

The percentage of subjects discontinued from treatment due to treatment-related adverse events was 6% in the trovafloxacin group and 2% in the flucloxacillin group. The overall percentage of adverse events was 22% in the trovafloxacin group and 20% in the flucloxacillin group; treatment-related adverse events were reported in 9% and 13% of subjects, respectively. The most commonly reported treatment-related adverse events in the trovafloxacin group were dizziness, headache, and vomiting. The most commonly reported treatment-related adverse events in the flucloxacillin group were dyspepsia and nausea.

Reviewer's Summary and Conclusion: *Trovafloxacin 100 mg once daily for 7 days demonstrated therapeutic equivalence to flucloxacillin 500 mg every six hours for 7 days for clinical success rates at both EOT and EOS. Of note, although the numbers are small, trovafloxacin did not appear very effective against leg ulcers (only 1/8 = 13% patients was considered a clinical success at EOS).*

A significantly higher proportion of trovafloxacin patients discontinued treatment due to an adverse event (12/140 = 9% trovafloxacin patients versus 3/138 = 2% flucloxacillin patients; $p = 0.03$ using Fisher's exact test). Higher proportions of flucloxacillin patients experienced dyspepsia and urinary tract infections; the difference in dyspepsia rates was statistically significant (< 1% trovafloxacin patients vs. 5% flucloxacillin patients; $p = 0.04$ using Fisher's exact test), the difference in urinary tract infection rates was marginally statistically significant (0% trovafloxacin vs. 3% flucloxacillin; $p = 0.06$ using Fisher's exact test).

VI.B. Protocol 154-130

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND ORAL CEFPODOXIME PROXETIL (VANTIN™) (400 MG BID) FOR THE TREATMENT OF UNCOMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE

Study Dates: 1 June 1995 - 18 April 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to that of cefpodoxime proxetil (Vantin™) in the treatment of subjects with uncomplicated infections of the skin and skin structure.

Study Design: Study 154-130 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily) administered orally for 7 to 10 days versus cefpodoxime proxetil (Vantin™) (400 mg bid) administered orally for 7 to 10 days for the treatment of uncomplicated infections of the skin and skin structure.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 18 years of age at the baseline visit, with clinically documented uncomplicated skin and skin structure infections were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical of infection) and bacteriological response (based on eradication of causative organisms isolated from culture specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8 or 11) and at the end of study (Visit 4; Day 30), or at the time of discontinuation from the study. A clinical evaluation to determine the length of treatment (7 or 10 days) was to be conducted at Visit 2 (Day 4). Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection such as disappearance or diminution in culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, or swelling, and improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of all signs and symptoms of uncomplicated skin and skin structure infection), improvement (incomplete resolution of signs and symptoms of uncomplicated skin and skin structure infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of uncomplicated skin and skin structure infection and a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), Visit 3 (Day 8 or 11) and at Visit 4 (Day 30), or at the time of discontinuation from the study. Subject bacteriological response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence or relapse; however, the protocol was amended to not include the analysis of subject bacteriological response. Instead, each pathogen was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection or colonization.

The primary efficacy endpoint was sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS.
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

***Reviewer's Note:** Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.*

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 6b.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

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Table 6b.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg daily)	Vantin (400 mg BID)
Entered Study ^a	221	225
All Treated	221 (100%)	225 (100%)
Completed Treatment	205 (93%)	205 (91%)
Completed Study	212 (96%)	204 (91%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	221 (100%)	225 (100%)
Clinically Evaluable ^b	211 (95%)	208 (92%)
Bacteriological Intent-to-Treat	176 (80%)	175 (78%)
Bacteriologically Evaluable ^b	167 (76%)	162 (72%)
Assessed for Safety		
Adverse Events	221 (100%)	225 (100%)
Laboratory Tests	210 (95%)	208 (92%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Of the 221 trovafloxacin and 225 Vantin clinical ITT subjects, 10 subjects in the trovafloxacin group and 17 subjects in the Vantin group were not clinically evaluable; therefore, 211 trovafloxacin and 208 Vantin subjects were clinically evaluable. The most common reason for exclusion from the clinically evaluable efficacy analyses was insufficient therapy (6/221 [3%], trovafloxacin and 13/225 [6%], Vantin). Other reasons were prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment and no post-baseline clinical assessment within the evaluable window.

Of the 221 trovafloxacin and 225 Vantin clinical ITT subjects, 45 subjects in the trovafloxacin group and 50 subjects in the Vantin group had negative baseline cultures; therefore, 176 trovafloxacin and 175 Vantin subjects were included in the bacteriological ITT analyses.

Of the 211 trovafloxacin and 208 Vantin clinically evaluable subjects, 44 subjects in the trovafloxacin group and 46 subjects in the Vantin group were not included in the bacteriologically evaluable analyses; therefore, 167 trovafloxacin subjects and 162 Vantin subjects were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (43/221 [19%], trovafloxacin and 46/225 [20%], Vantin). The other reason was no post-baseline culture.

Discontinuations

Of the 221 trovafloxacin and 225 Vantin treated subjects, 16 trovafloxacin and 20 Vantin subjects were prematurely discontinued from treatment as summarized in Table 6b.2.

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Table 6b.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)

	Trovafloracin 100 mg (N=221)	Vantin 400 mg BID (N=225)
	Number and Percentage (%) of Subjects	
Total Discontinued	16 (7%)	20 (9%)
Discontinuations Related to Study Drug:	10 (5%)	8 (4%)
Adverse Event	6 (3%)	6 (3%)
Insufficient Response	4 (2%)	2 (<1%)
Discontinuations Unrelated to Study Drug:	6 (3%)	12 (5%)
Adverse Event	0	4 (2%)
Lost to Follow-up	0	5 (2%)
Other	3 (1%)	1 (<1%)
Patient Died	0	1 (<1%)
Protocol Violation	1 (<1%)	0
Withdrew Consent	2 (<1%)	1 (<1%)

Demographics

One hundred twenty-seven (127) of the 221 treated trovafloxacin subjects (57%) were males and 94 were females (43%) and 118 of the 225 treated Vantin subjects (52%) were males and 107 were females (48%). The males and females in the trovafloxacin and Vantin treatment groups were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects. The mean age of subjects in the trovafloxacin and Vantin groups was 46.9 years and 45.6 years, respectively. Twenty-one percent of subjects in the trovafloxacin group and 17% of subjects in the Vantin group were ≥ 65 years of age.

