) received optional aztreonam therapy (dual therapy). There appeared to be no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy in sponsor-defined clinical response at end of treatment or end of study, however, due to the small number of subjects no definitive conclusions could be drawn.

The percentage of subjects discontinued from treatment due to adverse events was 15% in the alatrofloxacin/trovafloxacin group and 7% in the ciprofloxacin group. Five (5) subjects in the alatrofloxacin/trovafloxacin group and no subjects in the ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all and treatment-related adverse events was 95% and 22%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 81% and 17%, respectively, for subjects in the ciprofloxacin group. The most commonly reported treatment-related adverse event was nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and respiratory tract infection (3%) for subjects in the ciprofloxacin group.

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As per the Reviewer:

The MO's results were comparable to those of the sponsor, as were the clinically evaluable populations. The MO agreed with the sponsor's determinations of outcome, overall, in this trial, and thus accepted all of these determinations as well as those determinations applying to evaluability. The only differences were in the time of the application of the TOC, i.e. MO at EOS as opposed to sponsor TOC at the EOT, and in the MO's exclusion of "cures" who received less than 80% of the prescribed regimen.

Specifically as to the appropriate duration of therapy, most cases of true nosocomial pneumonia require 10-14 days of antimicrobial therapy if not 21, as is common in the general practice of medicine. The MO was reluctant therefore to accept a regimen of less than 8 days of therapy, this led to the ultimate exclusion of 4 patients, 2 from each arm.

The MO's evaluable population consisted of 70 patients on the trovafloxacin arm and 77 on the ciprofloxacin arm. The demographic characteristics of the 2 populations were very similar in terms of age, weight, sex, smoking status, and severity of illness.

At the EOS, the MO found a clinical success rate of 48/70 (68.6%) trovafloxacin versus 52/77 (67.5%) ciprofloxacin. These results revealed equivalence when a 95 % CI was applied, and were very similar to the sponsor's results. The MO's results differed from those of the sponsor at the EOT (Sponsor: 77% trovafloxacin versus 78% ciprofloxacin; MO: 71.4% trovafloxacin versus 70.1% ciprofloxacin), in that the sponsor's was 7% higher at the EOT for their clinically evaluable population with a 10 percentage point relapse rate at the EOS. This is compared to the MO's results, which revealed a much smaller "relapse/failure" rate between the EOT and the EOS.

For all subgroups analyzed, including patients with mild/moderate disease (EOS: success rate trovafloxacin 38/50 (76%) versus ciprofloxacin 39/53 (75%), patients with severe disease (EOS: success rate trovafloxacin 10/20 (50%) versus ciprofloxacin 13/25 (52%), patients requiring mechanical ventilation (EOS: success rate trovafloxacin 10/18 (55.6%) versus ciprofloxacin 8/16 (50%), and patients who were both clinically and bacteriologically evaluable (EOS: success rate trovafloxacin 23/37 (62.2%) versus ciprofloxacin 23/36 (63.9%), the MO found results comparable with those found by the sponsor in similar analyses. The MO ascertained that the effectiveness of trovafloxacin was equivalent to that of

ciprofloxacin in patients with mild/moderate disease and that it was numerically comparable if not equal for the other subgroups. As in the sponsor's analysis, the MO also found that those patients with mild/moderate disease had a higher clinical success rate by an almost 20 percentage point difference compared to those with severe disease.

Overall pathogen eradication rates were comparable between the 2 arms at 42/59 (71.2%) trovafloxacin versus 33/55 (66%) ciprofloxacin. This included all organisms designated as pathogens by the sponsor. Overall rates only for the requested pathogens were 23/35 (65.7%) trovafloxacin versus 18/29 (62.5%) ciprofloxacin. The MO determined that all of the above rates were comparable although, when an overall rate was utilized, it appeared that the MO's rate was more valid in terms of it's being representative of true pathogens without any contaminants.

