

1.1.2 Eligibility Criteria

The following inclusion/exclusion criteria are reproduced from the applicant's submission.

Inclusion Criteria

1. Males and females age ≥ 18 at baseline.
2. Females of childbearing potential must have had a negative urine pregnancy test immediately prior to entry into the study, and were to have used adequate contraception during the study and for one month after the end of the study. Childbearing potential was defined as not surgically sterile and < 1 year post-menopausal.
3. A clinically documented infection of the skin or skin structure. The following were included:
 - a. infected ischemic ulcers
 - b. diabetic foot ulcers without underlying osteomyelitis
 - c. infected burns
 - d. major abscesses
 - e. other skin structure infections requiring significant surgical intervention along with antimicrobial therapy
 - f. infections of the deeper soft tissues, including post-operative surgical wound infections
4. Written informed consent

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Exclusion Criteria

1. Treatment with other antibiotics under the following conditions:
 - a. Treatment with any other systemic antibiotic for 24 hours or longer, within 72 hours prior to the baseline visit (unless there was documented evidence of clinical failure).
 - b. Treatment with a topical antibiotic within 24 hours prior to the baseline visit or during the study.
 - c. The need for treatment with an antibiotic other than the study drugs or treatment for longer than 14 days.
2. Necrotizing fasciitis, or infections of prosthetic material.
3. Infection of the skin or skin structure whose severity did not warrant initial intravenous therapy.
4. Significant gastrointestinal, or other condition that could affect study drug absorption.
5. Immunologic compromise (including neutropenia, ARCS/AIDS, non-skin cancers, or malignant melanoma).
6. History of epilepsy or seizures.
7. Evidence of current or recent drug or alcohol abuse/dependence that, in the opinion of the investigator, suggested an inability to complete the protocol requirements.

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Medical Officer Comment
 The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient ID No.	Treatment arm	Type of deviation	Analyses performed by applicant					
			Clinical			Bacteriological		
			ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
Inclusion criteria								
5880-0079	Zosyn to Vantin	Enrolled with osteomyelitis	N	N	NA	N	N	NA
5880-0157	Zosyn to Vantin	Enrolled with osteomyelitis	Y	Y	N	Y	Y	N
5881-0315	Zosyn to Vantin	Enrolled with osteomyelitis	Y	Y	Y	N	N	NA
5881-0372	Zosyn to Vantin	Enrolled with osteomyelitis	Y	Y	Y			
Exclusion criteria								
5606-0133	Alatrofloxacin to trovafloxacin	Received > 24 hr. of IV tx before enrollment	Y	N	NA	Y	N	NA
5881-0320	Zosyn to Vantin	History of seizure disorder	Y	N	NA	Y	N	NA
6025-0172	Zosyn to Vantin	History of seizure disorder	Y	N	NA	Y	N	NA

All three patients that were deemed clinically evaluable at EOT by the applicant were in the Zosyn to Vantin treatment group. Their clinical response assessment were "improved" (5880-0157), "cured" (5881-0315), and "failed" (5881-0372). There was no explanation provided by the applicant as to why they were included in the clinically evaluable analyses, however, it is not believed that the inclusion of these three patients in the analysis had a significant impact on the results.

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1.1.3 Study Drugs and Randomization Method

A double-dummy technique was utilized in order to maintain blinding. Alatrofloxacin (equivalent to 200 mg of trovafloxacin) was provided for intravenous administration in vials of 5 mg/ml (100 mg/20 ml) to be reconstituted to 1 mg/ml concentration with 5% dextrose in water (D5W), for a total of 20 mg in 200 - 250 ml. Intravenous Zosyn or matching placebo was provided in 3.375 gram vials, reconstituted with 15 ml of D5W and diluted with D5W to 200 ml total volume.

All concomitant therapies were to be noted in the case report form. In particular, the protocol prohibited the use of any other investigational drug within 4 weeks prior to the baseline visit. Furthermore, if an antibiotic was taken for a different infection, the subject was to have a final efficacy assessment. Mineral supplements, calcium- or magnesium-based antacids were allowed, but not within two hours of dosing. Systemic corticosteroids were allowed for subjects receiving chronic low doses of oral steroids (defined as 10 mg of prednisone/day or less).

A computer generated blinded randomization list was provided to the investigators by the applicant. The treatment groups were balanced in a ratio of 1:1.

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1.1.4 Study Endpoints

The study protocol indicated that the clinical success rates would be utilized in the efficacy analyses, and that the primary efficacy endpoint would be the clinical response at the end of therapy. Bacteriological response at the end of therapy, and clinical and bacteriological response at the end of the study were to be secondary endpoints. The clinical evaluation would be assessed by the investigator at Visits # 3 and 4, and classified as either a cure, improvement or failure, based on the overall assessment of the clinical presentation compared to baseline. Bacteriological response was to be evaluated by the applicant, at the end of therapy (either Day 11 or 15) and at the end of follow-up (Day 30).

Medical Officer Comment

Although both timepoints were analyzed by the applicant, and both will be discussed in this review, the Division felt that the most important timepoint for clinical assessment would be the End of Study visit. The rationale was that the End of Treatment visit tended to be only about a day or so after treatment had terminated, allowing for the possibility that there might still be some residual drug levels. This would not have been a concern at the End of Study visit.

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Clinical outcome definitions

Clinical outcomes at the end of treatment were defined as follows (adapted from Appendix B of the Study Protocol):

1. **Cure** - Resolution of signs and symptoms, including the presence of a culturable exudate, warmth, erythema, induration, tenderness, pain, swelling, discoloration, fever, diaphoresis, and leukocytosis.
2. **Improvement** - Incomplete resolution of the signs and symptoms as described above, and no requirement for additional antibiotic.
3. **Failure** - Lack of resolution of any of the signs and symptoms as described above, and the need for additional antibiotics.

Clinical outcomes at the end of the study were to be categorized as follows:

1. **Success** - Cure or improvement with no relapse at the end of the study.
2. **Failure** - Failure at the end of therapy, as previously defined.
3. **Relapse** - Cure or improvement at the end of therapy, but requiring additional antibiotic therapy for their primary disease prior to the end of the study.

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The applicant also defined conditions under which the assessment would be defined "failure," superseding the investigator's assessment:

1. If the investigator-defined clinical response was failure at any visit.
2. If a subject was given a concomitant antibiotic for insufficient clinical response during any of the following: active therapy plus one day, anytime before the assessment plus one day, during an assessment window for which a subject did not have an assessment.
3. If a subject lacked a post-baseline assessment (in the Intent-to-treat analysis only).
4. If a subject required surgical treatment as adjunct or follow-up therapy due to failure of the study medication.

Further, the applicant would make an assessment of "relapse" if either of the following conditions occurred:

1. The subject was a clinical cure or improvement at the end of treatment but was assessed as a failure by the investigator at a subsequent visit.
2. The subject was a clinical cure or improvement at the end of treatment but required additional antibiotic for the primary disease before the end of the study.

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Bacteriological outcome definitions

The defined categories for bacteriological responses were as follows (also reproduced from Appendix B of the Study Protocol):

1. **Eradication** - Elimination of the original causative organism(s) from the same site during or upon completion of therapy.
2. **Presumed eradication** - Absence of adequate culture material for evaluation because the subject is clinically *cured* or improved.
3. **Persistence** - Failure to eradicate the original causative organism at all post-baseline time points from sites previously cultured, regardless of whether signs of infection are present or not. Includes subjects given concomitant antibiotics for bacteriologic persistence at a prior time point.
4. **Relapse** - Reappearance of the original causative organism from the original site of infection *after* a post-baseline culture has been negative.
5. **Superinfection** - Development of a new skin or skin structure infection during the study that is due to a new or resistant pathogen which was not recognized as the original causative organism.
6. **Colonization** - Positive culture (exudate, swab, or aspirate) yielding a bacterial strain other than the primary causative isolate, and not associated with fever or other signs and symptoms of a complicated skin or skin structure infection.
7. **Presumed Persistence** - Use of concomitant antibiotic therapy due to continued clinical symptoms of the infection at study entry in the absence of microbiologic data. Includes subjects lost to follow-up who had a persistent pathogen at a prior evaluation.
8. **Indeterminate** - This designation was used if any of the following occur prior to the evaluation time point:
 - a. no baseline causative pathogen is isolated or was done more than 48 hours before the first dose of study medication.
 - b. relevant post-baseline cultures were not obtained (unless it was due to the absence of adequate culture material due to investigator determined clinical cure or improvement).
 - c. the subject was not considered to be clinically evaluable.

In addition, subjects would be excluded from the evaluable end of treatment and/or end of study analysis for any of the following reasons:

- a. Received less than 5 days of dosing - unless the subject had been considered a treatment failure.
- b. Inapplicable diagnosis (the patient did not meet entry criteria for a complicated skin or skin structure infection).
- c. The subject took an antibiotic for more than 24 hours within 72 hours of study initiation, without any evidence of clinical failure.
- d. The subject received concomitant systemic antibiotic for intercurrent illness.
- e. The subject had an intercurrent illness that confounded the efficacy evaluation.
- f. The subject missed a visit at the evaluation (unless the subject had previously been designated a treatment failure).

