

Table 137.24
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
Number of Subjects Treated	135 (100%)	140 (100%)
Subject-Days of Exposure	1304	1529
Subjects With At Least One Event	88 (65%)	79 (56%)
Number of Adverse Events	176	167
Subjects with Serious Adverse Events	37 (27%)	36 (26%)
Subjects with Severe Adverse Events	38 (28%)	33 (24%)
Subjects Discontinued Due to Adverse Events	16 (12%)	6 (4%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0
Subjects Discontinued Due to Objective Test Findings	5 (4%)	4 (3%)
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

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Table 137.25
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	135 (100%)	140 (100%)
Subjects With At Least One Event	88 (65%)	79 (56%)
Subjects Discontinued due to Adverse Event	16 (12%)	6 (4%)
ADVERSE EVENTS BY BODY SYSTEM:		
Appl./Inj./Incision/Insertion Site	2 (1%)	8 (6%)
Autonomic Nervous	5 (4%)	0
Cardiovascular	23 (17%)	25 (18%)
Centr. & Periph. Nerv.	17 (13%)	9 (6%)
Endocrine	1 (<1%)	1 (<1%)
Gastrointestinal	24 (18%)	25 (18%)
General	30 (11%)	10 (7%)
Hematopoietic	6 (4%)	4 (2%)
Liver/Biliary	2 (1%)	3 (2%)
Metabolic/Nutritional	1 (<1%)	1 (<1%)
Musculoskeletal	2 (1%)	2 (1%)
Neoplasms	1 (<1%)	3 (2%)
Other Adverse Events	5 (4%)	7 (5%)
Psychiatric	5 (4%)	13 (9%)
Respiratory	25 (19%)	22 (16%)
Skin/Appendages	7 (5%)	6 (4%)
Special Senses	1 (<1%)	2 (1%)
Urinary System	9 (7%)	5 (6%)

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Table 137.26
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	135 (100%)	140 (100%)
Subjects With At Least One Event	16 (12%)	5 (4%)
Subjects Discontinued due to Adverse Event	7 (5%)	1 (<1%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	3 (2%)	0
Centr. & Periph. Nerv.	1 (<1%)	0
Gastrointestinal	10 (7%)	1 (<1%)
General	0	1 (<1%)
Psychiatric	1 (<1%)	1 (<1%)
Other Adverse Events	0	0
Skin/ Appendages	3 (2%)	1 (<1%)
Special Senses	0	1 (<1%)

Further breakdown of the treatment-related events, indicated that 3 (2%) of the events on the alatrofloxacin/trovafloxacin arm were severe in nature, as compared to 1 on the ceftazidime/ciprofloxacin arm. The 3 severe events on the alatrofloxacin/trovafloxacin arm, consisted of 2 episodes of skin rash and 1 episode of vomiting. The severe event on the ceftazidime/ciprofloxacin arm was multi-organ failure.

Table 137.27

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

# of subjects with at least 1 event	Alatrofloxacin/Trovafloxacin N = 135		Ceftazidime/Ciprofloxacin N = 140	
		16 (12%)	5 (4%)	
Autonomic Nervous system	3	(2%)	0	-
Flushing	3	(2%)	0	-
GI System	10	(7%)	1	(<1%)
Vomiting	6	(4%)	0	(<1%)
Skin/Appendages	3	(2%)	1	-
Rash	3	(2%)	1	-

Deaths:

Overall (ITT population), there were 37 deaths on the alatrofloxacin/trovafloxacin arm and 30 on the ceftazidime/ciprofloxacin arm during the study. 9 deaths on the alatrofloxacin/trovafloxacin arm and 7 on the ceftazidime/ciprofloxacin arm occurred while receiving therapy and were considered unrelated to the study drug by the investigator. 23 deaths on the alatrofloxacin/trovafloxacin arm and 22 on the ceftazidime/ciprofloxacin arm occurred after therapy but during the study period and were also considered unrelated to the study drugs. An additional 6 subjects per arm respectively, died > 30 days after the last dose of the study drug and these deaths were also considered unrelated to the study drugs.

The subjects who died during the study are reviewed below:

Alatrofloxacin/Trovafloxacin (N = 37):

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- #58770418: 83 YO male died of worsening pneumonia during the post-treatment period, study day 7.
- #59260068: 68 YO died post-therapy of worsening pneumonia. Therapy was discontinued on study day 5.
- 359350142: 78 YO female died on study day 21 of worsening pneumonia. Study drugs stopped on study day 3.
- #59559224: 65 YO male died on study day 14 of a CVA.
- #59550274: 73 YO female died on study day 15 of a pulmonary embolism.
- #59550291: 49 YO male died on day 60 of progression of coma.
- #59550130: 75 YO female died on study day 10 of worsening COPD.
- #59560230: 94 YO female died on day 27 of multiorgan failure.
- #60730476: 84 YO male died on study day 10 of exacerbation of respiratory failure.
- #63570484: 67 YO female died unexpectedly on day 48.
- #54140271: 89 YO female died on study day 4 of worsening pneumonia.
- #54140293: 82 YO male died on study day 4 of septic shock and pneumonia.
- #54140298: 86 YO male died on study day of ARDS.
- #54390218: 60 YO female died on study day 13 of worsening underlying neurologic disease.
- #57950577: 72 YO female died on study day 2 of renal insufficiency.
- #58690025: 61 YO male died on study day 9 of septic shock and worsening pneumonia.
- #58710072: 40 YO male died on study day 4 of an acute MI.
- #58710422: 62 YO male died on study day 8 of a CVA.
- #58710423: 48 YO female died on study day 2 of a CVA.
- #58710426: 70 YO male died on study day 5 of cardiac arrest an head injury.
- #58710429: 76 YO male died on study day 9 of cardiac arrest, post-therapy.
- #59240537: 70 YO female died on study day 6 of multiorgan failure.
- #59260065: 67 YO female died on study day 51 of a CVA.
- #59260083: 74 YO female died on study day 3 of a recurrent subarachnoid hemorrhage.
- #59360111: 79 YO male died on study day 21 of a new aspiration pneumonia.
- #59400113: 54 YO female died on study day 2 of a subarachnoid hemorrhage.
- #59420146: 67 Yo male died on study day 4 of progression of cardiogenic shock.
- #59550227: 70 YO female died on study day 14 of worsening pneumonia.
- #59570282: 67 YO male died on study day 2 or worsening pancreatitis.
- #59640321: 71 YO female died on study day 10 of cardiac failure.
- #59660312: 78 YO male died on study day 15 of a brain tumor.
- #59720328: 74 YO male died on study day 11 of multiorgan failure.
- #59770378: 51 YO male died on study day 2 of progression of a CVA.
- #59780411: 70 YO male died on study day 13 of septic chock.
- #59780558: 58 YO female died on study day 9 of multiorgan failure.
- #60720441: 72 YO male died on study day 7 of ARDS.
- #60720443: 68 YO male died on study day 7 of intra-abdominal sepsis.
- #60730478: 85 YO male died on study day 4 of sepsis.

Ceftazidime/Ciprofloxacin (N = 30):

- #58690028: 76 YO male died on study day 7 of CHF.
- #58710424: 72 YO male died on study day 8 of an MI
- #58710431: 67 YO male died on study day 3 of an MI.
- #58710549: 55 YO male died on study day 6 of a CVA.
- #58770414: 85 YO female died on study day 5 of CHF.
- #59240146: 43 YO male died on study day 5 of multiorgan failure.
- #59240047: 72 YO male died on study 3 of CHF.
- #59300049: 73 YO male died on study day 7 of sepsis/gallbladder.
- #59450173: 88 YO male died on study day 3 of ventilatory failure.
- #59520094: 82 YO male died on study day 26 of an MI.

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- #59550215: 64 YO male died on study day 8 of worsening pneumonia.
- #59530249: 71 YO male died on study day 2 of septic shock.
- #59550273: 63 YO male died on study day 4 of septic shock.
- #59580238: 83 YO female died on study day 4 of cardiogenic shock,
- #50660309: 79 YO female died on study day 18 of pneumonia and multiorgan failure.
- #59720326: 51 YO female died on study day 12 of cardiac arrest.
- #60750457: 84 YO male died on study day 2 of respiratory failure.
- #63570481: 71 YO male died on study day 10 of cardiac arrest.
- #54140294: 85 YO male died on study day 22 of COPD.
- #54140295: 63 YO male died on study day 21 of CHF.
- #58710074: 63 YO female died on study day 30 of cardiac arrest.
- #58710079: 74 YO male died on study day 16 of a CVA.
- #58710425: 65 YO male died on study day 12 of a pulmonary embolism.
- #58770415: 73 YO male died on study day 13 of progressive prostatic cancer.
- #59260081: 74 YO female died on study day 23 of a progressive brain tumor.
- #59260084: 75 YO male died on study day 19 of ventricular fibrillation.
- #59550248: 75 YO male died on study day 16 of hypoxic encephalopathy.
- #59580239: 83 YO male died on study day 19 of melanoma.
- #59730318: 83 YO male died on study day 8 of renal disease.
- #60730473: 90 YO female died on study day 24 of cachexia.

