

VII.B. Protocol 154-132

AN OPEN-LABEL, NON-COMPARATIVE, MULTICENTER TRIAL ON THE USE OF ORAL TROVAFLOXACIN FOR THE TREATMENT OF DIABETIC FOOT INFECTIONS.

Study Dates: 7 June 1995 - 16 May 1996

Study Objectives: The objective of this study was to evaluate the safety and efficacy of trovafloxacin in the treatment of subjects with diabetic foot infection requiring oral antibiotic therapy.

Study Design: Study 154-132 was an open-label, non-comparative, multicenter trial of trovafloxacin (200 mg once daily) administered orally for 10 or 14 days in the treatment of subjects with diabetic foot infection.

***Reviewer's Note:** Since this trial is uncontrolled, results should be interpreted with caution. This is especially true as clinical outcome is the primary efficacy variable, and may be judged somewhat subjectively by the investigator and/or the sponsor.*

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥ 18 years of age at the baseline visit with clinically documented diabetic foot infection (without underlying osteomyelitis) were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical signs 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 of culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, swelling, or leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of all signs and symptoms of diabetic foot infection), improvement (incomplete resolution of signs and symptoms of diabetic foot infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of diabetic foot 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. Bacteriological response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence or relapse; 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, in addition to sponsor-defined clinical response 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 7b.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 7b.1. Evaluation Groups

Evaluation Groups:	Trovanoxacin 200 mg/day	
Enrolled Subjects	225	
All Treated Subjects	225	(100%)
Withdrawn from Treatment	15	(7%)
Completed Treatment	210	(93%)
Completed Study	217	(96%)
Completed Treatment and Study	209	(93%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	224	(>99%)
Clinically Evaluable	214	(95%)
Bacteriologically Intent-to-Treat	190	(84%)
Bacteriologically Evaluable	180	(80%)
Assessed for Safety		
Adverse Events	225	(100%)
Laboratory Tests	221	(98%)

Of the 225 enrolled subjects, one subject had an inappropriate baseline diagnosis (i.e., no clinical signs or symptoms of infected diabetic foot at baseline as defined by protocol) and was excluded from all intent-to-treat and evaluable analyses.

Of the 224 clinical ITT subjects, 10 subjects were not clinically evaluable; therefore, 214 subjects were clinically evaluable. The most common reasons for exclusion from the clinically evaluable efficacy analyses were no post-baseline clinical assessments and no post-baseline clinical response in evaluable window (each, 5/225, 2%). Other reasons were

insufficient therapy, prior antibiotic therapy, and concomitant antibiotic therapy. (Subjects may have had more than one reason for exclusion from analysis.)

Of the 224 clinical ITT subjects, 34 subjects had negative baseline cultures; therefore, 190 subjects were included in the bacteriological ITT analyses.

Of the 214 clinically evaluable subjects, 34 subjects were not included in the bacteriologically evaluable analyses; therefore, 180 subjects were bacteriologically evaluable. The only reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (34/225, 15%).

APPEARS THIS WAY
ON ORIGINAL

Discontinuations

Of the 225 treated subjects, 15 were prematurely discontinued from treatment as summarized in Table 7b.2.

Table 7b.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Trovafloxacin 200 mg (N=225)	
	Number and Percentage (%) of Subjects	
Total Discontinued	15	(7%)
Discontinuations Related to Study Drug:	10	(4%)
Adverse Event	3	(1%)
Insufficient Response	7	(3%)
Discontinuations Unrelated to Study Drug:	5	(2%)
Lost to Follow-up	1	(<1%)
Withdrew Consent	4	(2%)

APPEARS THIS WAY
ON ORIGINAL

Demographics

One hundred-sixteen (116) of the 225 treated subjects (52%) were males and 109 were females (48%). The males and females 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 was 62.1 years. Forty-eight percent (48%) of subjects were ≥65 years of age.