1.1.5 Termination and Follow-up

Visit # 3 constituted the visit at the end of treatment, at which time safety and efficacy evaluations were performed, and the investigator was to provide an evaluation of the clinical response. Patients were to be followed until Day 30 (Visit # 4), which was considered the end of the study. Safety and efficacy evaluations were again performed, and the investigator provided a final evaluation of clinical response. Any patient that had clinically significant laboratory abnormalities at Visit # 3 was to have them re-assessed at this time.

Medical Officer Comment

The number of patients that were lost to follow-up were minimal and comparable between the two treatment groups (1 in the alatrofloxacin/trovafloxacin arm, and 2 in the Zosyn™/Vantin™ arm).

1.1.6 Sample Size and Statistical Plan

The applicant determined 95% confidence intervals for the difference seen in the success rates between the two treatment arms. As indicated above, the applicant defined clinical success as cure or improvement. An analysis controlling for center effect was also done with the Cochran - Mantel-Haenzel test.

The definition of equivalence that was used required that the 95% confidence interval for the difference in response rates between two arms must be within 15% when the satisfactory response rate for the reference treatment is 80%. Their calculations for sample size indicated that in order to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy between the two arms not exceed 15%, then 112 subjects would need to be clinically evaluable, for it was assumed that the response rate of the reference drug was 80%. The applicant assumed that 10% of patients would be clinically non-evaluable, therefore, they would need to enroll at least 124 patients per treatment group.

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1.1.7 Study Results

1.1.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 287 patients were randomized to therapy - 145 to the alatrofloxacin/trovafloroxacin arm, and 142 to the Zosyn™/Vantin™ treatment group. One patient in the in alatrofloxacin/trovafloroxacin treatment group did not receive therapy. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

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Demographic characteristics of treated Subjects

	Alatrofloxacin 200 mg IV to Trovafloroxacin 200 mg PO			Zosyn 3.375 mg IV q 6 hr to Vantin 400 mg PO bid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	87	57	144*	85	57	142
Age (yr)						
16-44	30 (34%)	14 (25%)	44 (31%)	23 (27%)	16 (28%)	39 (27%)
45-64	32 (37%)	17 (30%)	49 (34%)	36 (42%)	29 (51%)	65 (46%)
>=65	25 (29%)	26 (46%)	51 (35%)	26 (31%)	12 (21%)	38 (27%)
Mean	52.4	57.6	54.5	54.9	54.7	54.8
Minimum						
Maximum						
Race						
White	64 (74%)	30 (53%)	94 (65%)	56 (66%)	38 (67%)	94 (66%)
Black	16 (18%)	22 (39%)	38 (26%)	20 (24%)	16 (28%)	36 (25%)
Hispanic	6 (7%)	4 (7%)	10 (7%)	6 (7%)	3 (5%)	9 (6%)
Asian	1 (1%)	1 (2%)	2 (1%)	1 (1%)	0	1 (<1%)
Arabian	0	0	0	1 (1%)	0	1 (<1%)
Samoan	0	0	0	1 (1%)	0	1 (<1%)

*Includes a patient randomized who did not receive therapy.

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In addition, the type of skin infections present at baseline are summarized in the table below (Table B from the applicant's Study Report):

Table B. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects				
	Alatrofloxacin ↓ Trovafoxacin (N=143)		Zosyn ↓ Vantin™ (N=140)	
Type of Infection^a	Number and Percentage (%) of Subjects			
Diabetic Foot Ulcer Without Osteomyelitis	23	(16%)	19	(14%)
Other Ischemic Ulcer	11	(8%)	14	(10%)
Infected Burn	0		2	(1%)
Major Abscess	22	(15%)	23	(16%)
Other Skin Structure Infection Requiring Significant Surgical Intervention	13	(9%)	19	(14%)
Cellulitis	6	(4%)	5	(4%)
Post-operative Surgical Wound Infection	0		1	(<1%)
Abscess	3	(2%)	5	(4%)
Ulcer	1	(<1%)	2	(1%)
Hydrantitis	0		1	(<1%)
Erysipelas	0		0	
Other ^b	3	(2%)	5	(4%)
Other Deep Soft Tissue Infections (e.g., Post-Operative Surgical Wound Infection)	89	(62%)	82	(59%)
Cellulitis	67	(49%)	61	(44%)
Post-operative Surgical Wound Infection	13	(9%)	12	(9%)
Abscess	1	(<1%)	1	(<1%)
Ulcer	1	(<1%)	0	
Hydrantitis	2	(1%)	1	(<1%)
Erysipelas	3	(2%)	2	(1%)
Other ^c	3	(2%)	5	(4%)
Subjects Requiring Surgical Drainage Procedure^d	90	(62%)	88	(62%)
At Baseline	61	(42%)	47	(33%)
Post-Baseline	44	(30%)	53	(37%)
Before the EOT Assessment	36	(25%)	44	(31%)
After the EOT Assessment	18	(12%)	21	(15%)
<p>EOT = End of Treatment</p> <p>^a A subject may have had more than one type of infection.</p> <p>^b Other types of skin structure infections requiring surgery pressure sores, flexor tenosynovitis, septic arthritis, necrotizing soft tissue infection, human bite, cat bite, right medial knee and bursae and embedded foreign object.</p> <p>^c Other types of deep soft tissue infections included cellulitis, post-operative surgical wound infections, abscesses, erysipelas, hydrantitis, and others [a gun shot wound, bursitis, infected stump, IV infection, traumatic injury, right pretibial hallux and posterior medial malleolus on right leg and infected laceration]. One subject (5881-0081) in the alatrofloxacin/trovafoxacin group had both bursitis (classified as "other") and cellulitis listed as a deep soft tissue infection; neither was designated as the primary infection.</p> <p>^d Subjects were counted in each timepoint that they had a surgical drainage procedure. Therefore, numbers do not add up to the total.</p> <p>Ref.: Tables 2.3 and 2.4 in the submission.</p>				

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Medical Officer Comment

The demographic characteristics, baseline diagnoses and baseline medical histories were comparable between the two treatment arms. There were 60 patients (42%) in the

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alatrofloxacin/trovafoxacin arm and 71 patients (50%) in the Zosyn/Vantin™ with diabetes. It is noted that patients with infected burns were not enrolled in the trovafoxacin arm in this study.

It is also noted that the term “cellulitis” is used as a diagnostic category. This term is usually not used to designate a serious infection, and the Point to Consider Document lists this as an example of an “uncomplicated infection.” However, review of the case report forms of all the patients that had cellulitis as sole diagnosis revealed that the vast majority had complicated infections, either because of the extent of the infection, or concurrent medical conditions. Therefore, it is believed that the diagnostic classification of “cellulitis,” although less than optimal, represented patients with medical conditions suitable for this study.

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1.1.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Alatrofloxacin 200 mg IV to Trovafoxacin 200 mg PO	Zosyn™ 3.375 mg IV q 6 hr to Vantin™ 400 mg PO bid
Number of randomized subjects	145	142
Randomized not treated	1	0
Number of treated subjects	144	142
Withdrawn from treatment	50 (35%)	29 (20%)
Withdrawn from study when treatment stopped	14 (10%)	7 (5%)
Withdrawn from treatment but completed study	36 (25%)	22 (15%)
Completed treatment	94 (65%)	113 (80%)
Withdrawn from study during follow-up	13 (9%)	7 (5%)
Completed treatment and study	81 (56%)	106 (75%)

Of the patients that were discontinued while on treatment, a total of 50 patients (35%) were discontinued from the alatrofloxacin/trovafoxacin arm, and 29 (20%) discontinued from the Zosyn™/ Vantin™ arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table D of the Summary Report):

	Alatrofloxacin 200 mg IV to Trovafoxacin 200 mg PO	Zosyn 3.375 mg IV q 6 hr to Vantin 400 mg PO bid
Number of Treated Subjects	144	142
Discontinued Subjects	50 (35%)	29 (20%)
Related to Study Drug	24 (17%)	12 (8%)
Adverse event	12 (8%)	4 (3%)
Insufficient response	11 (8%)	8 (6%)
Laboratory abnormality	1 (<1%)	0
Not Related to Study Drug	26 (18%)	17 (12%)
Adverse event	8 (6%)	2 (1%)
Does not meet randomization criteria	0	1 (<1%)
Laboratory abnormality	0	1 (<1%)
Lost to follow-up	1 (<1%)	2 (1%)
Other	14 (10%)	7 (5%)
Protocol violation	1 (<1%)	2 (1%)
Withdrawn consent	2 (1%)	2 (1%)
Completed treatment	94 (65%)	113 (80%)

The applicant indicated that the most common reason listed under “other” that led to study drug discontinuation was the presence of methicillin-resistant *S. aureus*.