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***Medical Officer's Comment:** The MO detected no clear pattern in the deaths above that could be attributed to the either regimen. Approximately 8 patients died of complications related to the disease under study, nosocomial pneumonia, and therefore could be classified as therapeutic failures on the alatrofloxacin/trovafloxacin arm as compared to 4 patients on the comparator arm. These numbers are not unexpected and compatible with those seen in study 154-113.*

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Other Serious Adverse Events Related to the Study Drug:

Other than the deaths which were considered serious, a total of 49 (36%) of the alatrofloxacin/trovafloxacin patients and 47 (34%) of the ceftazidime/ciprofloxacin patients had serious adverse events. All events on the alatrofloxacin/trovafloxacin arm were considered unrelated to the study drug as compared to 47 on the ceftazidime/ciprofloxacin arm.

The following patients from each treatment group had other serious adverse events which were related to the study drug and which the MO determined should be reviewed further:

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Alatrofloxacin/Trovafloxacin (N = 2):

- #59720327: 60 YO female permanently discontinued study drug on day 3 after the development of a maculopapular skin rash described as severe in nature. The rash cleared without therapy by study day 5.
- #59240014: 67 YO female developed a maculopapular rash on the abdomen and legs on study day 4. This event led to the permanent discontinuation of therapy and resolved without therapy by study day 9.

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Ceftazidime/Ciprofloxacin (N = 1)

- #60750458: elevated international normalized ratio and bruising related to study drug which resolved off therapy.

Rash (Not severe):APPEARS THIS WAY
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- #59480127: 34 YO female permanently discontinued alatrofloxacin on study day because of a maculopapular skin rash. This reaction was considered mild in nature and resolved off the study drug

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- #59300049: 63 YO male developed a maculopapular rash on the chest on study day 2. No action was taken and the rash was present at the EOT.

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ON ORIGINAL**Clinical Laboratory Abnormalities:**

5 patients on the alatrofloxacin/trovafloxacin arm and 2 patients on the ceftazidime/ciprofloxacin were discontinued from study drug due to laboratory abnormalities. In only one alatrofloxacin/trovafloxacin patient was the abnormality correlated with study drug by the investigator. A short narrative of this patient follows:

- #59550224: 65 YO male, history of cerebral hemorrhage, received intravenous alatrofloxacin for 7 days and oral trovafloxacin for 3 days. At baseline the patient had a normal alkaline phosphatase, which had increased to _____ on day 8. The level decreased to normal on study day 11. The investigator determined causality.

In addition however, to the above patient, the following patients were found to have clinical significant laboratory abnormalities:

Alatrofloxacin/Trovafloxacin (N = 10):APPEARS THIS WAY
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- #5871-0078: 67 YO male with normal SGOT, SGPT and Alkaline Phosphatase at the start of the study, developed increased LFTs to twice normal on study day 9 and _____ on study day 15. After a 12 day course of therapy. The LFTs decreased to normal approximately 3 weeks later.
- #58710428: 75 YO female received 11 days of therapy. Patient developed neutropenia day 5 which resolved post-therapy.
- #59240048: 63 YO with a history of colon cancer and partial hepatectomy. This patient was withdrawn from the trial on study day 3 because of increased bilirubin. The patient had received _____ blood post-operatively. Renal failure was also present. None of the above appeared related to the study drug.
- #59260059: 32 YO male with an extradural hematoma, received study drug for 10 days. Patient had abnormal LFTs (5-x normal) prior to therapy. After IV R/x the LFTs had decreased to 2 x normal but subsequently reincreased at the EOT visit to > 5 x normal. LFTs normalized 3 weeks later.
- #59360110: 50 YO male with extradural hematoma, received study drug for 5 days and was discontinued because of increased LFTs to 3 x normal. Levels decreased after 4 weeks.
- #59360110: 79 YO male with a CVA received 8 days of study drug and was discontinued because of increased LFT, predominantly Alkaline Phosphatase. Phosphatase which was 2 x normal. A later assessment revealed that the AE was not due to study drug but to an ischemic hepatic event.

- #59420146: 67 YO male, history of MI. Discontinued from therapy on study day 3 because of increased LFTs to This increase was attributed to cardiogenic shock and the patient died of this 5 days later.
- #59550274: 73 YO male with angina and CVA received 9 days of study drug and developed an alkaline phosphatase elevation on day 7. The investigator attributed the elevation which peaked at the EOT at to the study drug. Patient died of a pulmonary embolism and no follow-up was obtained.
- #59570278: 26 YO male post-traumatic NP, received study drug f10 days. The patient had increased LFTs on study day 3 which later resolved with no action taken. Causality was attributed to hepatic cytolysis and not to the study drug
- #59780558: 57 YO female post-surgery NP received study drug for 8 days and then Zosyn® and gentamicin for 7 days because of clinical failure. The patient had increased LFT's, and thrombocytopenia. This patient died of multiple organ failure and septic shock on day 12.

Ceftazidime/Ciprofloxacin (N=9):

- #541240272: 64 YO male received study drug for 10 days. Leukopenia developed. Outcome not known but causality not attributed to study drug.
- #5871-0424: 72 YO male, Parkinsonian and angina as well as renal impairment had evidence of increased LFTs on study day 6. The investigator attributed the increase to the ceftazidime component of the therapy. The patient died of an acute MI on day 8.
- #58710427: 22 YO male, head injury, developed increased LFTs on study day 6. No follow-up.
- #59260042: 66 YO male with a malignant brain tumor had increased LFTs on study day 3. No causality assessed.
- #59360109: 43 YO male post-surgery with abnormal LFTs on study day 4. Attributed to trauma history.
- #59520094: 81 YO male with a history of CHF had abnormal LFTs on study day 8. Patient died and no follow-up were obtained. Patient was also receiving clindamycin and amiodarone to which increases were attributed.
- #59550289: 78 YO developed increased LFTs on study day 10. These subsequently resolved and were attributed to the study drugs.
- #59790369: 52 YO with a history of intracerebral aneurysm and clipping developed severe anemia on study day 4, which resolved on therapy. Causality unknown.
- #60750458: 75 YO female developed an increased prothrombin time during therapy with ceftazidime. Causality was attributed to study drug and resolved with the discontinuation of coumadin therapy.

As per the sponsor, clinically significant SGOT abnormalities were seen in 8 (7%) of subjects and 13 (10%) of subjects per arm respectively. SGPT abnormalities were seen in 10 (8%) for the alatrofloxacin/trovafloxacin subjects and 14 (11%) of the ceftazidime/ciprofloxacin subjects.

7 (6%) of the alatrofloxacin/trovafloxacin patients and 10 (8%) of the ceftazidime/ciprofloxacin patients had elevated creatinine, none attributed to study drug, 9 (6%) alatrofloxacin/trovafloxacin and 8 (6%) ceftazidime/ciprofloxacin had increased bilirubin values.

Medical Officer's Comment: *The MO determined that all of the above abnormalities were most likely secondary to underlying disease processes.*

Conclusions:

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As per the Sponsor: (Copied from page 74 of the study report):

Alatrofloxacin (equivalent to 300 mg trovafloxacin 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 was statistically equivalent to intravenous ceftazidime (2000 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 for sponsor-defined clinical success rate at the end of treatment.

Sponsor-defined eradication rates were generally comparable at the end of study for most pathogens isolated. Higher eradication rates for the most frequently baseline pathogen, *Staphylococcus aureus*, were seen both at the end of treatment and end of study in the alatrofloxacin/trovafloxacin group compared to the ceftazidime/ciprofloxacin group.

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The pathogen eradication rate for *Pseudomonas aeruginosa* was higher in the ceftazidime/ciprofloxacin group, although the clinical success rate was similar between subjects in both treatment groups with this baseline pathogen. In subjects with *Pseudomonas* infection, gentamicin was used as adjunctive therapy in approximately 60% of the subjects in each treatment group. There was no evidence of emergence of resistance in *Pseudomonas aeruginosa* to trovafloxacin. There was no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy (optional gentamicin), however, due to the small number of subjects no definitive conclusions could be drawn.

Of note, all isolates of *Streptococcus pneumoniae*, including two penicillin-resistant isolates, were eradicated in the alatrofloxacin/trovafloxacin group whereas all isolates in the ceftazidime/ciprofloxacin group were persistent.

The percentage of subjects discontinued from treatment due to adverse events was 12% in the alatrofloxacin/trovafloxacin group and 4% in the ceftazidime/ciprofloxacin group. Seven (7) subjects in the alatrofloxacin/trovafloxacin group and one subject in the ceftazidime/ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all causality and treatment-related adverse events was 65% and 12%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 56% and 4%, respectively, for subjects in the ceftazidime/ciprofloxacin group. The most commonly reported treatment-related adverse event was vomiting in the alatrofloxacin/trovafloxacin group; all treatment-related adverse events in the ceftazidime/ciprofloxacin were reported by <1% of subjects.

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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 timing of the TOC, i.e. MO at EOS as opposed to sponsor TOC at the EOT (in accordance with evaluability guidelines, and in the MO's exclusion of "cures" who received less than 80% of the prescribed regimen. Additionally the MO changed the outcome in 1 patient on each arm of the study.

The MO's evaluable population consisted of 85 patients on the alatrofloxacin/trovafloxacin arm and 89 on the ceftazidime/ciprofloxacin arm. The demographic characteristics of the 2 populations were very similar in terms of age, weight, sex, and smoking status. There was a question of whether the patients on the comparator arm were more severely ill based on a higher baseline mean APACHE score, however, there was no statistical significance in the difference between mean APACHE scores.