The primary diagnosis for clinical ITT subjects was diabetic foot infection. The median duration since onset of infection was 11.5 days. Twenty-nine (29) subjects had a duration since onset of infection of >50 days. The maximum duration since onset of infection was 1118 days (Subject 5845-0007). Seventy-nine (79/224, 35%) clinical ITT subjects had Type I diabetes and 145/224 (65%) had Type II diabetes. Similar results were observed for clinically evaluable subjects.

The most commonly reported type of infection among clinical ITT subjects was foot ulcer (183/224, 82%). Of note, subjects may have had more than one type of infection at baseline. Other types of infections included cellulitis with and without a baseline pathogen and "other" infections (including abscess, paronychia, traumatic wound infection, ingrown or infected nail, leg, ankle, or toe ulcer, dehiscence at surgical site, leg or toe infection).

One hundred-thirteen (113) clinical ITT subjects (50%) did not require a surgical drainage procedure at baseline or during the study. Ninety-eight (98) clinical ITT subjects (43%) had skin infections that required surgical intervention at baseline and 73 (32%) had skin infection that required surgical intervention post-baseline. The most frequently performed type of surgical intervention post-baseline was surgical debridement (71/224, 32%). The most commonly reported type of skin infection for subjects requiring surgical intervention was foot ulcer (86/111, 77%).

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

Table 7b.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT 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 Intervention ^b	111 (49%)
At Baseline	98 (43%)
Post-Baseline ^c	73 (32%)
Before the EOT Assessment	65 (29%)
After the EOT Assessment	48 (21%)

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.

Among all treated subjects, 97/225 (43%) had at least one disease/syndrome at baseline. The most common disease/syndrome reported at baseline was peripheral vascular disease (77/225, 34%).

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented in Table 7b.4.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 7b.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
		Trovafloxacin 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%)

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 in Table 7b.5.

Table 7b.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)				
Pathogen	Trovafloxacin 200 mg (N=180)		Trovafloxacin 200 mg (N=174)	
	Number of Subjects			
	End of Treatment		End of Study	
<i>St. aureus</i>	53/59	(90%)	48/60	(80%)
<i>St. epidermidis</i>	27/27	(100%)	25/27	(93%)
<i>E. faecalis</i>	27/32	(84%)	23/32	(72%)
<i>St. 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>St. simulans</i>	6/6		6/6	
<i>St. hominis</i>	6/6		5/6	
<i>Streptococcus sp.</i>	11/11		10/10	
<i>Str. agalactiae</i>	12/13		12/13	
<i>Peptostreptococcus sp.</i>	4/6		4/6	
<i>Peptostreptococcus magnus</i>	2/5		2/5	

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

BEST POSSIBLE COPY

A summary of clinical success rates for clinical intent-to-treat subjects subset by type of infection at baseline at the end of treatment and at the end of study is presented in Table 7b.6.

BEST POSSIBLE COPY

Table 7b.6. Summary of Sponsor-Defined Clinical Success Rates Subset by Type of Baseline Infection (Clinical ITT Subjects)				
	Trovafloxacin 200 mg (N=224)			
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection^a	EOT		EOS	
Foot Ulcers	161/179	(90%)	152/183	(83%)
Cellulitis Without a Baseline Pathogen	11/13	(85%)	11/13	(85%)
Cellulitis With a Baseline Pathogen	44/48	(92%)	43/48	(90%)
Other ^b	19/20	(95%)	20/21	(95%)

a A subject may have had more than one type of infection at baseline.
 b Other infections included abscess, blister, paronychia, bulla, traumatic wound infection, ingrown or infected nail, leg, ankle, or toe ulcer, dehiscence at surgical site, leg or toe infection.

A summary of clinical success rates for clinical intent-to-treat subjects subset by timing of surgical intervention at the end of treatment and at the end of study is presented in Table 7b.7.