Medical Officer Comment

It is noted that approximately 50% more patients were discontinued from the alatrofloxacin/ trovafloxacin treatment group compared to the Zosyn™/Vantin™. In addition, three times as many patients discontinued due to an adverse event. This will be addressed in more detail in the safety assessment section (Section 1.5).

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1.1.7.3 Primary Analyses

Utilizing the criteria identified above, in section 1.1.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

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1. Clinical

In the alatrofloxacin/trovafloxacin treatment arm, 145 patients were randomized. Two had inappropriate baseline diagnosis, and were not included in the intent-to-treat and evaluable analyses. Of the remaining 143 patients, 40 were not clinically evaluable.

In the Zosyn™/Vantin™ treatment arm, 142 patients were randomized. As in the other treatment arm, two had inappropriate baseline diagnosis, and were not included in the intent-to-treat and evaluable analyses. Of the remaining 140 patients, 17 were not clinically evaluable.

Reasons for exclusion included concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical response in the evaluable window, no post-baseline clinical assessment, prior antibiotic usage, and randomized but not treated. The most common reason was insufficient therapy.

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2. Bacteriological

Of the 143 clinical intent-to-treat patients in the alatrofloxacin/trovafloxacin arm, only 115 were included in the bacteriological intent-to-treat group, because 28 subjects had negative baseline cultures. It was noted that 23 of these were in the 103 clinically evaluable group, therefore, only 80 subjects were bacteriologically evaluable for purposes of the study.

In the Zosyn™/Vantin™ treatment arm, only 103 of the 140 clinical intent-to-treat were included in the bacteriological intent-to-treat group, because 37 had negative baseline culture. Thirty-four of these were in the 123 clinically evaluable group, therefore, only 89 were bacteriologically evaluable.

The following table summarizes the number of evaluable patients in each category for purposes of the primary analyses, for each treatment arm:

	Alatrofloxacin/ Trovafloxacin	Zosyn/ Vantin
Number Randomized	145	142
Not evaluable (inappropriate baseline diagnosis)	2 (1.3%)	2 (1.4%)
Treated and evaluable patients	143 (98.6%)	140 (98.6%)
Negative baseline cultures	28 (20%)	37 (26%)
Bacteriological Intent-to-Treat	115 (79%)	103 (73%)
Clinically Evaluable	103 (71%)	123 (87%)
Negative baseline cultures	23 (16%)	34 (24%)
Bacteriologically Evaluable	80 (55%)	89 (63%)

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Efficacy Results

The applicant performed several analyses comparing the results of the investigator-defined response rates and the applicant defined response rates. This was done for both timepoints - at the end-of-treatment and at the end-of-study visits. In addition, the patient subgroups analyzed included the clinically intent-to-treat, clinically evaluable, and bacteriologically evaluable patients.

1. Clinically evaluable

In the clinically evaluable group of subjects, the applicant-defined clinical success rates (cure and improvement) were as follows: In the alatrofloxacin/trovafoxacin arm, of the 103 in the clinically evaluable group, 99 were assessed at the end of treatment, with a success rate of 81%. In the Zosyn™/Vantin™ arm, of the 123 in the clinically evaluable group, 117 were assessed at the end of treatment, with a success rate of 85% [95% CI around the difference: (-14.0, 6.3)].

The applicant's analysis at the end-of-study timepoint reported the following: In the alatrofloxacin/trovafoxacin arm, of the 103 in the clinically evaluable group, 85 were assessed, with a success rate of 73%. In the Zosyn™/Vantin™ arm, of the 123 in the clinically evaluable group, 105 were assessed at the end of study, with a success rate of 77% [95% CI around the difference: (-16.6, 8.2)].

The following table, adapted from Table E in the applicant's submission, summarizes the clinical response rates for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafoxacin (N=103)		Zosyn ↓ Vantin™ (N=123)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	99	(100%)	117	(100%)	
Success (Cure + Improvement)	80	(81%)	99	(85%)	(-14.0%, 6.3%)
Distribution of Clinical Response:					
Cure	41	(41%)	41	(35%)	
Improvement	39	(39%)	58	(50%)	
Failure	19	(19%)	18	(15%)	
End of Study:					
Number of Subjects Assessed	85	(100%)	105	(100%)	
Success (Cure + Improvement)	62	(73%)	81	(77%)	(-16.6%, 8.2%)
Distribution of Clinical Response:					
Cure	55	(65%)	58	(55%)	
Improvement	7	(8%)	23	(22%)	
Failure	21	(25%)	18	(17%)	
Relapse	2	(2%)	6	(6%)	
CI=confidence interval Ref.: Table 5.1.1 in the submission.					

2. Clinical intent-to-treat

The clinically intent-to-treat group analysis yielded similar results: At the end of treatment, the alatrofloxacin/trovafoxacin arm had a 73% success rate in 134 subjects assessed out of a possible 143; the Zosyn™/Vantin™ arm, 80% success rate in 133 subjects assessed out of a possible 140. The 95% confidence interval around the difference was (-16.7, 3.6).

At the end of study the alatrofloxacin/trovafoxacin arm had a 71% success rate in 143 subjects assessed out of a possible 143; the Zosyn™/Vantin™ arm, 76% success rate in 140 subjects assessed out of a possible 140. The 95% confidence interval around the difference was (-15.7, 5.1).

Medical Officer Comment

The analysis of the clinically evaluable and clinically intent-to-treat patient groups supports the applicant's claim of equivalent efficacy compared to the combination of Zosyn™ and Vantin™.

It was also noted that the assessment of the clinical response differed between the applicant and the investigator for several patients, both at the end of treatment and at the end of study:

	Alatrofloxacin/ trovafoxacin	Zosyn™/ Vantin™
Number of disagreements		
At the end of treatment	1	3
At the end of study	19	26

In each of these cases, the applicant assigned a more conservative assessment - trending towards the more negative result.

3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Streptococcus agalactiae*. In the clinically evaluable subjects, the response rate was comparable between the treatment arms. The following table is reproduced from the Study Report (Table G):

Most frequently isolated baseline pathogens^a

Pathogen	Alatrofloxacin to Trovafoxacin (N=103)		Zosyn™ to Vantin™ (N=123)		Alatrofloxacin to Trovafoxacin (N=103)		Zosyn™ to Vantin™ (N=123)	
	Number of Subjects							
	End of Treatment				End of Study			
<i>S. aureus</i>	32/38 (84%)	31/37 (84%)	26/34 (76%)	26/33 (79%)				
<i>S. epidermidis</i>	8/10 (80%)	10/15 (67%)	6/8 (75%)	11/16 (69%)				
<i>Enterococcus faecalis</i>	9/11	9/13	7/10	7/11				
<i>S. Agalactiae</i>	7/11	6/7	4/9	7/8				

^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15 at least once for a given pathogen.
A subject could have had more than one pathogen isolated at baseline.
Ref.: Table 5.3.1

Medical Officer Comment

This study supports the use of alatrofloxacin, 200 mg intravenously, followed by oral trovafoxacin, 200 mg, for a total of 10-14 days of therapy for the treatment of complicated skin/skin structure infections due to the following organisms: *Staphylococcus aureus*, *Enterococcus faecalis*, and *Streptococcus agalactiae*.

The applicant had also listed *Staphylococcus epidermidis* as a baseline pathogen, however, review of the case report forms revealed that only three patients had pure cultures, and of

these, only one was bacteriologically evaluable. Therefore, it is believed that not enough patients with *Staphylococcus epidermidis* were studied in this trial to adequately assess the effectiveness of the therapeutic regimen against this potential pathogen.

1.1.7.4 Additional Analyses

The applicant also performed the following analyses:

1. Clinical response stratified by type of infection at baseline
2. Clinical response stratified by timing of surgical intervention
3. Presence and severity of clinical signs/symptoms at baseline, end-of-treatment, and end-of-study.

Medical Officer Comment

For the three analyses, the results were comparable between the treatment groups. Due to the limited number of patients with diabetic foot ulcers who ended up requiring amputation, it was not possible to make any definitive conclusions regarding any difference between the two treatment arms with respect to the study drug's ability to reduce the need for surgical amputations in this patient population.

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1.2 Study 154-132

Title: An open-label, non-comparative, multicenter trial on the use of oral trovafloxacin (CP-99,219) for the treatment of diabetic foot infections.

Study Dates

7 June 1995 - 16 May 1996

1.2.1 Study Design and Objectives

Open label, non-comparative, multicenter trial. All patients received trovafloxacin, orally, 200 mg/day in a single dose (2 x 100 mg tablets). The duration of treatment was 10 - 14 days.

The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 3-7)	(Day 11-16)	(Day 28-35)
Treatment period	Day 1 to Day 10 or Day 14			
Follow-up period			Day 11 or 15 to Day 35	
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Bone X-ray of infected area	x ²			
Microbiology				
exudate (or other specimen) culture & sensitivity	x	x	x	x ³
blood culture	x	x ⁴	abn	
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test ¹	x			
Adverse events				
routine events		x	x	x
serious adverse events		x	x	x
Investigator's evaluation of clinical response ⁵		x	x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing potential

² to be done if the skin and skin structure infection is proximal to bone to rule out contiguous osteomyelitis

³ to be done if clinically indicated

⁴ to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

⁵ to be done at time of discontinuation, if applicable

The objective of this study was to evaluate the safety and efficacy of trovafloxacin in the treatment of patients with diabetic foot infections, who required oral antibiotic therapy.