At the EOS, the MO found a clinical success rate of 54/85 (63.5%) alatrofloxacin/trovafoxacin versus 51/89 (57.3%) ceftazidime/ciprofloxacin. These results revealed equivalence of the alatrofloxacin/trovafoxacin arm when a 95 % CI was applied.

The MO's TOC visit outcomes differed from those of the sponsor at the EOT (Sponsor: 74% trovafoxacin versus 70% ciprofloxacin; MO: 67.5% trovafoxacin versus 62.8% ciprofloxacin), in that the sponsor established equivalence at the EOT, whereas the MO did not, although the Δ was the same for both the MO and the applicant.

For all subgroups analyzed by the MO, including patients with mild/moderate disease (EOS: success rate alatrofloxacin/trovafoxacin 33/39 (84.6%) versus ceftazidime/ciprofloxacin 29/41 (70.7%), patients with severe disease (EOS: success rate alatrofloxacin/trovafoxacin 21/46 (45.7%) versus ceftazidime/ciprofloxacin 22/48 (45.8%), patients requiring mechanical ventilation (EOS: success rate alatrofloxacin/trovafoxacin 15/33 (45.5%) versus ceftazidime/ciprofloxacin 14/31 (45.2%), and patients who were both clinically and bacteriologically evaluable (EOS: success rate alatrofloxacin/trovafoxacin 21/39 (53.9%) versus ceftazidime/ciprofloxacin 26/58 (51%), the MO found results comparable with those found by the sponsor in similar analyses. The MO ascertained that the effectiveness of alatrofloxacin/trovafoxacin was numerically comparable to that of ceftazidime/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 30 percentage point difference compared to severe disease.

Overall pathogen eradication rates were comparable between the 2 arms at 36/51 (70.5%) alatrofloxacin/trovafoxacin versus 47/68 (69.1%) ceftazidime/ciprofloxacin. This included all organisms designated as pathogens by the sponsor. Overall rates only for the requested pathogens were 22/30 (73.3%) alatrofloxacin/trovafoxacin versus 28/43 (65.1%) ceftazidime/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 its being representative of true pathogens without any contaminants.

Pathogen eradication rates based on follow-up culture results, for the requested in the labeling pathogens were as follows:

Alatrofloxacin/Trovafoxacin:

Haemophilus influenzae: 4/5 (80%)
Escherichia coli: 6/6 (100%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 9/10 (90%)
Pseudomonas aeruginosa: 1/5 (20%)

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Ceftazidime/Ciprofloxacin:

Haemophilus influenzae: 5/6 (83.3%)
Escherichia coli: 9/10 (90%)
Klebsiella pneumoniae: 1/2 (50%)
Staphylococcus aureus: 8/15 (55%)
Pseudomonas aeruginosa: 3/7 (53.8%)

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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, numerically, alatrofloxacin/trovafoxacin appeared superior to ceftazidime/ciprofloxacin in the eradication of *Staphylococcus aureus*.

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." but determined that the wording of this

statement should be revised to reflect the need for additional ant-pseudomonal coverage both in presumptive as well as documented cases of NP due to *Pseudomonas aeruginosa*.

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 picture and not a product of cultures. Below are the clinical response rates by pathogen, for those organisms requested by the sponsor:

Alatrofloxacin/Trovafloxacin:

Haemophilus influenzae: 4/5 (80%)
Escherichia coli: 5/6 (83.3%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 8/11 (72.7%)
Pseudomonas aeruginosa: 1/5 (20%)

Ceftazidime/Ciprofloxacin:

Haemophilus influenzae: 4/6 (83.3%)
Escherichia coli: 5/12 (41.7%)
Klebsiella pneumoniae: 1/3 (33.3%)
Staphylococcus aureus: 5/14 (35.7%)
Pseudomonas aeruginosa: 5/14 (42%)

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As can be appreciated from the above, the clinical success rates for patients with *Staphylococcus aureus* and *Pseudomonas aeruginosa* were very low in this trial for patients on the ceftazidime/ciprofloxacin arm. Additionally, success rates were very low for those alatrofloxacin/trovafloxacin-treated patients with *Pseudomonas aeruginosa* as the baseline pathogen and quite high, as compared to study 154-113 in those patients with *Staphylococcus aureus*. The MO will address this issue in the MO's overall conclusion for the indication of nosocomial pneumonia.

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 rare episodes of dizziness or headache in this population of non-ambulatory patients as compared to the previously reviewed indications. Vomiting was the most common AE seen in the alatrofloxacin/trovafloxacin-treated patients as compared no specific AE in the ceftazidime/ciprofloxacin-treated patients.

There were a similar number of patients on each arm with LFT elevations and in only 1 patient on the alatrofloxacin/trovafloxacin arm where these were determined to be severe and related to the study drug.

The MO concluded that alatrofloxacin/trovafloxacin was numerically superior to ceftazidime/ciprofloxacin in the treatment of nosocomial pneumonia of mild/moderate severity (APACHE < 13), and further that no safety issues were identified in the review of this second pivotal study.

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Reviewer's Overall Conclusion with regards to Nosocomial Pneumonia:

The sponsor submitted 2 trials in support of this indication, 154-113, a US, double-blinded, comparative trial comparing the efficacy and safety of alatrofloxacin/trovafloxacin versus ciprofloxacin, and study 154-137, a multinational, non-US, open trial comparing the efficacy and safety of alatrofloxacin/trovafloxacin versus ceftazidime/ciprofloxacin for the indication of nosocomial pneumonia.

Although, the US study was blinded, and the European open, the overall trial design was very similar between the two. Additionally, data management was performed in a blinded fashion, by the sponsor's representatives in a uniform *post-hoc* fashion.

Please refer to the MORs of each study for details, however, in both studies, patients with well-documented NP, were randomized to receive between 10 -14 days of study drug. The initial phase in both studies was intravenous and subsequently (after day 3), the patients could have been converted to an oral regimen if stable. In both trials, vancomycin was allowed on either arm, if patients had documented MRSA. Clindamycin or metronidazole was allowed in both studies on the comparator arms only, if the investigator suspected an anaerobic component to the infectious process. More importantly, in study 154-113, patients on either arm were allowed to receive aztreonam for a documented NP due to *Pseudomonas aeruginosa*, and in study 154-137, intravenous gentamicin was allowed by-protocol only to the patients on the ceftazidime/ciprofloxacin arm who had a documented infection with *Pseudomonas aeruginosa*. Patients on both arms received adjunctive antipseudomonal therapy and prior to unblinding, the sponsor elected to allow the inclusion of the trovafloxacin patients who received adjunctive therapy into the evaluable population.

There was overall agreement between the MO and the sponsor in terms of evaluability and outcome assessments in both trials. The major difference between the analyses was the application of the TOC. The sponsor applied the TOC to the EOT as opposed to the MO, who applied it to the EOS.

The results of both trials are summarized below in MO table 1. At issue is the pooling of the data between the 2 trials, clinically and bacteriologically. The MO elected to provide clinical response by baseline pathogen in lieu of pathogen eradication rates. This decision was made in conjunction with the MTL, Brad Leissa MD, and is justified by the clinical nature of this indication and the lack of EOS cultures.

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MO Table 1
Clinical and Bacteriologic Efficacy of Studies 154-113 and 154-137/MO Evaluable Population

Study	154-113	154-137
Location	US	Multinational
Design	Randomized, Blinded	Randomized, Open
Comparator	Ciprofloxacin IV/PO	Ceftazidime IV/Ciprofloxacin PO
# MO Eval. Patients	147	174
#MO Eval. Trovafloxacin	70	85
#MO Eval. Comparator	77	89
#MO Bacteriologically Eval.	71 (37 trovafloxacin vs. 36 comparator)	97(39 trovafloxacin vs. 58 comparator)
Mean APACHE Score	13.1 trovafloxacin vs. 13.4 comparator	12.3 trovafloxacin vs. 13.6 comparator
Clinical Response EOS	48/70 (68.5%) trovafloxacin vs. 52/77 (67.5%)comparator	54/85 (63.5%) trovafloxacin vs. 51/89 (57.3%)comparator
Clinical Response Mild/Moderate Disease	38/50 (76%) trovafloxacin vs. 39/52 (75%) comparator	33/39 (84.6%) trovafloxacin vs. 29/41 (70.7%) comparator
Clinical Response Severe Disease	10/20 (50%) trovafloxacin vs. 13/25 (52%) comparator	21/46 (45.7%) trovafloxacin vs. 22/48 (45.8%) comparator
Clinical Response Mechanically Ventilated	10/18 (55.6%) trovafloxacin vs. 8/16 (50%) comparator	15/33 (45.5%) trovafloxacin vs. 14/31 (45.2%) comparator
Clinical Response Clinically and Bacteriologically Evaluable	24/37 (64.9%) trovafloxacin vs. 23/36 (63.9%) comparator	21/39 (53.8%) trovafloxacin vs. 26/58 (44.8%) comparator
Clinical Response by Pathogen (Requested in labeling only)	22/37 (59.5%) trovafloxacin vs. 16/30 (53.3%) comparator	20/31 (64.5%) trovafloxacin vs. 21/50 (42%) comparator
<i>Haemophilus influenzae</i>	5/6 (83%) trovafloxacin vs. 6/7 (86%) comparator	4/5 (80%) trovafloxacin vs. 4/6 (67%) comparator
<i>Escherichia coli</i>	3/6 (50%) trovafloxacin vs. 4/5 (80%) comparator	5/6 (83.3%) trovafloxacin vs. 5/12 (41.7%) comparator
<i>Klebsiella pneumoniae</i>	2/4 (50%) trovafloxacin vs. 1/5 (20%) comparator	2/4 (50%) trovafloxacin vs. 1/3 (33%) comparator
<i>Staphylococcus aureus</i>	4/8 (50%) trovafloxacin vs. 4/6 (67%) comparator	8/11 (73%) trovafloxacin vs. 6/15 (40%) comparator
<i>Pseudomonas aeruginosa</i>	8/13 (62%) trovafloxacin vs. 1/7 (14%) comparator	1/5 (20%) trovafloxacin vs. 5/14 (36%) comparator