The primary diagnosis for clinical ITT subjects was uncomplicated skin and skin structure infection. The median duration since onset of infection was 6.0 days for subjects in both treatment groups. Eleven subjects in each treatment group had a duration since onset of infection of ≥ 50 days. The maximum duration since onset of infection was 135 days (Subject 5643-0321) for subjects in the trovafloxacin group and 190 days (Subject 5643-0326) for subjects in the Vantin group.

The most commonly reported type of infection reported among clinical ITT subjects in the trovafloxacin group was minor wound infection (52/221 [24%], trovafloxacin and 37/225 [16%], Vantin), and the most commonly reported type of infection reported among clinical ITT subjects in the Vantin group was simple abscess (50/221 [23%], trovafloxacin and 56/225 [25%], Vantin). Of note, subjects may have had more than one type of infection at baseline. Other types of infections included impetiginous lesion, furuncle, cellulitis with and without a baseline pathogen and others (including infected paronychia, ulcers, insect bites, cysts, hydradenitis, erysipelas, pyoderma, folliculitis, carbuncle, dermatitis, surgical wounds, boils, complex abscesses and perirectal abscesses). All types of infections were reported at similar rates in both treatment groups. Similar results were observed for clinically evaluable subjects.

The majority of clinical ITT subjects in both treatment groups did not require a surgical drainage procedure at baseline or during the study. Fifty-four (54) trovafloxacin subjects (24%) and 68 Vantin subjects (30%) had skin infections that required surgical intervention at baseline and four trovafloxacin subjects (1%) and seven Vantin subjects (3%) had skin infection that required surgical intervention post-baseline. The most commonly reported type of skin infection for subjects requiring surgical intervention in both treatment groups was simple abscess (26/59 [44%], trovafloxacin and 39/72 [54%], Vantin).

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical ITT subjects in Table 6b.3.

	Trovafloxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
Type of Infection^a	Number and Percentage (%) of Subjects	
Simple Abscess	50 (23%)	56 (25%)
Impetiginous Lesion	15 (7%)	17 (8%)
Furuncle	22 (10%)	21 (9%)
Minor Wound Infection	52 (24%)	37 (16%)
Cellulitis with a Baseline Pathogen	32 (14%)	40 (18%)
Cellulitis without a Baseline Pathogen	25 (11%)	17 (8%)
Other	34 (15%)	52 (23%)
Subjects Requiring Surgical Intervention ^b	59 (26%)	72 (32%)
At Baseline	54 (24%)	68 (30%)
Post-Baseline ^c	4 (1%)	7 (3%)
Before the EOT Assessment	3 (1%)	6 (2%)
After the EOT Assessment	1 (<1%)	1 (<1%)
<p>a A subject may have had more than one type of infection.</p> <p>b Two subjects in the trovafloxacin group (Subjects 5531-0463 and 5606-0359) and two subjects in the Vantin group (Subjects 5531-0340 and 5553-0426) had a surgical procedures done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report forms.</p> <p>c One subject (5017-0377) in the trovafloxacin group and five subjects (5013-0443, 5125-0283, 5177-0438, 5553-0511, and 5816-0286) in the Vantin group had surgical drainage procedures performed both prior to and post-baseline.</p>		

Reviewer's Note: *There was some imbalance between treatment groups with regard to type of infection at baseline. More trovafloxacin patients had a diagnosis of minor wound infection (this difference was marginally significant; $p=0.06$ using the test of equal proportions based on the normal approximation to the binomial distribution), while fewer trovafloxacin patients had a diagnosis which fell under the "other" category (this difference was significant; $p=0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution).*

There were no marked differences between subjects in the trovafloxacin and Vantin groups with respect to medical history at baseline. The most common disease/syndrome reported at baseline for subjects in both treatment groups was diabetes mellitus (25/221 [11%], trovafloxacin; 40/225 [18%], Vantin).

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 6b.4. Trovafloxacin was considered therapeutically equivalent to Vantin at both EOT and EOS.

Table 6b.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 100 mg (N=211)	Vantin 400 mg BID (N=208)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment			
Number of Subjects Assessed	207 (100%)	207 (100%)	
Success (Cure + Improvement)	194 (94%)	192 (93%)	(-3.9, 5.8)
Distribution of Clinical Response:			
Cure	114 (55%)	100 (48%)	
Improvement	80 (39%)	92 (44%)	
Failure	13 (6%)	15 (7%)	
End of Study			
Number of Subjects Assessed	204 (100%)	194 (100%)	
Success (Cure + Improvement)	179 (88%)	168 (87%)	(-5.4, 7.7)
Distribution of Clinical Response:			
Cure	152 (75%)	137 (71%)	
Improvement	27 (13%)	31 (16%)	
Failure	13 (6%)	15 (8%)	
Relapse	12 (6%)	11 (6%)	

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 6b.5.

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Table 6b.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Trovafloracin 100 mg (N=211)	Vantin 400 mg BID (N=208)	Trovafloracin 100 mg (N=204)	Vantin 400 mg BID (N=194)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>St. aureus</i>	71/76 (93%)	59/64 (92%)	63/73 (86%)	53/60 (88%)
<i>St. epidermidis</i>	30/34 (88%)	27/29 (93%)	30/35 (86%)	24/27 (89%)
<i>P. aeruginosa</i>	15/15 (100%)	8/8	15/15 (100%)	7/8
<i>E. faecalis</i>	13/13	13/13	12/13	10/13
<i>E. coli</i>	5/5	10/11	5/5	10/11
<i>Staphylococcus sp.</i>	10/10	2/2	9/10	2/2
<i>St. haemolyticus</i>	10/10	10/11	10/10	9/10
<i>St. hominis</i>	4/5	4/4	3/5	4/4
<i>St. simulans</i>	1/1	5/5	1/1	4/5
Coagulase Negative <i>Staphylococcus</i>	0/0	2/2	0/0	1/1
<i>Streptococcus sp.</i>	6/6	6/7	3/4	5/7
<i>Str. agalactiae</i>	8/9	10/13	8/10	9/12
<i>Str. aginosus</i>	2/2	0/0	2/2	0/0
<i>Str. mitis</i>	1/1	0/0	1/1	0/0
<i>Str. pyogenes</i>	9/9	6/6	9/9	5/5
<i>Str. sanguis I</i>	0/0	1/1	0/0	1/1
<i>Str. sanguis II</i>	1/1	2/2	1/1	1/2
Group G Beta <i>Streptococcus</i>	2/2	1/1	2/2	1/1
Alpha haemolytic <i>Streptococcus</i>	0/0	1/1	0/0	1/1

St. = *staphylococcus*; *Str.* = *Streptococcus*
 a ≥10 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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When sponsor-defined clinical response was subset by type of baseline infection (simple abscess, impetiginous lesion, minor wound infection, cellulitis with and without a baseline pathogen, furuncle or other) in clinical ITT subjects, a trend towards a higher (≥10 percentage points) clinical success rate at EOT was observed among trovafloracin subjects with cellulitis and a baseline pathogen compared to Vantin subjects (trovafloracin: 31/32, 97%; Vantin: 34/40, 85%) and among trovafloracin subjects with furuncle compared to Vantin subjects (trovafloracin: 21/21, 100%; Vantin: 19/21, 90%). In addition, a trend towards a higher clinical success rate at EOS was observed among trovafloracin subjects with baseline infections classified as other compared with Vantin subjects (trovafloracin: 33/34, 97%; Vantin: 42/52, 81%).