BEST POSSIBLE COPY

Table 7b.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)				
	Trovafloxacin 200 mg (N=224)			
	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	103/112	(92%)	99/113	(88%)
Surgical Intervention at Baseline	84/94	(89%)	81/98	(83%)
Surgical Intervention Post Baseline ^c				
Before the EOT Assessment	57/63	(90%)	54/65	(83%)
After the EOT Assessment	41/46	(89%)	37/48	(77%)

a Subjects may have had surgical intervention at more than one timepoint.
 b Five clinical intent-to-treat subjects were not assessed for clinical response at the end of treatment.
 c Two subjects (Subjects 5190-0007 and 5842-0008) had surgical procedures performed, 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).

Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects for the most frequently isolated pathogens at the end of treatment and the end of study are presented in Table 7b.8.

Table 7b.8 A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Trovafloracin 200 mg (N=180)	Trovafloracin 200 mg (N=174)
	Number of Pathogens	
Pathogen	End of Treatment	End of Study
<i>St. aureus</i>	48/58 (83%)	49/60 (82%)
<i>St. epidermidis</i>	25/28 (89%)	24/27 (89%)
<i>E. faecalis</i>	25/33 (76%)	25/32 (78%)
<i>St. haemolyticus</i>	14/16 (88%)	12/15 (80%)
<i>P. aeruginosa</i>	9/15 (60%)	10/16 (63%)
<i>Corynebacterium sp.</i>	10/11	12/12
<i>E. coli</i>	13/14	13/14
<i>P. mirabilis</i>	11/11	11/11
<i>Staphylococcus sp.</i>	7/7	6/7
<i>St. hominis</i>	6/6	5/6
<i>St. simulans</i>	5/6	6/6
<i>Streptococcus sp.</i>	9/11	8/10
<i>Str. agalactiae</i>	11/13	12/13
<i>Peptostreptococcus sp.</i>	6/6	5/6
<i>Peptostreptococcus magnus</i>	4/5	3/5

St. = *staphylococcus*; *Str.* = *Streptococcus*
 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.

BEST POSSIBLE COPY

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 7b.9. Tables 7b.10 and 7b.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 7b.9. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloracin 200 mg daily (N=225)
	Number and Percentage (%) of Subjects
Adverse Events: All Causalities	74/225 (33%)
Treatment-Related Adverse Events	37/225 (16%)
Discontinuations Due to an Adverse Event ^a	8/225 (4%)
Clinically Significant Laboratory Values	66/221 (30%)

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

BEST POSSIBLE COPY

Table 7b.10. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)	
Trovafloxacin 200 mg (N=225)	
Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	74 (33%)
BODY SYSTEM WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	26 (12%)
Dizziness	20 (9%)
Headache	5 (2%)
GASTROINTESTINAL SYSTEM	25 (11%)
Dyspepsia	5 (2%)
Nausea	9 (4%)
GENERAL	14 (6%)
Fever	5 (2%)
SKIN AND APPENDAGES	14 (6%)
Pruritus	4 (2%)
a ≥2 % of subjects.	
b Includes data up to 7 days after last dose of active study medication.	

BEST POSSIBLE COPY

Table 7b.11. A Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)	
Trovafloxacin 200 mg (N=225)	
Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	37 (16%)
BODY SYSTEM WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	22 (10%)
Dizziness	18 (8%)
Headache	5 (2%)
GASTROINTESTINAL SYSTEM	16 (7%)
Nausea	6 (3%)
a ≥2 % of subjects.	
b Includes data up to 7 days after last dose of active study medication.	

Two subjects died and both deaths occurred following completion of this study, as follows:

- Two subjects died >30 days after the last dose of study drug. Subject 5841-0024 died of cardiorespiratory arrest and Subject 6536-0010 died of acute myocardial infarction. Neither of these deaths was considered by the investigator to be related to study drug.

Seventeen (17) subjects had serious adverse events that occurred during or following completion of this study. None of the serious adverse events were considered by the investigator to be related to study drug; all serious adverse events were attributed to other illnesses, the disease under study, "other" reasons, or concomitant treatment.

Sponsor Summary and Conclusions: Trovafloxacin 200 mg once daily for 10 or 14 days was clinically effective in the treatment of diabetic foot infection. In addition, trovafloxacin was bacteriologically effective in eradicating the most frequently isolated baseline pathogens including *S. aureus*, *S. epidermidis*, *E. faecalis*, *P. aeruginosa*, *E. coli*, and anaerobic streptococci.