Combined clinical response rates at the EOS were: 102/155 (65.8%) trovafloxacin versus 103/166 (62.4%) comparators, 95%CI with CCF: - 7.4%, 14.8% ($\Delta = 20$)

The MO determined that the clinical results of the two studies could be pooled. This decision was reached because of the similarities between the populations studied as well as the relative similarities between the clinical efficacy results. In both studies, overall clinical response rates at the EOS were > 60% for the trovafloxacin arms. However, in the open study, the rates were lower on both arms and numerically inferior (not significant), for the comparator. This decrease was surprising in light of the fact that study 154-137 was an open trial. The MO believed that these lower rates were due to the choice of the comparator and specifically, ceftazidime as the initial antimicrobial utilized, as well as to local effects such as different microbial flora, including a higher incidence of *Staphylococcus aureus*, as well as differences in the local practice of medicine. The MO determined that there were a larger number of failures during the initial phase of therapy, thus leading to an almost 10 percentage point drop in clinical response on the comparator arm in study 154-137 as compared to 154-113.

A review of previous submissions for this indication revealed the following:

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Zosyn® NDA 50-684/S-001: Zosyn® was approved for the indication of severe NP, based on the results of one clinical study where ceftazidime was utilized as the comparator agent. APACHE scores were not provided. The patients were determined to be moderately to severely ill based on clinical picture and need for ventilatory support by both the sponsor and the RMO. The study population consisted of patients with both CAP as well as NP and the 2 groups were analyzed separately. Tobramycin was allowed and was utilized in the predominant number of patients. Clinical response rates (EOS) were 47/63 (74%) Zosyn® versus 22/35 (53%) ceftazidime. Pathogen eradication rates (EOS) were as follows, per arm respectively: *Escherichia coli*: 4/6 (67%) vs. 3/6 (50%), *Haemophilus influenzae*: 19/20 (95%) vs. 5/12 (42%),

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Klebsiella pneumoniae 4/5 (80%) versus 3/5 (60%), *Pseudomonas aeruginosa* 6/11 (55%) versus 4/10 (40%), and *Staphylococcus aureus* 13/16 (81%) versus 7/16 (44%). Clinical response by pathogen was provided only for patients with *Pseudomonas aeruginosa* and was 4/10 (40%) versus 4/8 (50%) per arm respectively. Based on this submission, Zosyn® was approved for moderate to severe presumptive nosocomial pneumonia caused by beta-lactamase producing strains of *Staphylococcus aureus*. The label requires the addition of tobramycin when used empirically and until infection with *Pseudomonas aeruginosa* is ruled out.

NOTE: The clinical response rates of Zosyn® are comparable to those of trovafloxacin in the population of patients with mild/moderate disease, and were higher than those of the total population which included patients with severe disease. From a bacteriological standpoint, Zosyn® was numerically superior to trovafloxacin versus all the requested pathogens with the exception of *Pseudomonas aeruginosa*.

NOTE: There was no comparison between the submissions with regards to design. The bacteriology of the ofloxacin submission pointed to a population of patients with CAP.

Ciprofloxacin NDA 19-847/S-008 and NDA 19-857/S008: The applicant submitted a well-designed US trial (Study #089-053), for the indication of severe LRTI and pneumonia. Data from foreign trials was also submitted. At the time of this submission ciprofloxacin was already approved for the LRTI of mild/moderate severity and the applicant was requesting approval for the same indication in patients with severe disease at a higher dosage. The dose of ciprofloxacin utilized was high at 400 mg IV q8 (previously approved dose: 400 mg IV q12), and the comparator agent was imipenem (1000 mg q8 or 500 mg IV q6). APACHE scores were provided and the mean score on both arms was > 16, thus indicating a population at increased risk of death. Other factors that the RMO determined to further bolster the argument that a severely ill population was being studied were age >50 (mean age 59.9), the presence of several underlying conditions the use of ventilators, and the presence of the predominant number of patients in an ICU. In a review of this document, the MO found that there was no severity scoring system. Rather, analyses were performed on subpopulations with low and high APACHE scores as well as by ventilator status (58/71 evaluable ciprofloxacin patients were ventilated (81.6%) as compared to 66/81 (81.4%) of the imipenem patients). Clinical cure rates (pivotal study only), at the EOS (late follow-up), visit were 42/71 (59.2%) versus 32/81 (39.5%), thus indicating superiority of ciprofloxacin versus imipenem. Clinical response by APACHE scores were ciprofloxacin: APACHE low (10-14): 9/25 (36%) and high (-14-49): 23/56 (41%). The respective rates for the imipenem arm were 22/30 (73%) and 20/41 (49%). Clinical response rates by ventilator status were ciprofloxacin: ventilator: 34/58 (59%) and non-ventilated: 24/58 (41%). The respective rates for imipenem were 21/66 (32%) and 45/66 (68%) respectively.

From the above, the reviewing MO concluded that there appeared to be a difference in response rates when the ciprofloxacin patients were divided into those with an APACHE score < 15 and those with an APACHE score >15. It seemed that ciprofloxacin had greater efficacy in those patients with lower scores, as compared to the imipenem arm, where it made no difference. Clinical response rates by pathogen were as follows (ciprofloxacin only): *Haemophilus influenzae*: 14/19 (74%), *Klebsiella pneumoniae*: 8/9 (89%), *Pseudomonas aeruginosa*: 18/29 (62%) and *Staphylococcus aureus*: 8/14 (57%). The applicant received approval for the requested addition of severe disease at the requested dose caused for *Haemophilus influenzae* and *Klebsiella pneumoniae*. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were not

approved for severe NP, because a determination was made that although the numbers of patients with these pathogens were large, the cure rates (57% and 62% respectively), were too low.

NOTE: Of all the aforementioned NDA's, the trial design in the ciprofloxacin SNDA closely approximated that of the trovafloxacin NDA. The MO points out that the ciprofloxacin population studied was more severely ill than that reviewed in the current submission (see above percentages for comparisons). This statement is made (see table 113.16) because in the US study, only 18/70 (25.7%) of evaluable patients were on a ventilator as compared to 16/77 (20.7%) on the ciprofloxacin arm. 15/70 (21.4%) and 24/77 (31.1%) per arm respectively, had compromised respiration (as previously defined). 20/70 (28.5%) had severe disease on the trovafloxacin arm as compared to 35/77 (45.4%) on the ciprofloxacin arm. Approximately 25% of the sponsor's evaluable population had underlying COPD, CAD, asthma, or DM.

In the European study, 33/85(38.8%) of the trovafloxacin patients as compared to 31/89 (34.8%) of the ceftazidime/ciprofloxacin patients were ventilated and 40/85 (47%) of the trovafloxacin patients versus 43/89 (48.3%) of the ceftazidime/ciprofloxacin patients had compromised respiration.

Even if the patients of both studies were added up, the MO still determined that the overall percentage of severely ill patients in the current NDA was lower than that of the ciprofloxacin SNDA.

A review of the CRF of the current submission, revealed that there was no severity of illness scoring system. The investigators merely provided information with regards to underlying illnesses, ventilator status, smoking history and calculated APACHE II scores. In the signs and symptoms, the investigators were able to place a mark in a box numbered 0., 1, 2, and 3 indicating that the symptom was present and if so, was mild, moderate, or severe.

A comparison of the results of the ciprofloxacin SNDA and the current trovafloxacin NDA reveal that the efficacy rates in the populations termed severely ill were very similar (Ciprofloxacin NDA 34/58 (59.5%) as compared to trovafloxacin 10/18 (55.6%) US and 15/33 (45.5%) European but the proportion of the ciprofloxacin (SNDA) population was more severely ill. In other words, comparatively, trovafloxacin did as well in a population of less severely ill patients. The clinical response rates by pathogen were notable for the same rate versus *Pseudomonas aeruginosa*; however, ciprofloxacin was used as monotherapy (SNDA) in most patients (additional antipseudomonal therapy not allowed by-protocol) as compared to trovafloxacin (NDA) where aztreonam or gentamicin could have been used. Clinical response rates in patients with *Staphylococcus aureus* were similar in the SNDA US trial for ciprofloxacin compared to trovafloxacin. Nevertheless, ciprofloxacin did not receive approval for this pathogen. Clinical response rates in patients with *Klebsiella pneumoniae* were superior versus trovafloxacin and slightly lower for *Haemophilus influenzae*.