Similar clinical success rates were observed between the two treatment groups among subjects with the other types of infection (simple abscess, impetiginous lesion, minor wound infection and cellulitis without a baseline pathogen) at both EOT and EOS, and similar clinical success rates were observed between the two treatment groups among subjects with cellulitis with a baseline pathogen and furuncle at EOS and subjects with other infections at EOT.

A summary of clinical success rates for clinical ITT subjects subset by type of infection at baseline at the end of treatment and at the end of study is presented by treatment group in Table 6b.6.

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Table 6b.6. Summary of Sponsor-Defined Clinical Success Rates Subset by Type of Baseline Infection (Clinical ITT Subjects)

	Trovafloracin 100 mg (N=221)		Vantin 400 mg BID (N=225)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection ^a	EOT		EOS	
Simple Abscess	46/49 (94%)	46/50 (92%)	50/56 (89%)	50/56 (89%)
Impetiginous Lesion	14/15 (93%)	12/15 (80%)	15/17 (88%)	12/17 (71%)
Minor Wound Infection	47/51 (92%)	45/52 (87%)	32/37 (86%)	32/37 (86%)
Cellulitis Without a Baseline Pathogen	20/25 (80%)	18/25 (72%)	14/17 (82%)	13/17 (76%)
Cellulitis With a Baseline Pathogen	31/32 (97%)	28/32 (88%)	34/40 (85%)	32/40 (80%)
Furuncle	21/21 (100%)	20/22 (91%)	19/21 (90%)	18/21 (86%)
Other ^b	32/33 (97%)	33/34 (97%)	45/51 (88%)	42/52 (81%)

a A subject may have had more than one type of infection at baseline.
 b Other infections included infected paronychia, ulcers, insect bites, cysts, hydradenitis, erysipelas, pyoderma, folliculitis, carbuncle, dermatitis, surgical wounds, boils and complex and perirectal abscesses

When sponsor-defined clinical response was subset by timing of surgical intervention in clinical ITT subjects, similar clinical success rates were observed between treatment groups at both EOT and EOS, for subjects with no surgical intervention and surgical intervention at baseline. Among subjects with surgical intervention before or after the end of treatment, subject subsets were too small for any definitive conclusions to be drawn.

A summary of clinical success rates for clinical ITT subjects subset by timing of surgical intervention at the end of treatment and at the end of study is presented by treatment group in Table 6b.7.

Table 6b.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)

	Trovafloracin 100 mg (N=221)		Vantin 400 mg BID (N=225)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention ^a	EOT ^b		EOS	
No Surgical Intervention	150/158 (95%)	143/162 (88%)	134/152 (88%)	125/153 (82%)
Surgical Intervention at Baseline	51/54 (94%)	50/54 (93%)	61/68 (90%)	61/68 (90%)
Surgical Intervention Post Baseline ^c				
Before the EOT Assessment	1/3 (33%)	1/3 (33%)	3/6 (50%)	3/6 (50%)
After the EOT Assessment	0/1	0/1	0/1	0/1

a Subjects may have had surgical intervention at more than one timepoint.
 b Four clinical intent-to-treat subjects in the trovafloracin group and one subject in the Vantin group were not assessed for clinical response at the end of treatment.
 c Two subjects in the trovafloracin group (Subjects 5531-0463 and 5606-0359) and two subjects in the Vantin group (Subjects 5531-0340 and 5553-0426) had a surgical procedures done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report forms.

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Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were similar between the two treatment groups for the most frequently isolated pathogens at the end of treatment and the end of study as presented in Table 6b.8.

Table 6b.8. A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Trovafoxacin 100 mg (N=167)	Vantin 400 mg BID (N=162)	95% CI	Trovafoxacin 100 mg (N=161)	Vantin 400 mg BID (N=149)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>St. aureus</i>	68/76 (89%)	52/64 (81%)	-3.6, 20.0	59/73 (81%)	50/60 (83%)	-15.6, 10.5
<i>St. epidermidis</i>	32/33 (97%)	25/29 (86%)	-3.1, 24.6	31/34 (91%)	24/26 (92%)	-15.1, 12.9
<i>P. aeruginosa</i>	9/15 (60%)	4/8	ND	12/15 (80%)	4/7	ND
<i>E. faecalis</i>	13/13	12/13	ND	11/13	11/13	ND
<i>E. coli</i>	5/5	9/11	ND	4/5	10/11	ND
<i>Staphylococcus</i> sp.	10/10	2/2	ND	9/9	2/2	ND
<i>St. haemolyticus</i>	10/10	11/11	ND	10/10	10/10	ND
<i>St. hominis</i>	4/5	4/4	ND	4/5	4/4	ND
<i>St. simulans</i>	1/1	5/5	ND	1/1	4/5	ND
Coagulase Negative <i>Staphylococcus</i>	0/0	2/2	ND	0/0	1/1	ND
<i>Streptococcus</i> sp.	6/6	7/7	ND	3/4	6/6	ND
<i>Str. agalactiae</i>	8/9	11/13	ND	8/10	10/12	ND
<i>Str. anginosus</i>	2/2	0/0	ND	2/2	0/0	ND
<i>Str. mitis</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. pyogenes</i>	9/9	6/6	ND	9/9	5/5	ND
<i>Str. sanguis I</i>	0/0	1/1	ND	0/0	1/1	ND
<i>Str. sanguis II</i>	1/1	2/2	ND	1/1	2/2	ND
Group G Beta <i>Streptococcus</i>	2/2	1/1	ND	2/2	1/1	ND
Alpha haemolytic <i>Streptococcus</i>	0/0	1/1	ND	0/0	1/1	ND

ND = not done; *St.* = *staphylococcus*; *Str.* = *Streptococcus*
^a ≥10 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events, and clinically significant laboratory values is presented in Table 6b.9. Tables 6b.10 and 6b.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

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Table 6b.9. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg daily (N= 221)	Vantin 400 mg BID (N= 225)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	71/221 (32%)	86/225 (38%)
Treatment-Related Adverse Events	38/221 (17%)	48/225 (21%)
Discontinuations from Treatment Due to an Adverse Event ^a	8/221 (4%)	11/225 (5%)
Clinically Significant Laboratory Values	28/210 (13%)	26/208 (13%)

a Six subjects in each treatment group were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.