1.2.2 Eligibility Criteria

Inclusion Criteria

The inclusion criteria were the same as in Study 153-131, except for the explicit statement that culturable material (exudate, swab, or aspirate) was to be obtained.

Exclusion Criteria

The exclusion criteria were the same as in Study 154-131, except that the following exclusions were not specifically mentioned:

1. Necrotizing fasciitis, or infections of prosthetic material.
2. Significant gastrointestinal or other condition that could affect study drug absorption.
3. Evidence of current or recent drug or alcohol abuse/dependence that, in the opinion of the investigator, suggested an inability to complete the protocol requirements.

Medical Officer Comment

No deviations from inclusion criteria were reported.

The following protocol deviations from the exclusion criteria were reported :

Patient ID No.	Type of deviation	Analyses performed by applicant					
		Clinical			Bacteriological		
		ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
5177-0005	Enrolled with osteomyelitis	Y	Y	Y	Y	Y	Y
6053-0001	Enrolled with osteomyelitis	Y	Y	Y	N	N	NA
6536-0027	Had UTI at baseline; tx'd with Bactrim	Y	Y	Y	Y	Y	Y

All three patients were deemed clinically evaluable by the applicant. Their clinical response assessment at the end of treatment were "cure" (5177-0005), failure (6053-0001), and "improvement" (6536-0027). It is not believed that inclusion of these three patients in the clinically evaluable analysis had a significant impact on the results.

1.2.3 Study Drugs and Randomization Method

The trovafloxacin tablets were packaged in blister packs (28 tablets/pack), and the patients received a single daily dose of 200 mg (2 x 100 mg tablets).

This was a single arm, open label study, therefore there was no randomization. Patients were assigned a study number sequentially as they were determined to be eligible for the study.

1.2.4 Study Endpoints

The primary efficacy endpoint was applicant-defined clinical response at the end of treatment visit. This assessment was based primarily on the overall evaluation made by the investigator. Secondary efficacy endpoints were: pathogen eradication (at the end of treatment visit, and end of study visit), and investigator defined clinical response (at the end of treatment visit, and at the end of study visit).

The definitions for the clinical response and bacteriological response classification were the same as for Study 153-131, as were the definitions for establishing whether a subject was evaluable.

Medical Officer Comment

As with Study 154-131, the timepoint for clinical assessment preferred by the Division was End of Study.

1.2.5 Termination and Follow-up

If the patient discontinued prior to the prescribed end of treatment, a final evaluation was to be performed. If the discontinuation was due to clinical failure, then the final clinical and microbiological evaluations were to be performed. If the discontinuation was due to adverse events, then appropriate therapeutic measures would be taken and the patient would be followed through Visit 4 (Day 30), with performance of all clinical and microbiological evaluations.

1.2.6 Sample Size and Statistical Plan

Since this is a single arm, open-label trial, sample size calculations were not performed by the applicant. Descriptive statistics were used in the analysis of the study's results. The applicant performed subgroup analyses based on the presence or absence of surgical interventions.

1.2.7 Study Results

1.2.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 225 patients were treated. The demographic features of the treatment group are summarized in the table below:

	Trovafloracin 200 mg PO daily		
	Male	Female	Total
Number of Subjects	116	109	225
Age (yr)			
16-44	12 (10%)	7 (6%)	19 (8%)
45-64	46 (40%)	52 (48%)	98 (44%)
>=65	58 (50%)	50 (46%)	108 (48%)
Mean	62.1	62.1	62.1
Minimum	-	-	-
Maximum	-	-	-
Race			
White	80 (69%)	53 (49%)	133 (59%)
Hispanic	26 (22%)	49 (45%)	75 (33%)
Black	10 (9%)	7 (6%)	17 (8%)

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The type of skin infections present at baseline in the clinical intent-to-treat group are summarized in the table below (Table B from the applicant's Study Report);

Table B. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects	
	Trovafloracin 200 mg (N=224)
Type of Infection^a	Number and Percentage (%) of Subjects
Cellulitis with a Baseline Pathogen	48 (21%)
Cellulitis without a Baseline Pathogen	13 (6%)
Foot Ulcer	183 (82%)
Other	21 (9%)
Subjects Requiring Surgical Interyention^b	111 (49%)
At Baseline	98 (43%)
Post-Baseline ^c	73 (32%)
Before the EOT Assessment	65 (29%)
After the EOT Assessment	48 (21%)

EOT = End of Treatment
a A subject may have had more than one type of infection.
b Two of these subjects (Subjects 5190-0007 and 5842-0008) required surgical intervention, which occurred either outside of the end of study window (Subject 5842-0008; excision of the toe nail) or the surgical procedure and timing of the procedure was not specified on the case report form (Subject 5190-0007).
c Sixty-two (62) subjects required surgical intervention both prior to and post-baseline (57 subjects had surgical drainage at baseline and before the end of treatment, and 43 subjects had surgical drainage at baseline and after the end of treatment). In addition, two subjects (Subjects 6027-0007 and 6447-0001) had surgical drainage procedures performed post-baseline both before and after the end of treatment.
Ref.: Tables 2.3 and 2.4 in the submission.

1.2.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

Trovafloracin 200 mg PO	
Number of randomized subjects	225
Randomized not treated	0
Number of treated subjects	225
Withdrawn from treatment	15 (7%)
Withdrawn from study when treatment stopped	7 (3%)
Withdrawn from treatment but completed study	8 (4%)
Completed treatment	210 (93%)
Withdrawn from study during follow-up	1 (< 1%)
Completed treatment and study	209 (93%)

The reasons for discontinuation from treatment for the 15 patients are summarized in the following table, (adapted from the applicant's submission; Table C of the Summary Report):

Trovafloracin 200 mg PO

Number of Treated Subjects

225

Discontinued Subjects
Related to Study Drug

15 (6.6%)
10 (4.4%)
3 (1.3%)
7 (3.1%)

Adverse event
Insufficient response

5 (2.2%)

Not Related to Study Drug

1 (<1%)

Lost to follow-up

4 (2%)

Withdrawn consent

210 (93%)

Completed treatment

1.2.7.3 Primary Analyses
Utilizing the criteria described in section 1.2.4 Study Endpoints, the number of patients that were excluded from evaluation were as follows:

1. Clinical

Of the 225 subjects enrolled, 1 had an inappropriate baseline diagnosis, and was excluded from all intent-to-treat and evaluable analyses. Of the remaining 224 subjects, 10 were not clinically evaluable. The most common reasons for exclusions were no post-baseline clinical assessment, no post-baseline clinical response in evaluable window, insufficient therapy, prior antibiotic therapy, and concomitant antibiotic therapy.

2. Bacteriological

Of the 214 clinically evaluable group, 34 did not have a baseline pathogen identified, therefore, only 180 subjects were bacteriologically evaluable for purpose of the study.

The following table summarizes the number of evaluable patients in each category:

Number Randomized	225
Not evaluable (inappropriate baseline diagnosis)	1 (<1%)
Treated and Evaluable Patients	224 (99%)
Negative baseline cultures	34 (15%)
Bacteriological Intent-to-Treat	190 (84%)
Clinical Evaluable	214 (95%)
No baseline pathogen	34 (15%)
Bacteriological Evaluable	180 (80%)

Efficacy Result

The primary endpoint was clinical response at the end of treatment visit, however, the applicant also determined bacteriological response at the end of treatment, and clinical and bacteriological response rates at the end of study, on both, the evaluable and intent-to-treat populations.

1. Clinically evaluable

The following table, adapted from Table D in the applicant's Study Report, summarizes the response rates for the different categories for the clinically evaluable population.

Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits - Clinically Evaluable Subjects

	Trovafoxacin 200 mg (N=214)	
	Number and Percentage (%) of Subjects	
End of Treatment		
Number of Subjects Assessed	209	(100%)
Success (Cure + Improvement)	195	(93%)
Distribution of Clinical Response:		
Cure	93	(44%)
Improvement	102	(49%)
Failure	14	(7%)
End of Study		
Number of Subjects Assessed	206	(100%)
Success (Cure + Improvement)	179	(87%)
Distribution of Clinical Response:		
Cure	146	(71%)
Improvement	33	(16%)
Failure	16	(8%)
Relapse	11	(5%)

Ref.: Table 5.1.1 in the submission.

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2. Clinically Intent-to-treat

The clinically intent-to-treat group analysis had similar results - end of treatment success rate was 91%, and the end of study success rate was 85%.