As per a literature review, (Antimicrobial Agents and Chemotherapy, Volume 38(3), 1984, 547-557: Ciprofloxacin versus Imipenem in severe Pneumonia; Fink et al), "Clinical studies to assess the efficacy of antibiotics for the treatment of pneumonia have been difficult to evaluate. Flaws have included lack of a double-blind design, exclusion of patients with underlying conditions associated with higher mortality, small sample sizes, and the absence of ITT analyses." In this double-blinded randomized comparative trial of high dose ciprofloxacin (400 mg IV TID), versus imipenem (1000 mg IV q6), as monotherapy in severely ill patients (APACHE 17.6), the clinical cure rates were ciprofloxacin 58/86 (67%) versus imipenem 44/83(53%). Pathogen eradication rates (EOS), included the following: *Staphylococcus aureus*: 13/20 (65%) ciprofloxacin versus 11/17 (65%) imipenem, *Escherichia coli*: 10/10 (100%) vs. 11/14 (79%), *Klebsiella* spp.: 10/11 (91%) vs. 12/18 (67%), and *Pseudomonas aeruginosa*: 11/33 (33%) vs. 11/27 (41%) respectively. As noted previously, this trial was performed in a more severely ill population and monotherapy was stipulated. The MO determined from this information that the presence of *Pseudomonas aeruginosa* as a respiratory pathogen is strongly associated with poor outcome and that even appropriate therapy with 2 anti-pseudomonal agents may not lead to a clinical cure.

The current literature overwhelmingly supports the MO's conclusion that NP is a difficult to treat clinical entity with a high mortality rate. Mortality rates are higher depending on the causative agent. In NP due to

Pseudomonas aeruginosa, mortality may approach 80% or higher (Foner et al: Bacterial pneumonia, pp 184 -7; Conn's Current Therapy 1995).

The treatment of NP is usually empirical and there is no consensus in the literature as to a gold standard or any one type of regimen that is associated with a high clinical response rate. Factors that influence the choice of an initial regimen are local experience and the severity of the NP as well as that of the underlying disease. The cornerstone of therapy remains combination therapy usually consisting of an aminoglycoside with a beta-lactam, thus providing for broad-spectrum coverage. A second or third generation cephalosporin is often used in combination with an aminoglycoside, and vancomycin is often also included in the regimen. As stated previously, anaerobic coverage may be added especially in ventilator-associated NP. Other than the ciprofloxacin versus imipenem study cited above, the MO also located the following information:

Hooper et al; NEJM 324:384 -394, 1991: IV ciprofloxacin versus ceftazidime: 15/17 (88%) ciprofloxacin-treated patients (with severe disease) had evidence of cure or improvement as compared to 13/15 (87%) ceftazidime-treated patients at the EOS. Failures on the ceftazidime arm were associated with Enterobacteriaceae or *Acinetobacter* spp. Failures on the ciprofloxacin arm were associated with *Staphylococcus aureus* or Streptococci.

Salta et al. Am J Med 1985; Suppl. 6A; 104 -109: Pneumonia treated with imipenem. Imipenem was effective versus *Pseudomonas aeruginosa*. An open trial of imipenem in bacterial pneumonia in 43 patients, 29 had NP (severity unknown). Clinical cure in 93% at the EOT.

Andrews et al: Clinical Therapeutics 16:236-52, 1994: Combined aztreonam/gentamicin for LRTIs: This study reported "excellent" efficacy for this combination even though only 47% of patients had a full response and an additional 37% had evidence of a partial response (severity unknown).

Mangi et al, AM J Med 84:68-74, 1988: Cefoperazone versus combination therapy of hospital-acquired pneumonia (severity unknown). Cefoperazone and ceftazidime were equally as effective in the treatment of NP. Specifically, clinical cure was seen in 45/62 (73%) of the cefoperazone patients as compared to 50/63 (79%) of the ceftazidime patients at the EOT.

Fernandez-Guerrero et al, Infection 19 (Suppl. 6):S320-5: Nosocomial pneumonia: Comparative multicenter trial between monotherapy with cefotaxime and treatment with antibiotic combinations (severity unknown).

The following cure rates have been obtained with various antibiotic regimens (unknown timepoint):

Cefotaxime: 79%

Cefotaxime and aminoglycoside: 77%

Cephalosporins with activity against Gram (-) organisms and aminoglycosides: 67%

Anti-pseudomonal cephalosporin and aminoglycoside: 76%

Clindamycin and aminoglycoside: 58%

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As stated above, the MO concluded from the literature review that NP is a difficult entity to treat. Mortality can be high especially when associated with *Pseudomonas aeruginosa*. Success rates usually range between 65 - 75% (EOS), depending on the causative pathogen, the patient's underlying condition, and the severity of the current episode. Optimal therapy provides broad-spectrum coverage. There is no consensus as to the usefulness of monotherapy versus combination but many ID specialists in the medical community believe that combination therapy with aztreonam or an aminoglycoside is useful. Vancomycin, clindamycin, and metronidazole are also utilized in the presence of the appropriate clinical setting or culture results.

From MO table 1, the MO determined that the overall clinical response rates in trial 154-113 (68.6% versus 67.5%) were within the expected range for a population of patients with mild to moderate disease. Additionally, the MO determined that the clinical response rates for the trovafloxacin-treated patients in

study 154-137 were within the expected range (63.5%) as compared to those on the comparator arm (57.3%). This lower clinical response rate may have been due to the inclusion of a more severely ill population on the comparator arm (difference in APACHE scores was not statistically significant, $p = 0.2147$), although this score is indicative of mortality and not severity of illness). Local factors such as hospital flora or differences in supportive measures may have also played a role. **The MO concluded that trovafloxacin is approvable for the indication of NP in patients with mild/moderate disease.**

Trovafloxacin is not approvable in patients who are severely ill or mechanically ventilated. Although the clinical response rates were numerically comparable not only between arms but between studies, the MO determined that clinical response rates in the 50% range were unacceptably low, especially in the face of potential monotherapy. More importantly, previously approved agents studied a higher proportion of severely ill patients (ciprofloxacin: 80%). This conclusion was not only based on a review of the literature (double-blinded randomized comparative trial of high dose ciprofloxacin versus imipenem as monotherapy in severely ill patients (APACHE 17.6): clinical cure rates: ciprofloxacin 58/86 (67%) versus imipenem 44/83(53%), but on previous regulatory history. Zosyn®, had an overall clinical response rate of 74% cured and improved versus the comparator (ceftazidime, which was 53%), in a population of severely ill patients. Additionally, the data from the ciprofloxacin NDA revealed a cure rate of 74% (or 59.5% in the mechanically ventilated) in a documented severely ill population with mean APACHE scores of 16 and of whom approximately 80% were on a ventilator. Furthermore, questions regarding the adequacy of the comparator regimen (ciprofloxacin 400 mgm bid as opposed to 400 mgm tid) preclude the granting of an approval for severe disease.

For the most frequently isolated baseline pathogens, and for which the sponsor is requesting approval, the MO determined that the sponsor met the divisional rule of "10" when the results of both studies were pooled. That is that "to include an organism in an indication, only those which are generally considered pathogenic and represent at least 10% of the evaluable cases OR 10 total (whichever is higher) AND the eradication rate must be clinically acceptable" can be considered. The only exception to the above was *Klebsiella pneumoniae* where the total number of evaluable patients with this isolate from both studies combined was 8 (as per the MO).

The MO determined that it was preferable to base the granting of organisms for this indication on the clinical response by pathogen rates as opposed to pathogen eradication rates.. The rationale for this decision was stated previously.

With regards to *Pseudomonas aeruginosa*, the results of study 154-113 indicated that trovafloxacin was effective versus this organism within the range that is currently clinically acceptable (8/13: 62%), in the case of monotherapy. The conflicting results of study 137 (1/5: 20%) were of concern, and therefore, although trovafloxacin is approvable for NP caused by *Pseudomonas aeruginosa* (total clinical response rate: 9/18 (50%)), the MO determined that the approval for this organism would be contingent upon the addition of a qualifying statement with regards to the addition of a second anti-pseudomonal agent, either aztreonam or an aminoglycoside. The above statement should be strongly worded because of the disparate results between the trials, questions regarding severity of illness, and the allowed use of combination therapy, and the sponsors inability to consistently show good evidence to support the use of trovafloxacin as effective monotherapy

The sponsor was requested to provide evidence of a lack of antagonism between trovafloxacin and other anti-pseudomonal agents. In response to this request, an abstract entitled "Synergistic Activity of Trovafloxacin with Other Agents (37th ICAAC, 1997) was submitted. The authors examined the synergistic activity of trovafloxacin with other agents via a checkerboard method. No antagonism was found with any combination. Synergy was seen for 10 strains of *Pseudomonas aeruginosa*: 4 with aztreonam, 3 with ticarcillin/clavulanate, 2 with ceftazidime, 1 with ceftriaxone, 1 with tobramycin, and 1 with cefoperazone. Additive or indifferent combinations included all those of trovafloxacin and imipenem, trovafloxacin and gentamicin, trovafloxacin and Zosyn®, and trovafloxacin and amikacin.

With regard to *Klebsiella pneumoniae*, the MO determined that both the sponsor's clinical response rates and the number of evaluable isolates in both studies were unacceptably low (2/4 (50%) both

studies separately or 4/8 (50%) combined), for a population of patients with mostly mild to moderate disease, and therefore trovafloxacin is not approvable for NP caused by this pathogen.

With regards to *Escherichia coli*, the MO determined that the additive results of both studies (5/6: 83.3% and 3/6 (50%) or total: 8/12: 67%), were adequate to support approval the approval for trovafloxacin in patients with NP caused by this pathogen.