Table 6b.10. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	71 (32%)	86 (38%)
BODY SYSTEM WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		
Dizziness	22 (10%)	23 (10%)
Headache	9 (4%)	6 (3%)
GASTROINTESTINAL SYSTEM		
Abdominal Pain	14 (6%)	15 (7%)
Diarrhea	22 (10%)	41 (18%)
Dyspepsia	5 (2%)	3 (1%)
Flatulence	10 (5%)	20 (9%)
Nausea	0 (0%)	4 (2%)
Vomiting	0 (0%)	5 (2%)
GENERAL		
Fatigue	7 (3%)	9 (4%)
OTHER		
Accidental Injury	3 (1%)	4 (2%)
SKIN/APPENDAGES		
Rash	11 (5%)	16 (7%)
	5 (2%)	4 (2%)
	5 (2%)	1 (<1%)
	4 (2%)	1 (<1%)
	13 (6%)	10 (4%)
	4 (2%)	2 (<1%)

a ≥2 % of subjects in any treatment group.
b Includes data up to 7 days after last dose of active study medication

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Reviewer's Note: A higher percentage of Vantin patients experienced gastrointestinal system adverse events (18% versus 10% for trovafloxacin; p=0.01 using the test of equal proportions based on the normal approximation to the binomial distribution).

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Table 6b.11. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)		
	Trovafloxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	38 (17%)	48 (21%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	15 (7%)	10 (4%)
Dizziness	7 (3%)	5 (2%)
Headache	9 (4%)	3 (1%)
GASTROINTESTINAL SYSTEM	14 (6%)	34 (15%)
Diarrhea	7 (3%)	18 (8%)
Flatulence	0 (0%)	4 (2%)
Nausea	5 (2%)	7 (3%)
a ≥2 % of subjects in any treatment group.		
b Includes data up to 7 days after last dose of active study medication.		

Five (5) subjects in the trovafloxacin group and 7 subjects in the Vantin group had serious adverse events that were considered by the investigator to be unrelated to study drug.

One subject in the Vantin group had a serious adverse event (migraine headache) that was considered to be related to study drug.

One subject in the Vantin group died from congestive heart failure and coronary artery disease on Day 7. This death was not considered to be related to study drug.

Sponsor Summary and Conclusion: Trovafloxacin 100 mg once daily for 7-10 days and cefpodoxime proxetil (Vantin) 400 mg twice daily for 7-10 days were statistically equivalent for clinical success rates at the end of treatment and the end of study for both intent-to-treat and evaluable subjects with uncomplicated skin and skin structure infection. Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and the end of study for the most frequently isolated pathogens of (*S. aureus* and *S. epidermidis*).

The percentage of subjects discontinued from treatment due to adverse events was 4% in the trovafloxacin group and 5% in the Vantin group. Six (6) subjects in the trovafloxacin group and six subjects in the Vantin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all and treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the Vantin group (32% and 17% versus 38% and 21% respectively). The most commonly reported treatment-related adverse events in the trovafloxacin group were dizziness (3%) and headache (4%), and diarrhea (3%). The most commonly reported treatment-related adverse events in the Vantin group were diarrhea (8%) and nausea (3%).

Reviewer's Summary and Conclusions: Trovafloxacin 100 mg once daily for 7-10 days and cefpodoxime proxetil (Vantin) 400 mg twice daily for 7-10 days were therapeutically equivalent in terms of clinical success rates at both EOT and EOS for evaluable subjects with uncomplicated skin and skin structure infections.

The most common adverse events reported in the trovafloxacin group were headache (6%), diarrhea (5%), and dizziness (4%). In the Vantin group, the most commonly reported adverse events were diarrhea (9%), headache (7%), and nausea (4%). A higher percentage of Vantin patients experienced gastrointestinal system adverse events (18% versus 10% for trovafloxacin; $p=0.01$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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VII. COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

The efficacy and safety of the IV-to-oral regimen in complicated skin infection was assessed in a double-blind, comparative trial versus IV piperacillin/tazobactam followed by oral cefpodoxime (154-131). The efficacy and safety of oral trovafloxacin in the treatment of complicated skin infections was assessed in one uncontrolled trial (diabetic foot; 154-132) and one open, comparative trial versus amoxicillin/clavulanate (154-139).

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the complicated skin infection trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, race, and age.*

VII.A. Protocol 154-131

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A RANDOMIZED, MULTICENTER, INVESTIGATOR/SUBJECT-BLIND (DOUBLE-BLIND) TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN AND INTRAVENOUS PIPERACILLIN SODIUM/TAZOBACTAM SODIUM (ZOSYN™) FOLLOWED BY ORAL CEFPODOXIME PROXETIL (VANTIN™) FOR THE TREATMENT OF COMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE.

Study Dates: 27 June 1995 - 28 May 1996

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Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin with intravenous piperacillin sodium/tazobactam sodium (Zosyn™) followed by oral cefpodoxime proxetil (Vantin™) in the treatment of subjects with complicated infections of the skin and skin structure requiring initial inpatient intravenous therapy.

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Study Design: Study 154-131 was a randomized, double-blind, double-dummy, comparative, multicenter trial of intravenous alatrofloxacin (200 mg) administered once daily for 2 to 7 days followed by oral trovafloxacin (200 mg) administered once daily to complete a maximum total treatment duration of 10 or 14 days versus intravenous Zosyn (3.375 g) administered four-times daily for 2 to 7 days followed by oral Vantin™ (400 mg) administered twice daily to complete a maximum total treatment duration of 10 or 14 days for the treatment of complicated infections of the skin and skin structure [e.g., infected ischemic ulcers including diabetic foot ulcers without underlying osteomyelitis, infected burns, major abscesses, other skin structure infections requiring significant surgical intervention along with antimicrobial therapy, and infections of the deeper soft tissues].

Diagnoses and Criteria for Inclusion of Subjects: Men or women ≥ 18 years of age at the baseline assessment, with clinically documented complicated infection of the skin or skin structure.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical signs and symptoms of infection) and bacteriologic response (based on eradication of causative organisms isolated from culture specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11 or 15) and at the end of study (Visit 4; Day 30), or at the time of discontinuation from the study. A clinical evaluation to determine the length of treatment (10 or 14 days) was to be conducted at Visit 2 (Day 4). Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection, such as resolution of fever, disappearance or diminution in culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, swelling or leukocytosis, and improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of the complicated skin or skin structure infection), improvement (incomplete resolution of signs and symptoms of complicated skin or skin structure infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of complicated skin or skin structure infection and a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), Visit 3 (EOT; Day 11 or 15) and at Visit 4 (EOS; Day 30), or at the time of discontinuation from the study. Subject bacteriological response was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence or relapse; however, the protocol was amended to not include the analysis of subject bacteriological response. Instead, each pathogen was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection or colonization, and pathogen eradication rates were to be examined.