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3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *S. aureus*, *S. epidermidis*, *E. faecalis*, and *S. haemolyticus*. The following table is reproduced from the Study Report (Table F):

Most frequently isolated baseline pathogens^a

Pathogen	Trovafoxacin 200 mg (N=180)		Trovafoxacin 200 mg (N=174)	
	Number of Subjects			
	End of Treatment		End of Study	
<i>S. aureus</i>	53/59	(90%)	48/60	(80%)
<i>S. epidermidis</i>	27/27	(100%)	25/27	(93%)
<i>E. faecalis</i>	27/32	(84%)	23/32	(72%)
<i>S. haemolyticus</i>	16/16	(100%)	13/15	(87%)
<i>P. aeruginosa</i>	11/14		8/16	(50%)
<i>Corynebacterium sp.</i>	10/10		11/12	
<i>P. mirabilis</i>	10/11		10/11	
<i>E. coli</i>	11/14		11/14	
<i>Staphylococcus sp.</i>	7/7		6/7	
<i>S. simulans</i>	6/6		6/6	
<i>S. hominis</i>	6/6		5/6	
<i>Streptococcus sp.</i>	11/11		10/10	
<i>S. agalactiae</i>	12/13		12/13	
<i>Peptostreptococcus sp.</i>	4/6		4/6	
<i>Peptostreptococcus magnus</i>	2/5		2/5	

^a ≥10 isolates of a given pathogen at either timepoint and ≥5 isolates of any *staphylococcus* and *streptococcus* species; percents displayed only when denominator is ≥15.

A subject could have had more than one pathogen isolated at baseline.

Ref.: Table 5.3.1 in the submission.

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Medical Officer Comment

Although uncontrolled and unblinded, this study is supportive of the findings of Study 154-131 with respect to the following organisms: *Staphylococcus aureus*, and *Enterococcus faecalis*. It is noted that although there were only thirteen (13) patients with *Streptococcus agalactiae*, efficacy was demonstrated. Therefore, although this study could not stand alone as demonstrating efficacy against *S. agalactiae*, it is supportive of Study 153-131. In addition, some of the efficacy data suggest that Trovan may be effective against *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Escherichia coli*.

Review of the case report forms indicates that of the cases identified as having *Staphylococcus epidermidis* (*S. epidermidis*), there were only six (6) patients with *S. epidermidis* as the sole isolate, and of these, only four (4) were bacteriologically evaluable. Due to the fact that *S. epidermidis* is a known component of skin flora, and a common contaminant, this study did not include enough patients where *S. epidermidis* was the sole pathogen to be able to determine the efficacy of this therapeutic regimen against this potential pathogen.

1.2.7.4 Additional Analyses

The sponsor also performed the following analyses:

1. Clinical response stratified by type of infection at baseline.
2. Clinical response stratified by timing of surgical intervention.

Medical Officer Comment

For the first analysis, there was no difference within category (type of infection) between the end of treatment analysis and the end of study analysis. For the second analysis, there was no difference between the two categories 9 those requiring surgical intervention at baseline and those not requiring surgery. This lack of difference was seen at the end of treatment as well as at the end of study evaluations.

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1.3 Study 154-139

Title: A randomized, multicenter, open trial comparing oral trovafloxacin (CP-99,219) (200 mg) and Augmentin™ for the treatment of complicated infections of the skin and skin structure.

Study Dates

23 September 1995 - 10 June 1996

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1.3.1 Study Design and Objectives

Randomized, comparative, multicenter open trial. The duration of treatment was 10-14 days. The treatment groups were:

1. Trovafloxacin, 200 mg/day, as a single active dose (2 x 100 mg tablets)
2. Augmentin™, 1500 mg/day, in three equally divided doses of 500 mg

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The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	EDT + 1d	Day 30
Allowable window	(~48 hours)	(Day 3-7)	(Day 11-15)	(Day 28-35)
Treatment period	Day 1 to Day 10 or Day 14			Day 11 or 15 to Day 35
Follow-up period				
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Microbiology				
exudate (or other specimen) culture & sensitivity	x	x	x	x ²
blood culture	x	x ³	abn	
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test ¹	x			
Investigator's assessment of clinical response ⁴			x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing 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 at time of discontinuation, if applicable

The objective of this study was to compare the safety and efficacy of trovafloxacin to Augmentin™ in the treatment of complicated infections of the skin and skin structures.

1.3.2 Eligibility Criteria**Inclusion Criteria**

The inclusion criteria were the same as in Study 154-131.

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Exclusion Criteria

The exclusion criteria were the same as in Study 154-131, except that the following were specifically not mentioned:

1. Significant gastrointestinal, or other condition that could affect study drug absorption.
2. Evidence of current or recent drug or alcohol abuse/dependence that, in the opinion of the investigator, suggested an inability to complete the protocol requirements.

Medical Officer Comment

The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient No.	ID	Treatment arm	Type of deviation	Analyses performed by applicant					
				Clinical			Bacteriological		
				ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
Inclusion criteria				N	N	NA	N	N	NA
6134-0019		Trovafloxacin	Enrolled with osteomyelitis						
Exclusion criteria				Y	Y	N	Y	Y	N
6243-0058		Trovafloxacin	Received >24 hrs of systemic antibiotics before baseline visit and received concomitant prednisone						
6009-0214		Augmentin	Received concomitant antibiotics	Y	Y	N	Y	Y	N
6296-0399		Augmentin	Received concomitant antibiotics	Y	Y	Y	Y	Y	Y
6296-0346		Augmentin	Received concomitant antibiotics and received concomitant prednisone	Y	Y	Y	N	N	NA
6296-0488		Trovafloxacin	Received concomitant antibiotics and received enzymatic chemical debridement	Y	Y	Y	Y	Y	Y
6009-0213		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
6240-0261		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
6240-0262		Trovafloxacin	Received topical antibiotics	Y	Y	N	Y	Y	N
6297-0349		Augmentin	Received topical antibiotics	Y	Y	Y	N	N	NA
6296-0400		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
6296-0486		Augmentin	Received topical antibiotics	Y	Y	Y	N	N	NA
6011-0193		Trovafloxacin	Received enzymatic chemical debridement	Y	Y	N	Y	Y	N
6296-0399		Augmentin	Received enzymatic chemical debridement	Y	Y	Y	Y	Y	Y
5294-0030		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6300-0380		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6370-0130		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6456-0387		Trovafloxacin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6577-0429		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6417-0439		Trovafloxacin	Previously enrolled in the study as another subject	Y	Y	Y	Y	Y	Y

After review of the case report forms, it was felt by the reviewer that most of the protocol violations did not have a significant impact on the study results. It was noted that there it appears that Subject #6417-0439 was deemed evaluable twice (as subject #6417-0416). However, it was felt that the inclusion of this subject twice in the analyses would not significantly alter the overall result of the study.

1.3.3 Study Drugs and Randomization Method

Subjects were given enough for 14 total course of treatment of one of the following:

Trovafloracin, 200 mg as a single daily dose (2 x 100 mg tablets)

Augmentin™, 1500 mg daily, in three divided doses of 500 mg

A masked randomization list was provided to the investigators by the applicant, consisting of a list of numbers to which the study drugs have been assigned. The investigator assigned study numbers sequentially to patients as it was determined that they were eligible for the study.

1.3.4 Study Endpoints

As with the other studies for this indication, the applicant indicated that the primary efficacy endpoint would be clinical response at the end of therapy. Bacteriological response at the end of therapy, and clinical and bacteriological response at the end of the study would be secondary endpoints. The clinical evaluation would be assessed by the investigator at Visits # 3 (Day 11 or 15) and 4 (Day 30), and classified as either a cure, improvement or failure, based on the overall assessment of the clinical presentation compared to baseline. Bacteriological response was to be evaluated by the applicant, at the end of therapy (either Day 11 or 15) and at the end of follow-up (Day 30).

The definitions for the clinical response and bacteriological response classification were similar as for Study 153-131, except for the following exceptions:

1. Concomitant antibiotic use for treatment of an intercurrent illness would classify a subject as *indeterminate*, and preclude the evaluation of a bacteriological response.
2. The category "Eradication with Reinfection" was included in the bacteriological definitions.

The definitions for establishing whether a subject was evaluable were comparable to those used in Study 154-131, except for the following additional conditions also made a subject non-evaluable:

1. No clinical signs or symptoms recorded at baseline.
2. Patient entered into study more than once.

Medical Officer Comment

As with the other two studies, the timepoint preferred by the Division for clinical assessment was the End of Study visit.

1.3.5 Termination and Follow-up

If the patient discontinued prior to the prescribed end of treatment, a final evaluation was to be performed. If the discontinuation was due to clinical failure, then the final clinical and microbiological evaluations were to be performed. If the discontinuation was due to adverse events, then appropriate therapeutic measures would be taken and the patient would be followed through Visit 4 (Day 30), with performance of all clinical and microbiological evaluations.

1.3.6 Sample Size and Statistical Plan

The definition of equivalence that was used required that the 95% confidence interval for the difference in response rates between two arms must be within 10% when the satisfactory response rate for the reference treatment is 90%. Their calculations for sample size indicated that in order to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy between the two arms not exceed 10%, then 142 subjects would need to be clinically evaluable, for it was assumed that the response rate of the reference drug was 90%. The

applicant also assumed that 10% of patients would be clinically non-evaluable, therefore, they would need to enroll at least 158 patients per treatment group.