The overall percentage of all and treatment-related adverse events was 33% and 16%, respectively. The most commonly reported treatment-related adverse event was dizziness (8%). The percentage of subjects discontinued from treatment due to adverse events was 4% (8 subjects), of whom three subjects were discontinued from treatment due to treatment-related adverse events.

Reviewer's Summary and Conclusions: *Clinical success rates for trovafloxacin 200 mg once daily for 10 or 14 days were 195/209 = 93% at EOT and 179/206 = 87% at EOS. Due to the nature of this trial (i.e., it is uncontrolled), however, it is difficult to know how these results should be interpreted.*

The most common adverse events experienced by patients in this trial were dizziness (9%) and nausea (4%).

VII.C. Protocol 154-139

APPEARS THIS WAY
ON ORIGINAL

A RANDOMIZED, MULTICENTER, OPEN TRIAL COMPARING ORAL TROVAFLOXACIN (200 MG) AND AUGMENTIN FOR THE TREATMENT OF COMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE.

Reviewer's Note: *"Open" is used here to indicate that the trial was unblinded.*

Study Dates: 23 September 1995 - 10 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin with Augmentin™ for the treatment of subjects with complicated infections of the skin and skin structure.

Study Design: Study 154-139 was a randomized, comparative, multicenter open trial of trovafloxacin (200 mg as a single dose in the morning) versus Augmentin (1.5 g daily in three equally divided doses of 500 mg), administered orally for 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].

Reviewer's Note: *Since the primary endpoint in this study is clinical outcome, it is of some concern that this study was not blinded. Results should be interpreted with caution.*

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. Bacteriological response was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence or relapse. Each pathogen was to be classified by the sponsor as eradication, presumed 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.

APPEARS THIS WAY
ON ORIGINAL

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).

APPEARS THIS WAY
ON ORIGINAL

Efficacy Results:

APPEARS THIS WAY
ON ORIGINAL

Analysis Groups

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

Table 7c.1. Evaluation Groups

Evaluation Groups:	Trovfloxacin		Augmentin	
	Number and Percentage (%) of Subjects			
Randomized	166		157	
All Treated Subjects	160	(96%)	156	(>99%)
Completed Treatment	145	(91%)	133	(85%)
Completed Study	150	(94%)	146	(94%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	165	(>99%)	156	(>99%)
Clinically Evaluable ^a	155	(93%)	146	(93%)
Bacteriological Intent-to-Treat	130	(78%)	114	(73%)
Bacteriologically Evaluable ^a	123	(74%)	108	(69%)
Assessed for Safety				
Adverse Events	160	(100%)	156	(100%)
Laboratory Tests	158	(99%)	149	(96%)

^a Based on End of Treatment assessment

One hundred sixty-six (166) subjects were randomized to trovafloxacin and 157 subjects were randomized to Augmentin treatment. Of the 166 randomized trovafloxacin subjects and 157 randomized Augmentin subjects, six trovafloxacin subjects and one Augmentin subject were not treated. Of the 160 trovafloxacin and 156 Augmentin-treated subjects, one subject (6134-0019) in the trovafloxacin group and one subject (6300-0378) in the Augmentin group were excluded from clinical intent-to-treat analysis due to incorrect administration of study drug.

Of the 165 trovafloxacin and 156 Augmentin clinical ITT subjects, 10 subjects in each group were not clinically evaluable; therefore, 155 trovafloxacin and 146 Augmentin subjects were clinically evaluable. The most common reasons for exclusion from the clinically evaluable efficacy analyses was randomized, not treated (trovfloxacin: 6/165, 4%; Augmentin: 1/156, ≤1%) in the trovafloxacin group and insufficient therapy (trovfloxacin: 3/165, 2%; Augmentin: 5/156, 3%) in the Augmentin group. Other reasons were no post-baseline clinical assessment, no post-baseline clinical assessment within the evaluable window, and concomitant antibiotic therapy for intercurrent illness.