The primary efficacy endpoint was sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS.
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

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Reviewer's Note: Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

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Analysis Groups

Table 7a.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 7a.1. Evaluation Groups

Evaluation Groups:	Alatrofloxacin (IV 200 mg/day) Trovafoxacin (200 mg/day)		Zosyn (IV 3.375g QID) Vantin™(400 mg BID)	
	Number and Percentage (%) of Subjects			
Randomized	145		142	
All Treated Subjects	144	(100%)	142	(100%)
Completed Treatment	94	(65%)	113	(80%)
Completed Study	117	(81%)	128	(90%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	143	(99%)	140	(99%)
Clinically Evaluable ^a	103	(71%)	123	(87%)
Bacteriological Intent-to-Treat	115	(79%)	103	(73%)
Bacteriologically Evaluable ^a	80	(55%)	89	(63%)
Assessed for Safety				
Adverse Events	144	(100%)	142	(100%)
Laboratory Tests	137	(95%)	139	(98%)

^a Based on End of Treatment assessment

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Reviewer's Note: A significantly lower proportion of alatrofloxacin/trovafoxacin patients completed treatment, completed the study, and were considered clinically evaluable ($p = 0.007, 0.03, \text{ and } 0.002$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution). Much of the difference in the percent of patients completing treatment can be accounted for by the significant difference in patients discontinuing treatment due to adverse events (regardless of relationship to study drug); 20 (14%) alatrofloxacin/trovafoxacin patients discontinued treatment due to an adverse event compared to 6 (4%) Zosyn/Vantin patients (see Table 7a.2), and this difference was highly statistically significant ($p = 0.004$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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Since a significantly lower proportion of alatrofloxacin/trovafoxacin patients were considered clinically evaluable, results will be presented below for the clinical intent-to-treat population, in addition to those given for the clinically evaluable population.

Of the 145 alatrofloxacin/trovafoxacin and 142 Zosyn/Vantin™ randomized subjects, one alatrofloxacin/trovafoxacin subject was randomized but not treated. Two alatrofloxacin/trovafoxacin subjects and two Zosyn/Vantin™ subjects had an inappropriate baseline diagnosis and were excluded from all intent-to-treat and evaluable analyses.

Of the 143 alatrofloxacin/trovafoxacin and 140 Zosyn/Vantin™ clinical ITT subjects, 40 in the alatrofloxacin/trovafoxacin group and 17 in the Zosyn/Vantin™ group were not clinically evaluable; therefore, 103 subjects in the alatrofloxacin/trovafoxacin group and 123 subjects in the Zosyn/Vantin™ group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy (20/145 [14%], alatrofloxacin/trovafoxacin and 11/142 [8%], Zosyn/Vantin™ subjects). Other reasons were concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical response in evaluable window, no post-baseline clinical assessment, prior antibiotic usage, and randomized, not treated.

Of the 143 alatrofloxacin/trovafoxacin and 140 Zosyn/Vantin™ clinical ITT subjects, 28 subjects in the alatrofloxacin/trovafoxacin group and 37 subjects in the Zosyn/Vantin™ group had negative baseline cultures; therefore, 115 subjects in the alatrofloxacin/trovafoxacin group and 103 subjects in the Zosyn/Vantin™ group were included in the bacteriological ITT analysis.

Of the 103 alatrofloxacin/trovafoxacin and 123 Zosyn/Vantin™ clinically evaluable subjects, 23 subjects in the alatrofloxacin/trovafoxacin group and 34 subjects in the Zosyn/Vantin™ group were not included in the bacteriologically evaluable analyses; therefore, 80 subjects in the alatrofloxacin/trovafoxacin group and 89 subjects in the Zosyn/Vantin™ group were bacteriologically evaluable. The more common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen 23/145 [16%], alatrofloxacin/trovafoxacin and 34/142 [24%], Zosyn/Vantin™. The other reason was 'baseline culture outside window'.

Discontinuations

Of the 144 alatrofloxacin/trovafoxacin and 142 Zosyn/Vantin™ treated subjects, 50 and 29 subjects, respectively, were prematurely discontinued from treatment as summarized in Table 7a.2.

Table 7a.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=144)		Zosyn ↓ Vantin™ (N=142)	
	Number and Percentage (%) of Subjects			
Total Discontinued	50	(35%)	29	(20%)
Discontinuations 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	
Discontinuations Unrelated to Study Drug:	26	(18%)	17	(12%)
Adverse Event	8	(6%)	2	(1%)
Did Not Meet Randomization Criteria	0		1	(<1%)
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-Up	1	(<1%)	2	(1%)
Other ^a	14	(10%)	7	(5%)
Protocol Violation	1	(<1%)	2	(1%)
Withdrawn Consent	2	(1%)	2	(1%)
a The most common "other" reason that led to discontinuation from treatment was the presence of methicillin-resistant <i>S. aureus</i> for subjects in the alatrofloxacin/trovafoxacin (4 subjects) and Zosyn/Vantin™ (3 subjects) groups.				

Demographics

Eighty-seven (87) of the 144 treated alatrofloxacin/trovafoxacin subjects (60%) were males and 57 were females (40%), and 85 of the 142 treated Zosyn/Vantin™ subjects (60%) were males and 57 were females (40%). The males and females in the alatrofloxacin/trovafoxacin

and Zosyn/Vantin™ treatment groups were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The mean age of subjects in the alatrofloxacin/trovafloxacin and Zosyn/Vantin™ groups was 54.5 years and 54.8 years, respectively. Thirty-five percent (35%) of subjects in the alatrofloxacin/trovafloxacin group and 27% of subjects in the Zosyn/Vantin™ group were ≥65 years of age.

The primary diagnosis for clinical intent-to-treat subjects was complicated skin and skin structure infection. The median duration since onset of infection was 6.0 days for subjects in both treatment groups. Similar durations since onset of infection were observed for clinically evaluable subjects in both treatment groups. There were no marked differences between all treated subjects in the alatrofloxacin/trovafloxacin and Zosyn/Vantin™ treatment groups with respect to medical history at baseline. Sixty (60) subjects (42%) in the alatrofloxacin/trovafloxacin group and 71 subjects (50%) in the Zosyn/Vantin™ group had diabetes mellitus and 40 alatrofloxacin/trovafloxacin subjects (28%) and 45 Zosyn/Vantin™ subjects (32%) had peripheral vascular disease at baseline.