The applicant also used the Cochran-Mantel-Haenzel test to control for center effect.

1.3.7 Study Results

1.3.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 323 patients were randomized to therapy - 166 to the trovafloxacin arm, and 157 to the Augmentin™ treatment group. Six patients in the in trovafloxacin treatment group did not receive therapy, 1 in the Augmentin™ group. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

Demographic characteristics of treated Subjects

	Trovafloxacin 200 mg PO			Augmentin™ 500 mg tid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	87	73	160	77	79	156
Age (yr)						
16-44	37 (43%)	18 (25%)	55 (34%)	34 (44%)	18 (23%)	52 (33%)
45-64	29 (33%)	14 (19%)	43 (27%)	24 (31%)	23 (29%)	47 (30%)
>=65	21 (24%)	41 (56%)	62 (39%)	19 (25%)	38 (48%)	57 (37%)
Mean	49.7	61.8	55.2	49.6	58.6	54.2
Minimum						
Maximum						
Race						
White	82 (94%)	72 (99%)	154 (96%)	75 (97%)	71 (90%)	146 (94%)
Black	0	1 (<1%)	1 (<1%)	1 (<1%)	6 (8%)	7 (4%)
Hispanic	3 (3%)	0	3 (2%)	1 (<1%)	1 (<1%)	2 (1%)
Asian	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Polynesian	1 (<1%)	0	1 (<1%)	0	0	0

In addition, the type of skin infections present at baseline are summarized in the table below (adapted from Table B from the applicant's Study Report):

Table B. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects				
	Trovafloxacin 200 mg (N=165)		Augmentin™ 500 mg tid (N=156)	
Type of Infection^a	Number and Percentage (%) of Subjects			
Diabetic Foot Ulcer Without Osteomyelitis	24	(15%)	26	(17%)
Other Ischemic Ulcer	36	(22%)	38	(24%)
Infected Burn	8	(5%)	7	(4%)
Major Abscess	26	(16%)	26	(17%)
Other Skin Structure Infection Requiring Surgery	9	(5%)	5	(3%)
Ulcer	1	(<1%)	1	(<1%)
Cysts	3	(2%)	0	
Hydrantitis	1	(<1%)	1	(<1%)
Post-Operative Surgical Wound Infection	1	(<1%)	0	
Other ^b	3	(2%)	3	(2%)
Other Deep Soft Tissue Infections (e.g., Post-Operative Surgical Wound Infection)	62	(38%)	55	(35%)
Abscess	0		1	(<1%)
Ulcer	3	(2%)	4	(3%)
Cellulitis	17	(11%)	13	(8%)
Erysipelas	2	(1%)	2	(1%)
Hydrantitis	1	(<1%)	1	(<1%)
Post-operative Surgical Wound Infection	16	(10%)	16	(10%)
Cysts	1	(<1%)	1	(<1%)
Other ^c	21	(13%)	17	(11%)
Subjects Requiring Surgical Drainage Procedure^d	39	(24%)	37	(24%)
At Baseline	33	(20%)	30	(19%)
Post-Baseline	16	(10%)	16	(10%)
Before the EOT Assessment	12	(7%)	12	(8%)
After the EOT Assessment	8	(5%)	10	(6%)

EOT = End of Treatment

^a A subject may have had more than one type of infection.

^b Other types of skin structure infections requiring surgery included a laceration, infected hematoma, pimple, abrasion, toe infection, and whitlow.

^c Other types of deep soft tissue infections included chronic infections, pyogenic granule, wound infections, sequelae [sic] of osteomyelitis, chronic edema, paronychia, furuncle, fistula, bursitis, eczema, infected insect bites, vasculitis, impetiginous lesion, thrombophlebitis, whitlow, pyoderma, and blister infected dermatitis.

^d Subjects were counted in each timepoint that they had a surgical drainage procedure. Therefore, numbers do not add up to the total.

Ref.: Tables 2.3 and 2.4.

Medical Officer Comment

The demographic characteristics, baseline diagnoses, and baseline medical histories were comparable between the two treatment arms. There were 40 (25%) patients in the trovafloxacin arm, and 33 (21%) patients in the Augmentin™ arm with diabetes mellitus. Peripheral vascular disease was slightly more prominent, with 47 (29%) patients in the trovafloxacin arm and 48 (31%) in the Augmentin™ arm reporting this condition.

1.3.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Trovafloracin 200 mg PO	Augmentin™ 500 mg tid
Number of randomized subjects	166	157
Randomized not treated	6	1
Number of treated subjects	160	156
Withdrawn from treatment	15 (9%)	23 (15%)
Withdrawn from study when treatment stopped	7 (4%)	9 (6%)
Withdrawn from treatment but completed study	8 (5%)	14 (9%)
Completed treatment	145 (91%)	133 (85%)
Withdrawn from study during follow-up	3 (2%)	1 (< 1%)
Completed treatment and study	142 (89%)	132 (85%)

Of the patients that were discontinued while on treatment, a total of 15 patients (9%) were discontinued from the trovafloxacin arm, and 23 (15%) discontinued from the Augmentin™ arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table C of the Summary Report):

	Trovafloracin 200 mg po	Augmentin™ 500 mg tid
Number of Treated Subjects	160	156
Discontinued Subjects	15 (9%)	23 (15%)
Related to Study Drug	5 (3%)	14 (9%)
Adverse event	4 (3%)	13 (8%)
Insufficient response	1 (< 1%)	1 (< 1%)
Not Related to Study Drug	10 (6%)	9 (6%)
Adverse event	4 (3%)	3 (2%)
Does not meet randomization criteria	1 (< 1%)	0
Other	4 (3%)	5 (3%)
Protocol violation	1 (< 1%)	0
Withdrawn consent	0	1 (< 1%)
Completed treatment	145 (91%)	133 (85%)

Medical Officer Comment

The number of patients that discontinued due to an adverse event related to the study drug was greater in the Augmentin™ treatment arm. This will be further addressed in more detail in the safety assessment section (Section 1.5).

1.3.7.3 Primary Analyses

Utilizing the criteria identified above in the section 1.3.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

1. Clinical

In the trovafloxacin treatment arm, 166 patients were randomized but only 160 were treated. One (1) had incorrect administration of study drug, therefore, only 165 were including in the clinical intent-to-treat group. Of these, ten (10) were not clinically evaluable leaving only 155 clinically evaluable.

In the Augmentin™ treatment arm, 157 were randomized, but only 156 were treated, One patient had incorrect administration of study drug, leaving only 155 in the clinical intent-to-treat group. The applicant indicates that of the treated patients, 10 were not evaluable, therefore 146 patients constitutes the clinically evaluable group for this treatment arm.

2. Bacteriological

Of the 155 clinically evaluable group in the trovafloxacin arm, 32 patients were excluding from the bacteriologically evaluable analyses due to the lack of a baseline culture. Therefore, the bacteriologically evaluable group consisted of 123 patients.

In the Augmentin™ treatment arm, 38 patients from the clinically evaluable group (N=146) lacked baseline culture information, therefore the bacteriologically evaluable group consisted of 108 patients.

Efficacy results

As was done in Study 154-131, the applicant performed several analyses comparing the results of the investigator-defined response rates for clinical success, with the applicant-defined clinical response rates. These were done for both timepoints - end of treatment as well as end of study. The outcomes for the for the clinically intent-to-treat group were also analyzed.

1. Clinically evaluable

In the clinically evaluable group of subjects, the applicant-defined clinical success rates (cure and improvement) were as follows: In the trovafloxacin arm, of the 155 in the clinically evaluable group, 154 were assessed at the end of treatment, with a success rate of 93%. In the Augmentin™ arm, of the 146 in the clinically evaluable group, 140 were assessed at the end of treatment, with a success rate of 93% [95% CI around the difference: (-5.9, 5.9)].

The applicant's analysis at the end-of-study timepoint reported the following: In the trovafloxacin arm, of the 155 in the clinically evaluable group, 139 were assessed, with a success rate of 86%. In the Augmentin™ arm, of the 146 in the clinically evaluable group, 141 were assessed at the end of study, with a success rate of 86% [95% CI around the difference: (-8.4, 8.0)].

The following table, adapted from Table D in the applicant's submission, summarizes the clinical response rate for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)					
	Trovafloxacin 200 mg q d (N=155)		Augmentin™ 500 mg tid (N=146)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	154	(100%)	140	(100%)	
Success (Cure + Improvement)	143	(93%)	130	(93%)	(-5.9, 5.9)
Distribution of Clinical Response:					
Cure	49	(32%)	45	(32%)	
Improvement	94	(61%)	85	(61%)	
Failure	11	(7%)	10	(7%)	
End of Study:					
Number of Subjects Assessed	139	(100%)	141	(100%)	
Success (Cure + Improvement)	119	(86%)	121	(86%)	(-8.4, 8.0)
Distribution of Clinical Response:					
Cure	86	(62%)	81	(57%)	
Improvement	33	(24%)	40	(28%)	
Failure	11	(8%)	11	(8%)	
Relapse	9	(6%)	9	(6%)	
CI=confidence interval Ref.: Table 5.1.1 in the submission.					