Of the 165 trovafloxacin and 156 Augmentin clinical ITT subjects, 35 subjects in the trovafloxacin group and 42 subjects in the Augmentin group had negative baseline cultures; therefore, 130 subjects in the trovafloxacin group and 114 subjects in the Augmentin group were included in the bacteriological ITT analysis.

Of the 155 trovafloxacin and 146 Augmentin clinically evaluable subjects, 32 subjects in the trovafloxacin group and 38 subjects in the Augmentin group were not included in the bacteriologically evaluable analyses; therefore, 123 subjects in the trovafloxacin group and 108 subjects in the Augmentin group were bacteriologically evaluable. The more common

reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (32/165 [19%], trovafloxacin and 38/156 [24%], Augmentin). The other reason was baseline culture performed outside window. One subject (6417-0466) in the trovafloxacin group was not bacteriologically evaluable due to both no baseline culture and culture performed outside evaluable window.

APPEARS THIS WAY
ON ORIGINAL

Discontinuations

Of the 160 trovafloxacin and 156 Augmentin treated subjects, 15 and 23 subjects, respectively, were prematurely discontinued from treatment as summarized in Table 7c.2.

Table 7c.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)		
	Trovafloxacin 200 mg (N=160)	Augmentin 500 mg TID (N=156)
	Number and Percentage (%) of Subjects	
Total Discontinued	15 (9%)	23 (15%)
Discontinuations Related to Study Drug:		
Adverse Event	5 (3%)	14 (9%)
Insufficient Response	4 (3%)	13 (8%)
	1 (<1%)	1 (<1%)
Discontinuations Unrelated to Study Drug:		
Adverse Event	10 (6%)	9 (6%)
Did Not Meet Randomization Criteria	4 (3%)	3 (2%)
Other	1 (<1%)	0
Protocol Violation	4 (3%)	5 (3%)
Withdrawn Consent	1 (<1%)	0
	0	1 (<1%)

Reviewer's Note: Significantly more Augmentin patients discontinued treatment due to treatment related causes (14/156=9% vs. 5/160=3%, p=0.03 using the test of equal proportions based on the normal approximation to the binomial distribution). Most of this difference was due to the higher percentage of Augmentin patients discontinuing due to treatment-related adverse events (13/156=8% vs. 4/160=3%, p=0.025 using Fisher's exact test).

APPEARS THIS WAY
ON ORIGINAL

Demographics

Eighty-seven (87) of the 160 treated trovafloxacin subjects (54%) were males and 73 were females (46%), and 77 of the 156 treated Augmentin subjects (49%) were males and 79 were females (51%). The subjects in the trovafloxacin and Augmentin 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 Augmentin groups was 55.2 years and 54.2 years, respectively. Thirty-nine percent (39%) of subjects in the trovafloxacin group and 37% of subjects in the Augmentin group were ≥65 years of age.

The primary diagnosis for clinical ITT subjects was complicated skin and skin structure infection. The median duration since onset of infection was 8.0 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 trovafloxacin and Augmentin treatment groups with respect to medical history at baseline. The most commonly reported disease/syndromes at study entry were peripheral vascular disease (trovafloxacin: 47/160, 29%; Augmentin: 48/156, 31%) and diabetes mellitus (trovafloxacin: 40/160, 25%; Augmentin: 33/156, 21%).

All types of infections were reported at similar rates in both treatment groups. The most commonly reported type of skin infections for subjects in both treatment groups were other deep soft tissue infections (e.g., post-operative surgical wound infections) (62/165 [38%], trovafloxacin; and 55/156 [35%], Augmentin). The most commonly reported type of deep soft tissue infections were classified as "other" (these are listed in Table 7c.3) and reported for 21 of 165 trovafloxacin subjects (13%) and 17 of 156 Augmentin subjects (11%).

The majority of clinical ITT subjects in both treatment groups (76%) did not require a surgical drainage procedure at baseline or during the study. Thirty-three (33) trovafloxacin subjects (20%) and 30 Augmentin subjects (19%) required surgical drainage at baseline, and 16 subjects (10%) in each treatment group 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 7c.3.