All types of infections were reported at similar rates in both treatment groups. The most commonly reported type of skin infection for subjects in both treatment groups was other deep soft tissue infections (post-operative surgical wound infections) (89/143 [62%], alatrofloxacin/trovafloxacin; and 82/140 [59%], Zosyn/Vantin™). For subjects in both treatment groups, the most commonly reported type of deep soft tissue infection was cellulitis (67/143 [47%], alatrofloxacin/trovafloxacin; and 61/140 [44%], Zosyn/Vantin™). Other types of deep soft tissue infections included 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]).

The majority of clinical ITT subjects in both treatment groups (62%) required a surgical drainage procedure at baseline or during the study. Sixty-one (61) alatrofloxacin/trovafloxacin subjects (42%) and 47 Zosyn/Vantin™ subjects (33%) required surgical drainage at baseline, and 44 alatrofloxacin/trovafloxacin subjects (30%) and 53 Zosyn/Vantin™ subjects (37%) had surgical drainage done post-baseline.

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical ITT subjects in Table 7a.3.

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Table 7a.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT 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		
At Baseline	90 (62%)	88 (62%)
Post-Baseline		
Before the EOT Assessment	61 (42%)	47 (33%)
After the EOT Assessment	44 (30%)	53 (37%)
Before the EOT Assessment	36 (25%)	44 (31%)
After the EOT Assessment	18 (12%)	21 (15%)
<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>		

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Clinical Response

A summary of clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 7a.4. Alatrofloxacin/trovafloracin was considered therapeutically equivalent to Zosyn/Vantin at both EOT and EOS.

Table 7a.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloracin (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%)	

A summary of clinical response rates for clinically ITT subjects at the end of treatment and at the end of study is presented by treatment group in Table 7a.5. Alatrofloxacin/trovafloracin was considered therapeutically equivalent to Zosyn/Vantin at EOS, but not at EOT.

Reviewer's Note: EOS is considered the more important timepoint for consideration of efficacy by this reviewer, as stated above.

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Table 7a.5. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically ITT Subjects)					
	Trovafloracin ↓ Alatrofloxacin (N=143)		Zosyn ↓ Vantin™ (N=140)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	134	(100%)	133	(100%)	
Success (Cure + Improvement)	98	(73%)	106	(80%)	(-16.7%, 3.6%)
Distribution of Clinical Response:					
Cure	49	(37%)	45	(34%)	
Improvement	49	(37%)	61	(46%)	
Failure	36	(27%)	27	(20%)	
End of Study:					
Number of Subjects Assessed	143	(100%)	140	(100%)	
Success (Cure + Improvement)	102	(71%)	107	(76%)	(-15.3%, 5.1%)
Distribution of Clinical Response:					
Cure	83	(58%)	74	(53%)	
Improvement	19	(13%)	33	(24%)	
Failure	38	(27%)	27	(19%)	
Relapse	3	(2%)	6	(4%)	

A summary of clinical success rates at EOT and EOS for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 7a.6.

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Table 7a.6. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloracin (N=103)		Zosyn ↓ Vantin™ (N=123)		
	Number of Subjects				
Pathogen	End of Treatment		End of Study		
<i>St. aureus</i>	32/38	(84%)	31/37	(84%)	26/34 (76%) 26/33 (79%)
<i>St. 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>Str. agalactiae</i>	7/11		6/7		4/9 7/8

St. = *Staphylococcus*; *Str.* = *Streptococcus*
^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.

A summary of clinical success rates at EOT and EOS is presented by type of baseline infection and treatment group for clinical ITT subjects in Table 7a.7.

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Table 7a.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Type of Baseline Infection (Clinical ITT Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=143)		Zosyn ↓ Vantin™ (N=140)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection ^a	EOT		EOS	
Diabetic Foot Ulcer Without Osteomyelitis	13/21 (62%)	15/23 (65%)	9/17 (53%)	11/19 (58%)
Other Ischemic Ulcer	7/10 (70%)	8/11 (73%)	11/14 (79%)	11/14 (79%)
Infected Burn	0/0	0/0	1/2 (50%)	0/2
Major Abscess	16/19 (84%)	17/22 (77%)	19/22 (86%)	20/23 (87%)
Other Skin-Structure Infection Requiring Significant Surgical Intervention	8/13 (62%)	7/13 (54%)	14/19 (74%)	13/19 (68%)
Other Deep Soft Tissue Infections (Post-Operative Surgical Wound Infections)	63/84 (75%)	64/89 (72%)	68/77 (88%)	69/82 (84%)

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

A summary of clinical success rates at EOT and EOS is presented by timing of surgical intervention and treatment group for clinical ITT subjects in Table 7a.8.

Table 7a.8. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=143)		Zosyn ↓ Vantin™ (N=140)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention ^a	EOT		EOS	
No Surgical Intervention	42/51 (82%)	43/53 (81%)	46/50 (92%)	46/52 (88%)
Surgical Intervention at Baseline	37/56 (66%)	40/61 (66%)	31/43 (72%)	34/47 (72%)
Surgical Intervention Post Baseline				
Before the EOT Assessment	20/32 (63%)	21/36 (58%)	28/41 (68%)	28/44 (64%)
After the EOT Assessment	7/16 (44%)	7/18 (39%)	11/20 (55%)	8/21 (38%)

^a Subjects may have had surgical intervention at more than one timepoint.

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Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were similar between the two treatment groups for the most frequently isolated pathogens at the end of treatment and the end of study as presented in Table 7a.9.

Table 7a.9. A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=80)	Zosyn ↓ Vantin™ (N=89)	95% CI	Alatrofloxacin ↓ Trovafoxacin (N=65)	Zosyn ↓ Vantin™ (N=77)	95% CI
Number of Pathogens						
Pathogen	End of Treatment			End of Study		
<i>St. aureus</i>	32/39 (82%)	26/37 (70%)	-7.2%, 30.8%	25/31 (81%)	23/33 (70%)	-10.0%, 31.9%
<i>St. epidermidis</i>	9/10 (90%)	14/15 (93%)	ND	7/8 (88%)	13/15 (87%)	ND
<i>Enterococcus faecalis</i>	10/11	9/13	ND	7/10	8/11	ND
<i>Str. agalactiae</i>	6/11	6/7	ND	5/8	7/8	ND

St. = *Staphylococcus*; *Str* = *Streptococcus*
^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.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuations from treatment due to adverse events, and clinically significant laboratory values are presented in Table 7a.10. Tables 7a.11 and 7a.12 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: A significantly higher proportion of alatrofloxacin/trovafoxacin patients discontinued treatment due to an adverse event ($p=0.0003$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 7a.10. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Alatrofloxacin ↓ Trovafoxacin	Zosyn ↓ Vantin™
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	101/144 (70%)	98/142 (69%)
Treatment-Related Adverse Events	39/144 (27%)	37/142 (26%)
Discontinuations from Treatment Due to an Adverse Event ^a	29/144 (20%)	8/142 (6%)
Clinically Significant Laboratory Values	61/137 (45%)	63/139 (45%)

^a Twelve (12) subjects in the alatrofloxacin/trovafoxacin group and four subjects in the Zosyn/Vantin™ group were discontinued due to adverse events that were considered by the investigator to be study drug-related.