With regards to *Haemophilus influenzae*, the MO found the clinical cure rate of 5/6 (83%) seen in study 154-113 was consistent with that of the supportive study 154-137 (4/5:80%). This rate was also consistent with that seen in the literature where it is pointed out that *Haemophilus influenzae* is one of the common pathogens associated with NP. However, it is usually seen in patients who aspirate early during the course of their hospitalization. In other words an "early" hospital-acquired infection. The MO determined that trovafloxacin was effective in patients with NP caused by *Haemophilus influenzae* and recommended unqualified approval.

With regards to *Staphylococcus aureus*, the MO determined that the clinical response rate of patients with this isolate was too low (study 154-113: 4/8 (50%), study 154-137:8/11 (72.7%) or TOTAL 12/19 (63.1%), in view of the higher cure rates that can be obtained in a more severely ill population. (Zosyn NDA: 81%) to support approval. Additionally, as per previous regulatory history, ciprofloxacin was NOT granted approval for this pathogen, despite its similar efficacy rate in a more severely ill population. Therefore, the MO could not recommend approval for this organism. It should be pointed out, that at this time, no fluoroquinolone is approved for this indication due to this organism. As *Staphylococcus aureus* is a common pathogen within this disease entity, the MO believes that the standard should be set at a higher level.

RECOMMENDED REGULATORY ACTION:

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The following statement can be added to the indications section of the labeling:

It is suggested that a clinical studies section be appended to the labeling with regards to this indication. This section should contain MO table 1.

The recommended dosage is alatrofloxacin 300 mg IV daily, which may be converted to trovafloxacin 200 mg PO daily for 10- 14 days.

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Regina Alivisatos, MD
Medical Officer, DSPIDPs

- Orig. NDA #20-759
- Orig. NDA #20-760
- HFD-590
- HFD-590/Div. Dir./MGoldberger */S/*
- HFD-590/Dep. Dir./RALbrecht
- HFD-590/MTL/BLeissa
- HFD-590/MO/RAlivisatos */S/ 12 18 97*
- HFD-590/CSO/PFogarty
- HFD-725/Biostat/Silliman
- HFD-344/Thomas

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Addendum to MOR of NDA 20 - 759/Nosocomial Pneumonia

In response to a request by the FDA, at the closure of a Telecon with Pfizer representatives on October 29, 1997, the sponsor submitted additional information to support their claim of efficacy of trovafloxacin in patients suffering from severe nosocomial pneumonia (Nov. 7, 1997). This information is reviewed below and consisted of extensive re-analyses of the data for efficacy utilizing ATS criteria as a determinant of severity of illness

At the conclusion of the review of the original submission, the MO determined that trovafloxacin was effective in the treatment of nosocomial pneumonia of mild to moderate severity, (APACHE scores not to exceed 13), caused by *Haemophilus influenzae*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

Approval was not recommended for the treatment of nosocomial pneumonia caused by *Klebsiella pneumoniae* and *Staphylococcus aureus*.

The MO agreed that the following statement should be added to the labeling:

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As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

Based on the data in the original submission, the MO found the following clinical efficacy rates:

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Table 1
Clinical Response Overall and by Disease Severity/FDA Evaluable Population (as per the MO)

Study	154-113	154-137
Location	US	Multinational
Design	Randomized, Blinded	Randomized, Open
Comparator	Ciprofloxacin IV/PO	Ceftazidime IV/Ciprofloxacin PO
Clinical Response EOS	48/70 (68.5%) trovafloxacin vs. 52/77 (67.5%) comparator	54/85 (63.5%) trovafloxacin vs. 51/89 (57.3%) comparator
Clinical Response Mild/Moderate Disease	38/50 (76%) trovafloxacin vs. 39/52 (75%) comparator	33/39 (84.6%) trovafloxacin vs. 29/41 (70.7%) comparator
Clinical Response Severe Disease	10/20 (50%) trovafloxacin vs. 13/25 (52%) comparator	21/46 (45.7%) trovafloxacin vs. 22/48 (45.8%) comparator
Clinical Response Mechanically Ventilated	10/18 (55.6%) trovafloxacin vs. 8/16 (50%) comparator	15/33 (45.5%) trovafloxacin vs. 14/31 (45.2%) comparator

Thus indicating that 18/70 (25.7%) of the FDA evaluable population from the US study, 154-113 were mechanically ventilated and therefore by definition, suffering from a severe NP as compared to 33/85 (39%) of the multinational population (study 154-137). The respective numbers for those patients suffering from "severe" disease, defined by the sponsor as patients requiring mechanical ventilation or supplemental oxygenation of > 35% in order to maintain an arterial oxygen saturation of 90%, were 20/70 (25.6%) and 46/85 (54.1%) per study respectively.

As noted in the MO's conclusion and repeated here, a comparison of trovafloxacin's data with those from previously reviewed antimicrobials that received an indication for severe disease revealed that:

Ciprofloxacin NDA 19-847/S-008 and NDA 19-857/S008: (See conclusion to MOR)

The dose of ciprofloxacin utilized was high at 400 mg IV q8 (previously approved dose: 400 mg IV q12), and the comparator agent was imipenem (1000 mg q8 or 500 mg IV q6). APACHE scores were provided and the mean score on both arms was > 16, thus indicating a severely ill population with an expected poor prognosis. Other factors that the reviewing MO determined to further bolster the argument that a severely ill population was being studied were age >50 (mean age 59.9), the presence of several underlying conditions, the use of ventilators, and the presence of the predominant number of patients in an ICU. In a review of this document, the MO found that there was no severity scoring system. Rather, analyses were performed on subpopulations with low and high APACHE scores as well as by ventilator status (58/71 evaluable ciprofloxacin patients were ventilated (81.6%) as compared to 66/81 (81.4%) of the imipenem

patients. Clinical cure rates (pivotal study only), at the EOS (late follow-up), visit were 42/71 (59.2%) versus 32/81 (39.5%), thus indicating superiority of ciprofloxacin versus imipenem. Clinical response by APACHE scores were ciprofloxacin: APACHE low (10-14): 9/25 (36%) and high (-14-49): 23/56 (41%). The respective rates for the imipenem arm were 22/30 (73%) and 20/41 (49%). Clinical response rates by ventilator status were ciprofloxacin: ventilator: 34/58 (59%) and non-ventilated: 24/58 (41%). The respective rates for imipenem were 21/66 (32%) and 45/66 (68%) respectively.

Therefore, in the ciprofloxacin SNDA, the applicant provided a more detailed analysis of the severely ill population including breakdown by age, ventilatory status, comorbid conditions, ICU admission status, and APACHE II scores. In that submission, 80% of patients per arm were severely ill and ventilated. The results from that trial can be seen above, however, the MO points out that in a truly severely ill population, ciprofloxacin efficacy was approximately 59%. Additionally, ciprofloxacin was utilized at a higher dose; thus causing the MO concern over the applicability of comparing trovafloxacin to an inadequate dose in a severely ill population as was done in this trial. (Adequacy of comparator regimen).

The MOR of the NDA of the only other antimicrobial approved for "severe" NP, Zosyn®, did not contain adequate information for the current MO to be able to make a judgement on the true severity of the disease process in the population studied. Clinical response rates (EOS) were 47/63 (74%) Zosyn® versus 22/35 (53%) ceftazidime (comparator).

With regard to the adequacy of the comparator, ceftazidime as monotherapy (the comparator agent utilized for the intravenous portion of the treatment regimen in study 154-137), this agent is approved for LRTI of mild to moderate severity. Approval was granted prior to the agency differentiating types of LRTI labeling. The labeling however does include a statement reflecting that this agent can be used in "severe" infections. No mention is made of the adequacy of this agent as monotherapy. The MO agrees however, that this agent is an adequate comparator when the use of other antimicrobials is allowed for as in this submission (aztreonam, gentamicin, vancomycin, clindamycin, and metronidazole).

The MO briefly reviews the demographics of the sponsor's evaluable population at this point as all further references will be made to the sponsor's and not the MO's evaluable population. This was done because the additional data submitted did not refer to the MO evaluable population and, as stated, in the MORs of studies 154-113 and 154-137, the MO mostly agreed with the sponsor's determinations of evaluability and outcome.

In study 154-113, of the clinically evaluable subjects, 29/88 (33%) of the alatrofloxacin/trovafloxacin subjects and 35/103 (34%) of the ciprofloxacin subjects required respiratory supportive therapy at baseline. This support was in the form of supplemental oxygen therapy or mechanical ventilation. 24/88 (27%) of the alatrofloxacin/trovafloxacin subjects and 22/103 (21%) of the ciprofloxacin subjects required mechanical ventilation.

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

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

In study 154-137, of the clinically evaluable subjects 56/103 (54%) alatrofloxacin/trovafloxacin-treated subjects and 60/109 (55%) of the ceftazidime/ciprofloxacin treated subjects had severe disease. 48/103 (47%) and 54/109 (50%) respectively, had compromised respiratory function (included all subjects who were mechanically ventilated or required a fractional oxygen concentration of ≥ 0.35 to maintain an arterial oxygen tension of ≥ 60 mm Hg.).

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

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

Thus, as per the MO's calculations, if both studies were combined, 85/191 (44.5%) of the clinically evaluable trovafloxacin subjects had severe disease as compared to 95/212 (44.8%) of the clinically evaluable comparator subjects (ciprofloxacin (113) and ceftazidime/ciprofloxacin (137), when the parameters of ventilatory support and/the need for high supplemental oxygen concentrations were utilized as determinants of disease severity.