Pathogen eradication rates based on follow-up cultures for those requested in labeling were as follows:

Trovafloxacin:

Haemophilus influenzae: 5/6 (83%)
Escherichia coli: ¾ (75%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 3/8 (37.5%)
Pseudomonas aeruginosa: 10/13 (76.9%)

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Ciprofloxacin:

Haemophilus influenzae: 7/7 (100%)
Escherichia coli: 5/5 (100%)
Klebsiella pneumoniae: 1/4 (25%)
Staphylococcus aureus: 4/6 (67%)
Pseudomonas aeruginosa: 1/7 (14.3%)

The MO determined that the 2 agents were numerically comparable in their eradication of *Haemophilus influenzae* and that the numbers of evaluable *Escherichia coli* and *Klebsiella pneumoniae* isolates were too small to be able to draw any valid conclusions. Additionally, trovafloxacin appeared superior to ciprofloxacin in the eradication of *Pseudomonas aeruginosa*. Trovafloxacin's activity versus *Staphylococcus aureus* appeared inferior to that of ciprofloxacin but again the number of isolates was small.

The MO agreed with the sponsor's statement that "additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population."

As the primary efficacy variable was clinical response at the EOS, the MO elected to utilize clinical response by pathogen as the primary determinant of microbiologic efficacy. It should be noted that bacterial eradication rates were often presumptively assigned according to the clinical outcome and not based on culture results because follow-up cultures cannot always be obtained or they may contain of bacteria of uncertain significance, i.e. contaminants versus pathogens. Below are the clinical response rates by pathogen, for those organisms requested by the sponsor:

Trovafloxacin:

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Haemophilus influenzae: 5/6 (83.3%)
Escherichia coli: 3/6 (50%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 4/6 (50%)
Pseudomonas aeruginosa: 8/13 (62%)

Ciprofloxacin:

Haemophilus influenzae: 6/7 (86%)
Escherichia coli: 4/5 (80%)
Klebsiella pneumoniae: 1/5 (20%)
Staphylococcus aureus: 4/6 (67%)
Pseudomonas aeruginosa: 1/7 (53.5%)

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From the above it is evident that success rates were comparable in those patients with *Haemophilus influenzae* at baseline. With regards to *Escherichia coli,* trovafloxacin was numerically inferior to ciprofloxacin and the opposite was true with regards to *Klebsiella pneumoniae*. Response rates were not radically different for patients with *Pseudomonas aeruginosa* and *Staphylococcus aureus* at baseline, with ciprofloxacin numerically superior to trovafloxacin in patients with *Staphylococcus aureus* and trovafloxacin superior to ciprofloxacin in patients with *Pseudomonas aeruginosa.*

From the safety review, the MO found that overall mortality was similar in both arms of the study and that causes of death were similar on both arms. There were fewer to no episodes of dizziness or headache in this population of non-ambulatory patients as compared to the previously reviewed indications. Nausea was the most common AE seen in the trovafloxacin-treated patients as compared to respiratory events in the ciprofloxacin patients.

There were a similar number of patients on each arm with LFT and/or creatinine elevations and a single patient on each arm where these were determined to be severe. The elevations returned to normal in both instances.

The MO concluded that trovafloxacin was equivalent to ciprofloxacin 400 mg IV q12h in the treatment of nosocomial pneumonia and further that no safety issues were identified in the review of this single pivotal study.

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Study 154-137:

TITLE:

Randomized, multicenter, open trial comparing intravenous alatrofloxacin followed by oral trovafloxacin with intravenous ceftazidime followed by oral ciprofloxacin with optional gentamicin and vancomycin for the treatment of nosocomial pneumonia.

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Study Dates: September 6, 1995 – August 21, 1996

Objective: The objective of this Phase III, open study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin (with optional vancomycin) compared to intravenous ceftazidime followed by oral ciprofloxacin (with optional vancomycin, gentamicin, clindamycin, and/or metronidazole), for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

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List of Principal Investigators:

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	5962	Christian Brambilla, MD
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	5937	Peter James McDonald, MD
	5940	Anthony Bell, MD
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	5945	David Barrie McGechie, MD
	5948	John Wilson, MD
Germany	5877	Wolfgang Rosch, MD
	5975	Hendrik Dienemann, MD
	5977	Detlef Barckow, MD
	5978	Thomas Henneberg, MD
	5979	Claudia Spies, MD
	6342	Friedrich Eckart Isemer, MD
United Kingdom	5869	Iain MacDonald McLaren, MD
	5924	Mervyn Singer, MD
	5926	Christopher Andrews, MD
	5930	Pushpinder Singh Mangat, MD
Canada	5795	Doria Grimard, MD
	5800	Gordon Ford, MD
	5996	Gary Mann, MD
	6072	George Pylupchuk, MD
	6073	Ronald Grossman, MD
	6075	Irving Salit, MD
Belgium	5437	Jean-Louis Vincent, MD
	5964	Michel Staroukine, MD
	5966	M. DeHovre, MD
	5972	Ignace Demeyer, MD