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Reviewer's Note: Alatrofloxacin/trovafloxacin patients experienced significantly more application/injection/incision/insertion site reaction and constipation than did Zosyn/Vantin patients (11/144=8% vs. 1/142 or <1%, p=0.005 using Fisher's exact test; and 22/144=15% vs. 7/142=5%, p=0.004 using the test of equal proportions based on the normal approximation to the binomial distribution, respectively). Zosyn/Vantin patients experienced significantly more diarrhea than did alatrofloxacin/trovafloxacin patients (17/142=12% vs. 7/144=5%, p=0.03 using the test of equal proportions based on the normal approximation to the binomial distribution). Of note, more alatrofloxacin/trovafloxacin patients experienced aggravated infection as an adverse event (this difference was marginally statistically significant: 9/144=6% vs. 2/142=1%, p=0.06 using Fisher's exact test).

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Table 7a.11. A Summary of the Most Commonly Reported Adverse Events ^{a, b} by Body System - All Causalities (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=144)		Zosyn ↓ Vantin™ (N=142)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	101	(70%)	98	(69%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE Appl./Inj./Incision/Insertion Site Reaction	17	(12%)	8	(6%)
	11	(8%)	1	(<1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	29	(20%)	26	(18%)
Headache	17	(12%)	15	(11%)
GASTROINTESTINAL SYSTEM	49	(34%)	48	(34%)
Constipation	22	(15%)	7	(5%)
Diarrhea	7	(5%)	17	(12%)
Nausea	20	(14%)	23	(16%)
Vomiting	10	(7%)	11	(8%)
GENERAL	27	(19%)	26	(18%)
Infection (aggravated)	9	(6%)	2	(1%)
PSYCHIATRIC	15	(10%)	10	(7%)
Insomnia	4	(3%)	8	(6%)
REPRODUCTIVE SYSTEM	3	(2%)	8	(6%)
Vaginitis ^c	3	(5%)	6	(11%)
SKIN/APPENDAGES	24	(17%)	15	(11%)
Pruritus	7	(5%)	6	(4%)
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.				

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Table 7a.12. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a, b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovfloxacin (N=144)		Zosyn ↓ Vantin™ (N=142)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	39	(27%)	37	(26%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	9	(6%)	4	(3%)
Appl./Inj./Incision/Insertion Site Pain	4	(3%)	2	(1%)
Appl./Inj./Incision/Insertion Site Reaction	7	(5%)	0	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	11	(8%)	8	(6%)
Dizziness	4	(3%)	1	(<1%)
Headache	8	(6%)	7	(5%)
GASTROINTESTINAL SYSTEM	15	(10%)	19	(13%)
Diarrhea	5	(3%)	12	(8%)
Nausea	8	(6%)	5	(4%)
REPRODUCTIVE	3	(2%)	4	(3%)
Vaginitis ^c	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.

Twenty-seven (27) subjects in the alatrofloxacin/trovfloxacin group and 38 subjects in the Zosyn/Vantin™ group had serious adverse events that were considered by the investigator to be unrelated to study drug.

One subject each in the alatrofloxacin/trovfloxacin group had presumed pseudomembranous colitis and allergic reaction and one subject in the Zosyn/Vantin™ group had *C. difficile* diarrhea, which were serious adverse events that were considered to be related to study drug.

Five subjects in the alatrofloxacin/trovfloxacin group and six subjects in the Zosyn/Vantin™ group died during this study. Two subjects in each group died within 30 days of the last dose of study drug. No death was considered to be treatment-related.

Sponsor Summary and Conclusions: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovfloxacin (200 mg daily) for 10 or 14 days of total therapy and intravenous piperacillin sodium/tazobactam sodium (Zosyn™ - 3.375 g four times daily) followed by oral cefpodoxime proxetil (Vantin™ -400 mg twice daily) for 10 or 14 days of total therapy were equivalent for the sponsor-defined clinical success rate at the end of treatment and the end of study in clinically evaluable subjects with complicated skin and skin structure infection. Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and the end of study for the most frequently isolated pathogens of (*S. aureus* and *S. epidermidis*).

The percentage of subjects discontinued from treatment due to adverse events (all causality) was 20% in the alatrofloxacin/trovafoxacin group and 6% in the Zosyn/Vantin™ group. For subjects in the alatrofloxacin/trovafoxacin group, the most common treatment-related adverse events that led to discontinuation from treatment were insertion site reaction/pain, dizziness, flushing/hot flushes, headache, and nausea. For subjects in the Zosyn/Vantin™ group, the most common treatment-related adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system (nausea and diarrhea). The overall percentage of all and treatment-related adverse events in the alatrofloxacin/trovafoxacin group was comparable to that of subjects in the Zosyn/Vantin™ group (70% and 27% versus 69% and 26%, respectively). The most commonly reported treatment-related adverse events were headache (6%), nausea (6%) and vaginitis (5%) in the alatrofloxacin/trovafoxacin group and diarrhea (8%), vaginitis (7%) and headache (5%) in the Zosyn/Vantin™ group.

Reviewer's Summary and Conclusions Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafoxacin (200 mg daily) for 10 or 14 days of total therapy was considered therapeutically equivalent to intravenous Zosyn™ (3.375 g four times daily) followed by oral Vantin™ (400 mg twice daily) for 10 or 14 days of total therapy at both EOT and EOS in clinically evaluable patients. In clinically ITT patients, alatrofloxacin/trovafoxacin and Zosyn/Vantin were considered therapeutically equivalent at EOS but not EOT. EOT was considered the test of cure visit by the sponsor. However, as the EOT visit was scheduled for only a day after the patient discontinued therapy, this reviewer places more emphasis on EOS results.