APPEARS THIS WAY
ON ORIGINAL

Table 7c.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT 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%)
Ulcers	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 (Post-Operative)	62 (38%)	55 (35%)
Abscess	0	1 (<1%)
Ulcers	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%)

APPEARS THIS WAY
ON ORIGINAL

- 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 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.

APPEARS THIS WAY
ON ORIGINAL

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 7c.4. Trovafloxacin was considered therapeutically equivalent to Augmentin at both EOT and EOS.

Table 7c.4. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 200 mg (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%)	

APPEARS THIS WAY ON ORIGINAL

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 7c.5.

Table 7c.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Trovafloracin 200 mg (N=155)	Augmentin 500 mg TID (N=146)	Trovafloracin 200 mg (N=155)	Augmentin 500 mg TID (N=146)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>St. 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>St. 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>St. haemolyticus</i>	0/1	1/1	0/1	1/1
<i>St. hominis</i>	1/1	3/3	1/1	3/3
<i>St. 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>Str. agalactiae</i>	7/8	5/5	5/8	4/5
<i>Str. anginosus</i>	1/1	0/0	1/1	0/0
<i>Str. equisimilis</i>	5/5	3/3	2/2	3/3
<i>Str. oralis</i>	1/1	0/0	1/1	0/0
<i>Str. 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

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

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.

A summary of clinical success rates for clinical intent-to-treat 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 7c.6.

Type of Infection ^a	EOT		EOS	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
	Trovafloxacin 200mg (N=165)	Augmentin 500 mg TID (N=156)	Trovafloxacin 200mg (N=165)	Augmentin 500 mg TID (N=156)
Diabetic Foot Ulcer Without Osteomyelitis	21/24 (88%)	21/23 (91%)	19/24 (79%)	20/26 (77%)
Other Ischemic Ulcer	34/35 (97%)	33/37 (89%)	33/36 (92%)	31/38 (82%)
Infected Burn	7/8 (88%)	7/7 (100%)	7/8 (88%)	7/7 (100%)
Major Abscess	21/26 (81%)	22/25 (88%)	20/26 (77%)	22/26 (85%)
Other Skin Structure Infection Requiring Significant Surgical Interventions	8/9 (89%)	4/5 (80%)	8/9 (89%)	4/5 (80%)
Other Deep Soft Tissue Infections (Post-Operative)	53/62 (85%)	48/53 (91%)	49/62 (79%)	48/55 (87%)

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

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 7c.7. Comparable clinical success rates were observed between treatment groups at both EOT and EOS for subjects with no surgical intervention and subjects with surgical intervention at baseline. Among subjects with post-baseline surgical intervention before or after the end of treatment, subject subsets were too small for definitive conclusions to be drawn.

Timing of Surgical Intervention ^a	EOT		EOS	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
	Trovafloxacin 200 mg (N=165)	Augmentin 500 mg TID (N=156)	Trovafloxacin 200 mg (N=165)	Augmentin 500 mg TID (N=156)
No Surgical Intervention	111/125 (89%)	106/115 (92%)	104/126 (83%)	102/119 (86%)
Surgical Intervention at Baseline	27/33 (82%)	24/28 (86%)	26/33 (79%)	24/30 (80%)
Surgical Intervention Post Baseline				
Before the EOT Assessment	10/12 (83%)	8/11 (73%)	10/12 (83%)	8/12 (67%)
After the EOT Assessment	6/8 (75%)	6/9 (67%)	5/8 (63%)	6/10 (60%)

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

Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were comparable between the two treatment groups for *S. aureus*, *P. aeruginosa* and *E. faecalis* at the end of treatment and the end of study as presented in Table 7c.8.