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	5973	Raymond Zakhia, MD
Finland	5952	Esa Rintala, MD
Greece	5871	Harry Bassaris, MD
Italy	6357	Tommaso Todisco, MD
	6557	Miele Nazareno, MD
	6569	Paolo Battocchi, MD

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Study Design: Study 154-137 was a randomized, open, comparative, multicenter trial (conducted at non-US sites only), of alatrofloxacin administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (to complete 10 to 14 days of total treatment), versus intravenous ceftazidime administered for 2 to 7 days followed by oral ciprofloxacin (to complete 10 to 14 days of total treatment), for the treatment of nosocomial pneumonia requiring initial intravenous therapy. In subjects unable to tolerate oral medication (intubated patients), the total duration of intravenous therapy could have been extended to 14 days. In addition, in subjects with documented methicillin-resistant *Staphylococcus aureus*, vancomycin may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added to the ceftazidime/ciprofloxacin treatment regimen only. For subjects with documented *Pseudomonas* infection, gentamicin may have been added to the ceftazidime/ciprofloxacin treatment regimen. Although not originally specified by protocol, subjects in the alatrofloxacin/trovafloxacin group with documented *Pseudomonas aeruginosa* at baseline who were subsequently treated with gentamicin were considered evaluable for efficacy by the sponsor.

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Protocol Overview:

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

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SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number Study day: Allowable Window	1 Day 1 (-24 hours)	2 Day 4 (Day 3-7)	3 Day 14 (Day 12-16)	4 Day 30 (Day 28-35)
Treatment Period Follow-up period	Day 1 to Day 10 to Day 14		Day 15 to Day 35	
Informed consent	X			
Demographic Information	X			
Targeted Physical Exam	X			
APACHE II Score	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record		X	X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X		X	abn
Microbiology				
sputum Gram stain	X	X	X	X2
culture & sensitivity	X	X	X	X2
blood culture	X	X3	X4	
Serology	X			X
Safety laboratory tests				
haematology	X	X	X	abn
biochemistry	X	X	X	abn
urinalysis	X		X	abn
Pregnancy test1	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's assessment of clinical response5			X	X

abn = abnormal at previous visit or clinically significant adverse event

1 to be done by local site for women of child bearing potential

2 to be done if clinically indicated

3 to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

4 to be done if a positive culture was obtained at visit 2

5 to be done at the time of discontinuation, if applicable

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As can be appreciated from the above schedule, at the baseline assessment (Visit 1, Day 1), all subjects were to have had a medical history and clinical and radiological findings consistent with nosocomial pneumonia, requiring initial intravenous therapy, acquired at least 48 hours after a hospitalization for reasons other than respiratory infection. Nonambulatory institutionalized (nursing home) subjects who were admitted to a hospital for suspected gram negative pneumonia were also eligible for enrollment.

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The following characteristics were to have been present:

- New infiltrate(s) on chest x-ray;

and

- At least one of the following
  - Cough or increasing severity of coughing.
  - Acute changes in the quality of sputum.
  - Body temperature >38°C (100.4°F) or <36.1°C (97°F).
  - Auscultatory findings such as rales or evidence of pulmonary consolidation.
  - Leukocytosis (blood leukocyte count >10,000/mm^3 or >15% bands).

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All patients who met the clinical diagnosis of NP at V1 and who gave informed consent and met all additional inclusion criteria and none of the exclusion criteria were eligible for randomization.