The results from the original analyses are provided below:

Table 2

Sponsor-Defined Clinical Response/Clinically Evaluable Populations (as per the sponsor) at EOS:

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Success (Cure + Improvement)	Trovafloxacin	Ciprofloxacin	Ciprofloxacin /Ceftazidime	Comparators
Study 154-113/Overall	50/72 (69%)	54/79 (68%)		
Study 154-113/Severe	11/21 (52%)	14/26 (54%)		
Study 154-113/Mechanically Vent.	10/18(56%)	8/16 (50%)		
Study 154-113/Mild/Moderate	39/51 (76%)	40/53 (75%)		
Study 154-137/Overall	56/85 (66%)		52/89 (58%)	
Study 154-137/Severe	22/56 (49%)		22/60 (47%)	
Study 154-137/Mechanically Vent.	16/32 (50%)		14/30 (47%)	
Study 154-137/Mild/Moderate	34/40 (85%)		30/42 (71%)	
Total/Overall	106/157 (68%)			106/168 (63.1%)
Total/Severe	33/66 (50%)			36/86 (42%)
Total/Mechanically Vent.	26/50 (52%)			22/46 (48%)
Total/Mild/Moderate	73/91 (80%)			70/95 (74%)

Overall clinical response (success) rates at the EOS in study 154-113, (as per the sponsor), were: 50/72 (69%) versus 54/79 (68%) and in study 154-137 56/85 (66%) versus comparator 52/89 (58%). In study 154-113 equivalence but not superiority was demonstrated based on a 95% CI with CCF of -13.7%, 15.9% ($\Delta = 20$). In study 154-137, numerical superiority was demonstrated at the EOS with a 95% CI (with CCF) of -8.1%, 23% ($\Delta = 20$) but statistical significance was not achieved (as per FDA statistician, Dr. Nancy Silliman). Overall EOS clinical success rates for NP (combined results) were 106/157 (67.5%) and 106/168 (63.1%) comparators 95% CI: - 6.5%, 15.4% ($\Delta = 20$). Overall EOS clinical success rates for sponsor evaluable patients with severe disease were 33/66 (50%) versus comparators 36/73 (49.3%), 95% CI: - 17.4%, 18.7% ($\Delta = 20$). Mortality was as expected (ITT: 113:27% trovafloxacin versus 28% ciprofloxacin and ITT: 137: 27% trovafloxacin versus 21% ceftazidime/ciprofloxacin).

The MO concluded from the above that trovafloxacin was equally efficacious to both comparator regimens in the clinically evaluable severely ill population (as defined by the sponsor). Additionally, the MO had no objections to the pooling of the populations although, the MO did not determine that this lack of objection obviated the inadequacy of the comparator regimens utilized.

Therefore the MO determined that the sponsor's supplemental data could be utilized in lieu of requesting reanalyses on the MO's population not only because of general agreement with regard to evaluability and outcome issues but because the MO was convinced that the ATS scoring system was a more accurate indicator of severe disease.

The current submission consisted of a Word document as well as additional tables illustrating the sponsor's reanalyses by a variety of severity factors.

The sponsor initially provided the ATS criteria for severe nosocomial pneumonia. These are generally accepted criteria and are the same for both CAP and NP. These criteria were copied below:

Severity factors in pneumonia:

Severe pneumonia may be defined as the presence of one of the following factors:

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- Admission to the intensive care unit (NOS)
- Respiratory failure defined as the need for mechanical ventilation (NOS and CAP) or the need for >35% oxygen to maintain arterial oxygen saturation >90%(NOS), severe respiratory failure defined by a PaO₂/FIO₂ ratio <250 mm Hg (CAP)
- Respiratory frequency > 30 breaths per minute at admission (CAP)
- Multilobar pneumonia (NOS, CAP), rapid radiographic progression (NOS, CAP), bilateral involvement(CAP) or cavitation of a lung infiltrate(NOS)
- Evidence of severe sepsis with hypotension and/or end-organ dysfunction: (NOS and CAP)
- Shock (systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm)
- Requirement for vasopressors for more than 4 hours
- Urine output <20 mL/h or total urine output < 80 mL in 4 hours (unless another explanation is available)
- Acute renal failure requiring dialysis

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CAP - ATS Guideline on Community-acquired Pneumonia (Niederman, 1993)
NOS - ATS Guideline on Nosocomial Pneumonia (Campbell, 1996)

Medical Officer's Comment: *The MO agreed with the general acceptability of these criteria.*

The sponsor also stated that other measuring systems such as the Fine score and the APACHE score are not severity measurements as such but rather predictive in nature to assess potential for good versus poor outcomes (independent of infection and anti-infective therapy).

Medical Officer's Comment: *The MO agreed with this determination.*

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The sponsor stated that (11/7/97):

"Two studies were presented in support of the indication of nosocomial pneumonia. These studies included 533 patients in the ITT analysis with an approximately 25% mortality. The comparative agents selected were those recommended in the ATS Consensus Statement (Campbell, 1996). It is important to note that no single agent is available that is always suitable for use in all nosocomial pneumonias, particularly with respect to infection due to *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Indeed, ethical conduct of the clinical study requires that appropriate therapy be used and consequently additional agents are necessary where certain organisms are identified. In any event, that the use of concomitant study antibiotics was greater in the comparator groups than in the trovafloxacin treated group implies potential superiority of trovafloxacin. One of the studies was double-blind, while the other was a randomized, open comparative design. However, an open design was not *a priori* inadequate. In the absence of evidence of unequal randomization in the groups and when the results of such a study are consistent with other blinded data, such data are fully acceptable and are considered appropriate

to pool to facilitate assessment of appropriate sub-groups. It should be noted that all sponsor assessments were done blinded to treatment group and in most cases were applied by computer algorithms. Since outcomes such as clinical success with no need for further antibiotic therapy and mortality are "hard" endpoints, the sponsor felt this open study is justified for inclusion."

The two study groups were comparable at baseline for a number of factors associated with increased risk or directly with the severity of the pneumonia. The original analysis presented by the sponsor for the overall nosocomial pneumonia groups demonstrated therapeutic equivalence. The original protocol specified analysis of severe patients (those on mechanical ventilation or high fractional oxygen) also showed comparable results. As mentioned above, a new analysis based on the ATS criteria for severe hospital-acquired pneumonia was performed. For the purpose of selecting patients for this subgroup analysis the following specific criteria were collected in the case report forms and applied: admission to intensive care; need for mechanical ventilation; need for oxygen therapy (>35% oxygen to maintain arterial oxygen saturation >90%); respiratory rate >30; multilobar pneumonia; systolic blood pressure <90 mm Hg; diastolic blood pressure <60 mm Hg. Efficacy in patients meeting the ATS criteria for severe nosocomial pneumonia is shown below.**

*The following tables were modified by the MO to reflect only clinically evaluable patients at the EOS.

Table 3
Clinical Outcome in Patients with Severe Nosocomial Pneumonia
(Pooled data 154-137 and 154-113/ ATS definition/As per the sponsor)

Total Assessed EOS Evaluable (n =)	Clinical Success (%)	CI
Ala > Trovafloxacin (n = 117)	59%	- 11.7, 13.3
Comparators (n = 122)	58.2%	

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Medical Officer's Comment: Thus the trovafloxacin group outcome was equivalent to the comparator outcomes when the ATS severity of illness scoring system was utilized. The 95% CI applied above is as per the sponsor and without continuity correction factor. Below is clinical outcome without ATS criteria as per the sponsor.

Table 4
Clinical Outcome in Nosocomial Pneumonia
(Pooled analysis - 154-113, 154-137/As per the sponsor)

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Clinical Success	Alatrofloxacin/ Trovafloxacin	Comparators	95%CI
Overall (EOS Eval)	106/157 (68%)	106/168 (63%)	-5.9, 14.8
Severe (vent or high O2)/EOS	33/66 (50%)	36/73 (49%)	-16.0, 17.3
Mechanical Ventilation/EOS	26/50 (52%)	22/46 (48%)	-15.8, 24.2
APACHE score > 16	22/39 (56%)	25/49 (51%)	-15.5, 26.3

Medical Officer's Comment: The sponsor provided additional analyses for other specific subgroups associated with increased severity or poor outcome (advanced age, multilobar infiltration, or comorbidity), and found equivalence between the treatment arms for all variables.