2. *Clinical intent-to-treat*

The clinical intent-to-treat group analysis also showed equivalence between the two treatment groups. At the end of treatment, the trovafloxacin arm had a 88% success rate in 164 subjects assessed out of a possible 165; the Augmentin™ arm, 90% success rate in 149 subjects assessed out of a possible 156. The 95% confidence interval around the difference was (-9.1, 4.8).

At the end of study the trovafloxacin arm had a 82% success rate in 165 subjects assessed out of a possible 165; the Augmentin™ arm, 84% success rate in 156 subjects assessed out of a possible 156. The 95% confidence interval around the difference was (-9.7, 6.6).

Medical Officer Comment

The assessment of the clinical response differed between the applicant and the investigator for several patients at the end of study. There were 11 patients in the trovafloxacin group and 10 patients in the Augmentin™ group. In each of these cases, the applicant assigned a more conservative assessment.

The 95% confidence interval around the difference supported the applicant's claim of equivalence.

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3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Proteus mirabilis*. In the clinically evaluable subjects, the response rates were comparable between the two arms, although it was noted that trovafloxacin tended to do a little better than Augmentin™ against *Pseudomonas aeruginosa*, but a little worse than Augmentin™ against *Enterococcus faecalis*. The following table is reproduced from the Study Report (Table F):

Most frequently isolated baseline pathogens^a

Pathogen	Trovafloxacin 200 mg (N=155)	Augmentin 500 mg TID (N=146)	Trovafloxacin 200 mg (N=155)	Augmentin 500 mg TID (N=146)
	Number of Subjects			
	End of Treatment		End of Study	
<i>S. aureus</i>	56/59 (95%)	52/58 (90%)	48/54 (89%)	48/56 (86%)
<i>P. aeruginosa</i>	21/21 (100%)	14/15 (93%)	18/20 (90%)	12/15 (80%)
<i>E. faecalis</i>	15/16 (94%)	11/11 (100%)	13/14 (93%)	13/13 (100%)
<i>P. mirabilis</i>	14/15 (93%)	5/5 (100%)	12/13 (92%)	6/6 (100%)
<i>S. epidermidis</i>	6/8	8/10	4/6	8/10
<i>E. coli</i>	8/9	5/5	7/9	5/5
<i>K. oxytoca</i>	7/7	5/5	5/6	5/5
<i>Staphylococcus sp.</i>	4/5	4/4	3/4	4/4
<i>S. haemolyticus</i>	0/1	1/1	0/1	1/1
<i>S. hominis</i>	1/1	3/3	1/1	3/3
<i>S. saprophyticus</i>	0/0	1/1	0/0	1/1
Coagulase Negative <i>Staphylococcus</i>	0/0	1/1	0/0	1/1
<i>Streptococcus sp.</i>	0/1	2/4	0/1	2/4
Anaerobic <i>Streptococcus</i>	1/1	0/0	1/1	0/0
<i>S. agalactiae</i>	7/8	5/5	5/8	4/5
<i>S. anginosus</i>	1/1	0/0	1/1	0/0
<i>S. equisimilis</i>	5/5	3/3	2/2	3/3
<i>S. oralis</i>	1/1	0/0	1/1	0/0
<i>S. pyogenes</i>	4/4	6/6	2/2	6/6
Group A Beta <i>streptococcus</i>	0/0	2/2	0/0	2/2
Group B Beta <i>streptococcus</i>	0/0	1/1	0/0	0/1
Group G Beta <i>streptococcus</i>	4/4	0/0	1/2	0/0
Beta hemolytic <i>streptococcus</i>	0/0	1/1	0/0	1/1
<i>Peptostreptococcus sp.</i>	0/0	2/2	0/0	2/2
<i>P. prevotti</i>	0/1	2/2	0/1	2/2
<i>P. magnus</i>	0/0	2/2	0/0	2/2

a ≥5 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15 at least once for a given pathogen in either treatment group. A subject could have had more than one pathogen isolated at baseline.
Ref.: Table 5.3.1

Similar results were noted among clinical intent-to-treat subjects.

Medical Officer Comment

This study is supportive of the applicant's claim for treatment of complicated infections due to the following organisms: *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. Although the study did not have many patients with *Streptococcus agalactiae*, the clinical response observed in this study was consistent with the other two studies, and therefore, supportive. In addition, this study was also supportive of trovafloxacin's efficacy against *Escherichia coli*.

This study reported 8 patients with *Staphylococcus epidermidis* as the baseline pathogen in the trovafloxacin treatment group, but as with the other studies, there was a paucity of bacteriologically evaluable patients with pure *S. epidermidis* cultures. Therefore, this

study was not able to support the applicant's claim of efficacy against this potential pathogen.

1.3.7.4 Additional Analyses

The applicant also performed the following analyses:

1. Clinical response stratified by type of infection at baseline.
2. Clinical response stratified by timing of surgical intervention.
3. Presence and severity of clinical signs/symptoms at baseline, end-of-treatment, and end-of-study.

Medical Officer Comment

The results were comparable for the three analyses between the two arms.

1.4 Efficacy Summary

The applicant provided data from three studies to support their claim of efficacy in the treatment of complicated skin and skin structure infections, including diabetic foot infections. The pivotal study was 154-131, a multi-center, randomized, double-blind study using Zosyn™, followed by Vantin™, as the comparator treatment. The other studies were supportive, with 154-132 being an open-labeled, uncontrolled study in diabetic patients, and 154-139 being a multi-center, randomized, open-labeled, controlled study using Augmentin™ as the comparator.

The following summarizes the observations made regarding the three studies:

- 1) The combination of alatrovafloxacin/trovafloxacin demonstrated similar efficacy to the combination of Zosyn™ and Vantin™. This equivalence was seen at the end of study, as well as at the end of treatment visits.
- 2) The alatrovafloxacin/trovafloxacin treatment combination appears to have more toxicity associated with it than the comparator arm. The more common side effects particular to this treatment group were dizziness and injection site complications. This will be expanded upon in the safety section (see below).
- 3) Based on the number of patients studied in the three studies, the applicant was able to support the claim of efficacy against the following pathogens: *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, and *Proteus mirabilis*.

1.5 Safety Assessment

1.5.1 Integrated Safety Assessment

It is acknowledged that the patient population between the three studies were not exactly alike. However, it is believed that they were similar enough in demographic characteristics, baseline diagnoses, and disease severity that it may be possible to evaluate the safety profile for the three studies simultaneously.

1.5.2 Extent of Drug Exposure

The applicant reported the following amounts of subject-day exposures.

	Study 154-131	Study 154-132	Study 154-139
	Alatrofloxacin to Trovafoxacin (200 mg q d)	Zosyn™ (3.375 mg IV) to Vantin™ (400 mg bid)	Trovafoxacin (200 mg q d)
Subject-days of exposure	1445	1622	2882
			Trovafoxacin (200 mg q d)
			Augmentin™ (500 mg tid)
			1978
			1914

1.5.3 Adverse Events

As noted above, there were some minor differences in the patient populations between the three studies, however it is believed that it would be useful to compare the three studies simultaneously.

1.5.3.1 All causalities

The following table summarizes the total number of adverse events (all causality) reported for the three studies:

Number of subjects ...	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafoxacin	Zosyn™/ Vantin™	Trovafoxacin	Trovafoxacin	Augmentin™
who were treated	144	142	225	160	156
with at least 1 AE*	101 (70%)	98 (69%)	74 (33%)	54 (34%)	53 (34%)
with serious AE's	22 (15%)	24 (17%)	10 (4%)	9 (6%)	5 (3%)
with severe AE's	21 (15%)	18 (13%)	4 (2%)	9 (6%)	5 (3%)
who discontinued due to AE's	29 (20%)	8 (6%)	8 (4%)	9 (6%)	16 (10%)
with dose reductions/ temp. discontinuation due to AE's	4 (3%)	3 (2%)	1 (<1%)	3 (2%)	5 (3%)
who discontinued due to objective test findings	3 (2%)	2 (1%)	0	0	0

*AE - Adverse event

There were no patients in any study who had a dose reduction or temporary discontinuation due to objective test findings.

Adapted from Table 6.1 of the applicant's submission

Medical Officer Comments

The oral studies (154-132 and 154-139) were comparable in the number of serious and severe adverse events observed, and in the number of discontinuations due to adverse events. Study 154-131, which had an intravenous administration component, had a higher incidence of in almost all categories. It is noted that the increased incidence was comparable in both arms of 154-131, except for the number of discontinuations due to adverse events, which was disproportionately higher in the trovafloxacin treatment arm. The types of adverse events reported by body system are enumerated further on in this review.