V1 assessments included collection of demographic information, medical history and physical examination (including APACHE II score), concomitant medication use, antibiotic therapy within the last 7 days, and vital signs (pulse, respiration, blood pressure, and temperature). The illness leading to the patient's hospitalization was recorded as well as the type of NP the patient had (post-surgical, suspected aspiration, occurring in a mechanically ventilated subject, or other causes). Clinical assessment of signs and symptoms of nosocomial pneumonia included sputum characteristics, cough, dyspnea, chills/rigors, pleuritic chest pain, lung sounds, and chest X-ray (PA and lateral views). In addition, a standard panel of blood (including culture), and urine tests were performed. Initial serology testing for evidence of infection with *Legionella spp.* was performed. Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per low power field [LPF], squamous epithelial cells per LPF) of sputum were performed. If a satisfactory specimen could not be obtained the investigator could have induced sputum with nebulised saline solution or physiotherapy. If this technique was unsuccessful the investigator could have used such techniques as transtracheal aspiration, bronchial brushings or biopsy material obtained by bronchoscopy.

Susceptibility to the study drugs, trovafloxacin, ciprofloxacin, and ceftazidime was determined for all potentially significant organisms isolated from respiratory specimens, that were considered adequate. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture or if a pathogen was resistant to study medication, study therapy could continue, at the discretion of the investigator.

At Visit 2 (V2: Day 3 to 7), a patient's need for continued intravenous therapy was assessed, (daily from study day 3 to 7). Subjects were switched to oral therapy if the following situations applied:

- resolution of fever;
- improvement of symptoms;
- no progression of x-ray changes.

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Efficacy observations were performed during this visit, including clinical assessment of signs and symptoms of nosocomial pneumonia to assess response to study therapy; bacteriologic response was assessed through respiratory samples. Blood cultures were repeated only if they had been positive at the previous visit. In addition to efficacy observations, safety was assessed through recording of concomitant medications, vital signs, study drug dosing, adverse events, and laboratory (hematology and biochemistry), evaluations.

At Visit 3 (V3: Day 14; EOT) efficacy observations were performed including clinical assessment of signs and symptoms of nosocomial pneumonia to assess response to study therapy; bacteriologic response was assessed through respiratory samples. Blood cultures were repeated only if they had been positive at the previous visit; a chest X-ray was also performed. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology, biochemistry, and urinalysis), evaluations. The investigators provided an evaluation of clinical response.

At Visit 4 (V4: Day 30; EOS), efficacy observations were performed including clinical assessment of signs and symptoms of nosocomial pneumonia to assess response to study therapy; bacteriologic response was assessed through respiratory samples. Blood cultures were repeated only if they had been positive at the previous visit. If the V3 CxR had not resolved to the subject's baseline, a final X-ray was done at this visit. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, and adverse events. Laboratory evaluations were performed if a clinically significant abnormality was present as V3 or if the subject was experiencing a clinically significant adverse event. A final serology was performed and the investigators provided a final evaluation of clinical response.

***Medical Officer's Comment**: Study 154-137 was identical to study 113 with the exception that this was an open study and that the intravenous comparator agent was ceftazidime and not ciprofloxacin. Additionally, additional anti-pseudomonal coverage was provided with gentamicin instead of aztreonam. The MO elected to present only those details specific to this study in the ensuing review and to refer back to the introduction of the MOR for the general details.*

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Compliance:

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

Concomitant Illnesses and Medications:

Please see MOR of study 154-113, page 392, for the MO's comment.

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Discontinuation of Study Therapy:

Please see MOR of study 154-113, page 392.

Protocol Amendments:

The protocol was amended twice. Once, on June 14, 1995 for the Australian centers only, to reflect the addition to the exclusion criteria of the exclusion of all patients on chronic immunosuppressive therapy including those patients on > 10 mg/day of systemic corticosteroids. Additionally excluded were patients with moderate to severe hepatic or renal dysfunction and patients on concomitant theophylline or warfarin, unless monitored closely. The schedule of visits was amended to reflect the monitoring of all laboratory parameters every 72 hours while on alatrofloxacin and every 7 days while receiving trovafloxacin.

The second amendment on December 15, 1995 applied to all centers and reflected the ability to add clindamycin or metronidazole to the ceftazidime/ciprofloxacin arm of the study in patients with suspected anaerobic infections, the extension of the duration of treatment to 14 days, a standardized dose reduction regimen for patients on ceftazidime and ciprofloxacin who had renal dysfunction, the addition of the APACHE scoring system for all patients at V1, and the application of a 95% CI and p-values as a method for comparison of efficacy.

Precautions:

Please see MOR of study 154-113, page 393.