A significantly higher proportion of alatrofloxacin/trovafoxacin patients discontinued treatment due to an adverse event, experienced application/injection/incision/insertion site reaction, and developed constipation than did Zosyn/Vantin patients (29/144 = 20% vs. 8/142 = 6%, $p=0.0003$ using the test of equal proportions based on the normal approximation to the binomial distribution; 11/144 = 8% vs. 1/142 or < 1%, $p=0.005$ using Fisher's exact test; and 22/144 = 15% vs. 7/142 = 5%, $p=0.004$ using the test of equal proportions based on the normal approximation to the binomial distribution, respectively). Of note, more alatrofloxacin/trovafoxacin patients experienced aggravated infection as an adverse event (this difference was marginally statistically significant: 9/144 = 6% vs. 2/142 = 1%, $p=0.06$ using Fisher's exact test). Zosyn/Vantin patients experienced significantly more diarrhea than did alatrofloxacin/trovafoxacin patients (17/142 = 12% vs. 7/144 = 5%, $p=0.03$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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III. COMMUNITY-ACQUIRED PNEUMONIA

The efficacy and safety of oral trovafloxacin in the treatment of community-acquired pneumonia was assessed in three double-blind, comparative trials. The comparator agents were cefaclor (154-102), amoxicillin with optional erythromycin (154-112), and clarithromycin (154-134). The use of the IV-to-oral regimen in the treatment of community-acquired pneumonia was assessed in two additional double-blind, comparative trials versus IV ciprofloxacin plus IV ampicillin followed by oral ciprofloxacin plus oral amoxicillin (154-110) or IV ceftriaxone followed by oral cefpodoxime with optional erythromycin (154-111).

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the community-acquired pneumonia trials as part of the Integrated Summary of Efficacy. This was done separately for the oral and IV-to-oral trials.*

For the oral trials, results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower clinical response rate was observed in elderly subjects (≥ 75 years of age versus subjects < 75 years of age) in both the trovafloxacin and comparator treatment groups at EOT and EOS.

For the IV-to-oral trials, results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower clinical response rate was observed in elderly subjects (≥ 75 years of age versus subjects < 75 years of age) in both the trovafloxacin and comparator treatment groups at EOT and EOS.

III.A. Protocol 154-102

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (200 MG OR 300 MG DAILY) OR CEFACTOR (1500 MG DAILY) FOR THE TREATMENT OF UNCOMPLICATED COMMUNITY-ACQUIRED PNEUMONIA.

Study Dates: 07 December 1993 - 11 November 1994

Study Objectives: The objective of this study was to compare the safety and efficacy of two doses of trovafloxacin and cefaclor in the treatment of subjects with uncomplicated community-acquired pneumonia.

***Reviewer's Note:** This was a Phase II study designed to examine the efficacy and safety of two different doses of trovafloxacin. It was not adequately powered to demonstrate equivalence of either trovafloxacin regimen to cefaclor. The study was also not adequately powered to detect significant treatment differences (e.g., between the two trovafloxacin regimens). As a result, any findings from this study should be interpreted with caution.*

Study Design: Study 154-102 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg or 300 mg daily as a single dose in the morning) versus cefaclor (500 mg in the morning, afternoon, and evening),

administered orally for 10 days for the treatment of uncomplicated community-acquired pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, between the ages _____ at the baseline assessment, with clinically and radiologically documented community-acquired pneumonia were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the sponsor and was evaluated at the end of therapy (Day 11) and at the end of study (Day 25). Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point or at the time of discontinuation from the study. The investigator was to classify the clinical response of the subject as cure (resolution of signs and symptoms of pneumonia to a baseline level that existed prior to the occurrence of pneumonia), improved (incomplete resolution of any of the signs and symptoms) or failure (lack of resolution of any of the signs or symptoms).

Bacteriological response was to be determined by the sponsor and evaluated at the end of therapy (Day 11) and at the end of study (Day 25) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as indeterminate (unevaluable), eradication, presumptive eradication, persistence, relapse, superinfection, colonization, eradication with reinfection, or presumed persistence.

The primary efficacy endpoint was the sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS,
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, including serious adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, blood cultures, and urinalysis), physical examinations, concomitant medication use, and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results: One planned and two unplanned interim analyses were done during the course of this study. These were done for administrative reasons only and resulted in no unblinding of individual subject data or modification of the design of the study. No adjustments were made to the nominal p-values to account for these analyses.

Reviewer's Note: As this study is underpowered to begin with, this reviewer also did not make any adjustments to the final analysis.

Analysis Groups

Table 3a.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3a.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (200 mg/day)	Trovafloxacin (300 mg/day)	Cefaclor (500 mg TID)
Entered Study ^a	50	52	47
Completed Treatment	48 (96%)	41 (79%)	40 (85%)
Completed Study	48 (96%)	39 (75%)	40 (85%)
Evaluated for Efficacy			
Clinical Intent-to-treat	50 (100%)	52 (100%)	46 (98%)
Clinically Evaluable	47 (94%)	42 (81%)	42 (89%)
Assessed for Safety			
Adverse Events	50 (100%)	52 (100%)	47 (100%)
Laboratory Tests	50 (100%)	47 (90%)	45 (96%)

a Subjects who were randomized.

***Reviewer’s Note:** There were significant treatment differences in the proportion of patients who completed both treatment and the study ($p=0.04$ and 0.01 , respectively, using the Chi-square test). Trovafloxacin 300 mg/day patients were the least likely to complete treatment and the study. Somewhat fewer trovafloxacin 300 mg/day patients were considered evaluable for the efficacy analysis, however this difference was not statistically significant ($p=0.11$ using the Chi-square test).*

One subject in the cefaclor group had an inappropriate baseline diagnosis and was excluded from both the clinical intent-to-treat and evaluable analysis. Seventeen (17) additional, of 149 randomized, subjects were not clinically evaluable (3/50 [6%] subjects in the trovafloxacin 200 mg group; 10/52 [19%] subjects in the trovafloxacin 300 mg group; and 4/47 [9%] subjects in the cefaclor group. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (1/50 [2%], trovafloxacin 200 mg; 9/52 [17%], trovafloxacin 300 mg; and 2/47 [4%], cefaclor). Other reasons were noncompliance, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness and lost to follow-up.

Eighty-two (82) of 149 randomized subjects were not bacteriologically evaluable (33/50 [66%] subjects in the trovafloxacin 200 mg group; 22/52 [42%] subjects in the trovafloxacin 300 mg group; and 27/47 [57%] subjects in the cefaclor group). The most common reason for exclusion from bacteriological efficacy analyses was no baseline pathogen (30/50 [60%], trovafloxacin 200 mg; 20/52 [38%], trovafloxacin 300 mg; and 26/47 [55%], cefaclor). Other reasons were baseline culture outside specified visit window, outcome not assessable at end of treatment, and not clinically evaluable.