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Table 5
Patients with the Severity Factor at Baseline (As per the sponsor)

	Evaluable				ITT			
	Tro. N=	Comp. N=	Tro. %	Comp. %	Tro. N=	Comp. N=	Tro. %	Comp. %
Total Eval	191	212			259	274		
Mean age	63.6	66.7			64.8	67.2		
Age \geq 65	103	54	133	63	147	57	180	66
Age \geq 75	66	35	87	41	94	36	112	41
AT least one comorb	98	51	113	53	137	53	159	58
AT least two comorb	41	21	57	27	64	25	83	30
Original severe (Hi O ₂ +MV)	85	45	95	45	126	49	133	49
RR>30	26	14	20	9	37	14	29	11
SysBP<90	4	2	3	1	8	3	5	2
DiBP<60	38	20	39	18	54	21	57	21
Multilobar	78	41	89	42	111	43	121	44
ICU	77	40	91	43	113	44	127	46
High fractional O ₂	71	37	85	40	105	41	115	42
Mechanical Ventilation	65	34	59	28	98	38	89	32
At least one ATS severe	145	76	153	72	203	78	209	76
Pseudomonas	23	12	28	13	30	12	32	12
Apache \geq 16	47	25	57	27	80	31	82	30

Table 6
Clinical Success at End of Study by Severity Factor/Group (As per the sponsor)

	Evaluable					ITT				
	Tro. N=	Comp. N=	Tro. %	Comp. %	CI	Tro. N=	Comp. N=	Tro. %	Comp. %	CI
Total Eval	157	68	168	63	-5.9,14.8	259	61	274	64	-11.5,5.0
Age \geq 65	87	67	103	63	-12.3,9.9	147	57	180	63	-16.8,4.5
AT least one comorb	79	66	91	62	-10.2,18.8	137	59	159	58	-10.0,12.5
AT least two comorb	33	67	48	56	-10.9,31.8	64	58	83	58	-16.1,16.1
Original severe (Hi O ₂ +MV)	66	73	50	49	-16.0,17.3	126	49	133	53	-16.3,8.0
Mechanical Ventilation	50	52	46	48	-15.8,24.2	98	51	89	51	-13.9,14.8
At least one ATS severe	117	59	122	58	-11.7,13.3	203	55	209	60	-14.6,4.4
Multilobar	61	56	69	61	-22.1,11.8	111	56	121	60	-17.2,8.2
Pseudomonas	18	50	22	32	ND	30	53	32	44	ND
Apache \geq 16	39	56	49	51	-15.5,26.3	80	46	82	48	-16.7,14.1

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The sponsor's conclusion is attached below:

"It is remarkable that when the data on severe nosocomial pneumonia are examined, using internationally recognized definitions for severity, or other definitions, the results consistently demonstrate that trovafloxacin is equivalent to the alternative regimens. It is important to recall that in studies reviewed here, the trovafloxacin regimen was a monotherapy regimen (except for a few uncommon situations equally applicable to both study arms) while the comparator was frequently a multidrug regimen. Indeed, although the results are equivalent, adjunctive antibiotic therapy was utilized much more commonly on the alternative regimens, providing yet another indication of the efficacy of trovafloxacin. In severe nosocomial pneumonia, less induction of bacterial resistance in the sentinel organism *Pseudomonas aeruginosa* was noted. The new subgroup analysis comparing clinical outcomes in patients with defined severe nosocomial pneumonia confirms overall equivalent efficacy between the regimens. Additional comparisons using a variety of individual severity factors also demonstrate equivalence. Substantial numbers of patients with significant severity factors were treated. In fact over 200 patients in each group met ATS criteria for severe pneumonia. Consequently, the overall equivalence to the comparative agents observed in the individual studies and pooled analysis (in both the evaluable and ITT analyses) supports the use of alatrofloxacin/trovafloxacin in nosocomial pneumonia including patients with severe pneumonia."

Medical Officer's Comment: *Based on the above, the sponsor claimed equivalence with the comparators when the populations studied were analyzed applying a number of variables and in accordance with ATS guidelines. The MO does not disagree with the sponsor's numerical claims. However, it is again pointed out that the MO determined that the comparator regimen utilized in the pivotal, double-blind, US trial is not approved for severe nosocomial pneumonia. Ciprofloxacin is approved at a higher dose (400 mg every 8 hours) than that used in these studies. An extrapolation of the known data suggests that if the clinical efficacy rate in the ciprofloxacin NDA was 59% overall in a population that was compromised of 80% severely ill patients, then the 49% efficacy with 43% of the population determined to have severe disease, attained in this trial is indicative of the inadequacy of the dosage utilized. Ultimately the sponsor's results cannot be construed as superior to either comparator regimen (superiority necessary versus low dose ciprofloxacin as it is not approved at the lower dose for the indication), and therefore, the MO continues to recommend a non-approval for severe nosocomial pneumonia. On Nov. 10, 1997, the sponsor was requested to provide additional information as to the reason that ciprofloxacin was utilized at a lower dose and to state the rationale that could be used to justify the adequacy of the comparator.*

*With regards to the sponsor's statement regarding the use of concomitant antimicrobials to a greater degree on the comparator arms, thus implying potential superiority of the trovafloxacin regimen, the MO reminds the reader that in study 154-113, aztreonam was allowed on both study arms in the face of a documented infection with *Pseudomonas aeruginosa*. Vancomycin was allowed on both treatment arms in the face of a NP caused by MRSA and clindamycin or metronidazole were allowed on the ciprofloxacin arm, at the investigators discretion.*

In that study, aztreonam was utilized in 9 trovafloxacin subjects and 11 ciprofloxacin subjects (as per the sponsor). Vancomycin was utilized in 9 trovafloxacin and 7 ciprofloxacin subjects. Clindamycin was utilized in 14 ciprofloxacin subjects (11 trovafloxacin subjects received clindamycin placebo), and metronidazole was utilized in 2 ciprofloxacin subjects.

In study 154-137, adjunctive therapy use was similar to that seen in 154-113 with the exception that gentamicin was substituted for aztreonam. A priori, adjunctive therapy was allowed only on the comparator arm, however, because patients did receive adjunctive therapy against protocol, the sponsor made a post-hoc decision to include these patients in the analyses of efficacy. In that trial, 5 alatrofloxacin/trovafloxacin ITT subjects received gentamicin as compared to 17 ITT subjects on the ceftazidime/ciprofloxacin arm. 5 ITT alatrofloxacin and 17 ITT ceftazidime/ciprofloxacin subjects received vancomycin and only 1 ceftazidime/ciprofloxacin subject received adjunctive therapy with clindamycin.

The MO does not agree with the sponsor's statement with regards to the increased antimicrobial usage on the comparator arms with the exception of the use of clindamycin in study 154 -113. Additionally, the MO did not determine that clindamycin usage was not a major determinant in the establishment of efficacy.

On December 4, 1997, the sponsor faxed a response intended to address the FDA concern with regards to the adequacy of the comparator regimen in study 154 -113. The sponsor stated the following:

“Pfizer maintains that the ciprofloxacin dosing used in the #113 nosocomial pneumonia study was, for all practical purposes equivalent to that used by Bayer to obtain labeling for ‘severe’ nosocomial pneumonia. There is no evidence that the currently approved dose of ciprofloxacin for severe nosocomial pneumonia is superior to the previously approved dose, and there are theoretical reasons to question the benefits of the dosing method used for ciprofloxacin in the pivotal study. The primary rationale for the additional ciprofloxacin probably related to spectrum weaknesses and resistance issues that are irrelevant to the dosing used in the trovafloxacin studies. In any event, there are suggestions of superiority of trovafloxacin over ciprofloxacin in the data. Finally, Pfizer presented the dosing to FDA in good faith prior to study start and would have been subject to criticism had we used something other than the then approved dose.

Medical Officer's Comment: *The MO agrees with the sponsor's claim that the dosage selected was the approved dosage of ciprofloxacin at the time of study design. Additionally, the protocol was submitted to the FDA and no comment was issued with regards to the dosage.*

The ciprofloxacin dosing in study #113 was equivalent to that used by Bayer in the pivotal study it conducted to secure the severe nosocomial pneumonia claim

It appears that a single pivotal study provided the basis for the approval of ciprofloxacin at a dose of 400mg TID for ‘severe nosocomial pneumonia’ (1). In this study however, there were two significant deviations from the labeled dosing regimen. Firstly, the protocol allowed investigators, at their discretion, to reduce the dose from 400 mg TID to 400 mg BID if the patient had a ‘sensitive organism’. The definition of such organisms is not provided in the literature report. However, 24% of ciprofloxacin patients received less than the TID regimen for parts or all of the dosing period. It can not be determined from the published report which patients received how much drug. Secondly, ciprofloxacin dosing was adjusted downward for reduced renal function. Although the frequency with which this happened can not be determined from the paper, it is stated that the mean baseline creatinine was slightly elevated at 1.28 mg/dL and that BUN elevations occurred in 24% of the ciprofloxacin patients during the study. The package insert for IV ciprofloxacin calls for dose reductions to 200-400 mg q18-24 hours with creatinine clearances below 30 mL/min. It is likely that a substantial number of the patients in this study had reductions in their doses.

Medical Officer's Comment: *The MO has no comment with regards to the rationale for the development of a higher dosage form for ciprofloxacin. The MO acknowledges however, that there was the ability to decrease the dosage of ciprofloxacin in the previously cited study. This decrease to 400 mg IV bid was investigator-driven as well as dependent upon susceptibility reporting.*

These factors are significant because they did not occur in the trovafloxacin #113 study, resulting in effectively higher doses of ciprofloxacin. There was no reduction of ciprofloxacin dose for ‘sensitive’ organisms. Also, because blinding in the trovafloxacin studies included the pharmacy so that there was no one at the study site who knew the drug allocation (unlike the ciprofloxacin study), it would have been extremely difficult to dose adjust ciprofloxacin for renal function and still maintain blinding, especially given the additional antibiotics that were used in the ciprofloxacin arm. The median baseline creatinine in study #113 for the ciprofloxacin patients was 1.1 mg/dL, meaning that a substantial number were above the upper limit of normal even at baseline, but did not have dose reductions. Thus, the ‘effective’ ciprofloxacin dose used in the #113 study was greater than initially apparent, and probably equivalent, over all, to the dose used in the pivotal ciprofloxacin study.