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The type of adverse event, by WHO term classification are summarized in the following table, adapted from the respective "All-Causalities Adverse Events" tables from the Study Reports:

Most Commonly Reported Adverse Events by Body System - All Causalities

	Study 154-131 a,b,c,d		Study 154-132 b, d, e		Study 154-139 b, d, f	
	Alatrofloxacin/ Trovafoxacin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafoxacin (N=225)	Trovafoxacin (N= 160)	Augmentin™ (N=156)	
No. of subjects with at least one adverse event	101 (70%)	98 (69%)	74 (33%)	54 (34%)	53 (34%)	
Body System (WHO Terminology)						
APPL./INJ./INCISION/ INSERTION SITE	17 (12%)	8 (6%)	--	--	--	--
-Appl./inj./Incision/Insertion Site Reaction	11 (8%)	1 (<1%)	--	--	--	--
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	29 (20%)	26 (18%)	26 (12%)	19 (12%)	4 (3%)	
Headache	17 (12%)	15 (11%)	5 (2%)	5 (3%)	2 (1%)	
Dizziness	--	--	20 (9%)	12 (8%)	1 (<1%)	
GASTROINTESTINAL SYSTEM	49 (34%)	48 (34%)	25 (11%)	19 (12%)	35 (22%)	
Constipation	22 (15%)	7 (5%)	--	5 (3%)	1 (<1%)	
Diarrhea	7 (5%)	17 (12%)	--	2 (1%)	23 (15%)	
Nausea	20 (14%)	23 (16%)	9 (4%)	5 (3%)	9 (6%)	
Vomiting	10 (7%)	11 (8%)	--	3 (2%)	4 (3%)	
Dyspepsia	--	--	5 (2%)	--	--	
Abdominal pain	--	--	--	3 (2%)	8 (5%)	
GENERAL	27 (19%)	26 (18%)	14 (6%)			
Infection (aggravated)	9 (6%)	2 (1%)	--	9 (6%)	6 (4%)	
Fever	--	--	5 (2%)	4 (3%)	0	
PSYCHIATRIC	15 (10%)	10 (7%)	--	--	--	
Insomnia	4 (3%)	8 (6%)	--	--	--	
REPRODUCTIVE SYSTEM	3 (2%)	8 (6%)	--	--	--	
Vaginitis °	3 (5%)	6 (11%)	--	--	--	
SKIN/APPENDAGES	24 (17%)	15 (11%)	14 (6%)	--	--	
Pruritus	7 (5%)	6 (4%)	4 (2%)	--	--	

- ^a ≥5 % of subjects in either treatment group.
- ^b Includes data up to 7 days after last dose of active study medication.
- ^c Term is gender specific, and the percentages are based on the number of females.
- ^d Ref.: Tables 6.2 and 6.4 in the submission
- ^e ≥2 % of subjects
- ^f ≥3 % of subjects in either treatment group.

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Medical Officer Comment

Although the number of subjects that experienced at least one adverse event in Study 154-131 was comparable between the two arms, it is noted that a disproportionate number of trovafoxacin patients had insertion site adverse events. This is despite the fact that Zosyn was a thrice daily intravenous administration, and trovafoxacin was only once daily. The other notable observation is that a disproportionate number of trovafoxacin patients in Study 154-139 complained of dizziness. This particular adverse event was also noted in Study 154-132, but its incidence was not as high in Study 154-131. It is hypothesized that the patients in Study 154-131 were more likely to be hospitalized, and that this particular adverse event was not as prominent - perhaps because they were not as ambulatory as the patients in the other studies.

1.5.3.2 Treatment related

The treatment related adverse events reported are summarized in the table below:

Most Commonly Reported Adverse Events by Body System - Treatment Related

No. of subjects with at least one adverse event Body System (WHO Terminology)	Study 154-131 a,b,c,d		Study 154-132 b, d, e		Study 154-139 b, d, e		
	Alatrofloxacin/ Trovafoxacin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafoxacin (N=225)	Trovafoxacin (N=160)	Trovafoxacin (N=160)	Augmentin™ (N=156)	
APPL./INJ./INCISION/ INSERTION SITE	39 (27%)	37 (26%)	37 (16%)	25 (16%)	36 (23%)		
APPL./Inj./Incision/Insertion Site Pain	9 (6%)	4 (3%)	--	--	--		
APPL./Inj./Incision/Insertion Site Reaction	4 (3%)	2 (1%)	--	--	--		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	7 (5%)	0	22 (10%)	14 (9%)	1 (<1%)		
Headache	11 (8%)	8 (6%)	5 (2%)	4 (3%)	0		
Dizziness	8 (6%)	7 (5%)	18 (8%)	8 (5%)	1 (<1%)		
GASTROINTESTINAL SYSTEM	4 (3%)	1 (<1%)	16 (7%)	11 (7%)	31 (20%)		
Constipation	15 (10%)	19 (13%)	--	3 (2%)	0		
Diarrhea	--	--	--	1 (<1%)	22 (14%)		
Nausea	5 (3%)	12 (8%)	6 (3%)	4 (3%)	7 (4%)		
Vomiting	8 (6%)	5 (4%)	--	2 (1%)	4 (3%)		
Abdominal pain	--	--	--	2 (1%)	8 (5%)		
REPRODUCTIVE SYSTEM	3 (2%)	4 (3%)	--	--	--		
Vaginitis ^e	3 (5%)	4 (7%)	--	--	--		

- ^a ≥3 % of subjects in either treatment group.
- ^b Includes data up to 7 days after last dose of active study medication.
- ^c Term is gender specific, and the percentages are based on the number of females.
- ^d Ref.: Tables 6.3 and 6.5 in the submission
- ^e ≥2 % of subjects

Medical Officer Comment

Several of the adverse events noted in the previous table have dropped out, as one would expect, however, the overall impressions regarding the intravenous administration in Study 154-131 and the dizziness in the oral studies are unchanged. It is also noted that dizziness was still reported in Study 154-131, but the incidence was much lower.

1.5.3.3 Serious adverse events

The number of serious adverse events per study are summarized in the table below:

No. of subjects with serious adverse events No. of subjects with serious adverse events - treatment related	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafoxacin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafoxacin (N=225)	Trovafoxacin (N=160)	Augmentin™ (N=156)
	30 (21%)	39 (27%)	17 (8%)	12 (8%)	7 (4%)
	3 (2%)	1 (<1%)	0	0	0

Medical Officer Comment

This summary is supportive of the observations made in the previous two tables - a higher incidence and a greater severity of adverse events were reported in Study 154-131. It is noted, however, that the investigators felt that most of the serious adverse events were not study drug related.

1.5.3.4 Discontinuation from studies

1.5.3.4.1 Discontinuation due to adverse events

The number of patients that discontinued due to adverse events are summarized below:

	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafloracin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafloracin (N=225)	Trovafloracin (N= 160)	Augmentin™ (N=156)
No. of subjects discontinued due to adverse events	29 (20%)	8 (6%)	8 (4%)	9 (6%)	16 (10%)
No. of subjects discontinued due to adverse events - treatment related	13 (9%)	3 (2%)	3 (1%)	4 (3%)	13 (8%)
Temporary discontinuations	5 (3%)	3 (2%)	1 (<1%)	3 (2%)	5 (3%)

Medical Officer Comment

In Study 154-131, the most common treatment related adverse event that resulted in discontinuation in the trovafloracin group were insertion site pain/reaction, dizziness, flushing/hot flushes, headache, and nausea.

1.5.3.4.2 Discontinuation due to laboratory abnormalities

The following table summarizes the incidence of significant laboratory abnormalities, with special emphasis on liver enzymes, creatinine, and hemoglobin.

	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafloracin (N=137)	Zosyn™/ Vantin™ (N=139)	Trovafloracin (N=221)	Trovafloracin (N= 158)	Augmentin™ (N=149)
No. of subjects with clinically significant lab. abnormalities	61 (45%)	63 (45%)	66 (30%)	50 (32%)	48 (32%)
Liver enzyme abnormalities	14 (10%)	12 (9%)	6 (3%)	3 (2%)	1 (<1%)
Creatinine abnormalities	5 (4%)	4 (3%)	5 (2%)	1 (<1%)	1 (<1%)
Decrease in hemoglobin	12 (9%)	11 (8%)	5 (2%)	3 (2%)	3 (2%)
No. of subjects discontinued due to lab. abnormalities	1 (<1%)	1 (<1%)	0	0	0

Medical Officer Comment

The number of subjects in each of the treatment groups has changed because the applicant corrected these totals for baseline laboratory abnormalities. The laboratory abnormalities were slightly higher in the intravenous study, but they were comparable between the treatment arms.

1.5.3.5 Mortality experience

There were a total of 11 deaths in Study 143-131, and two (2) in each in the other two studies. The following table summarizes their distribution among the treatment arms.

	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafoxacin	Zosyn™/ Vantin™	Trovafoxacin	Trovafoxacin	Augmentin™ M
Within 30 days of last dose of study drug	2	2	0	1	1
After 30 days of last dose of study drug	3	4	2	0	0

Medical Officer Comment

All case report forms of the patients that died were reviewed; this reviewer agrees that none of the deaths could be attributed to the study drug.