	Trovafoxacin (N=123)	Augmentin (N=108)	95% CI	Trovafoxacin (N=110)	Augmentin (N=104)	95% CI
Number of Pathogens						
Pathogen	End of Treatment			End of Study		
<i>St. aureus</i>	46/59 (78%)	47/58 (81%)	-17.7, 11.5	43/54 (80%)	41/56 (73%)	-9.4, 22.2
<i>P. aeruginosa</i>	13/21 (62%)	6/15 (40%)	-10.4, 54.2	14/20 (70%)	9/15 (60%)	-21.9, 41.9
<i>E. faecalis</i>	14/16 (88%)	10/12 (83%)	ND	13/14 (93%)	11/13 (85%)	ND
<i>P. mirabilis</i>	9/15 (60%)	2/5 (40%)	ND	8/13 (62%)	5/6 (83%)	ND
<i>St. epidermidis</i>	4/7	9/11	ND	4/5	8/10	ND
<i>E. coli</i>	8/9	3/5	ND	8/9	3/5	ND
<i>K. oxytoca</i>	7/7	3/5	ND	5/6	3/5	ND
<i>Staphylococcus sp.</i>	5/5	4/4	ND	4/4	4/4	ND
<i>St. haemolyticus</i>	0/0	1/1	ND	0/1	1/1	ND
<i>St. hominis</i>	1/1	3/3	ND	1/1	3/3	ND
<i>St. saprophyticus</i>	0/0	1/1	ND	0/0	1/1	ND
Coagulase Negative <i>Staphylococcus</i>	0/0	1/1	ND	0/0	1/1	ND
<i>Streptococcus sp.</i>	0/1	4/4	ND	0/1	3/4	ND
Anaerobic <i>Streptococcus</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. agalactiae</i>	5/8	5/5	ND	5/8	4/5	ND
<i>Str. anginosus</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. equisimilis</i>	2/5	1/3	ND	1/2	1/3	ND
<i>Str. oralis</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. pyogenes</i>	4/4	6/6	ND	2/2	6/6	ND
Group A Beta <i>Streptococcus</i>	0/0	2/2	ND	0/0	2/2	ND
Group B Beta <i>Streptococcus</i>	0/0	1/1	ND	0/0	0/1	ND
Group G Beta <i>Streptococcus</i>	2/4	0/0	ND	1/2	0/0	ND
Beta hemolytic <i>Streptococcus</i>	0/0	1/1	ND	0/0	1/1	ND
<i>Peptostreptococcus sp.</i>	0/0	2/2	ND	0/0	2/2	ND
<i>P. prevoti</i>	1/1	2/2	ND	1/1	2/2	ND
<i>P. magnus</i>	0/0	2/2	ND	0/0	2/2	ND

ND = not done; *St.* = *Staphylococcus*; *Str.* = *Streptococcus*
^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.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events, and clinically significant laboratory values are presented in Table 7c.9. Tables 7c.10 and 7c.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 7c.9. Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin (N=160)	Augmentin (N=156)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	54/160 (34%)	53/156 (34%)
Treatment-Related Adverse Events	25/160 (16%)	36/156 (23%)
Discontinuations From Treatment Due to an Adverse Event^a	9/160 (6%)	16/156 (10%)
Clinically Significant Laboratory Values	50/158 (32%)	48/149 (32%)
a Four (4) subjects in the trovafloxacin group and 13 subjects in the Augmentin group were discontinued due to adverse events that were considered by the investigator to be study drug-related.		

Reviewer's Note: As can be seen in Table 7c.10, significantly more trovafloxacin patients experienced dizziness (12/160=8% vs. 1/156 which is < 1%, p=0.003 using Fisher's exact test), while significantly more Augmentin patients experienced diarrhea (23/156 = 15% vs. 2/160= 1%, p<0.001 using Fisher's exact test).

Table 7c.10. Summary of the Most Commonly Reported Adverse Events ^{a, b} by Body System - All Causalities (All Treated Subjects)				
	Trovafloxacin 200 mg (N=160)		Augmentin 500 mg TID (N=156)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	54	(34%)	53	(34%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	19	(12%)	4	(3%)
Dizziness	12	(8%)	1	(<1%)
Headache	5	(3%)	2	(1%)
GASTROINTESTINAL SYSTEM	19	(12%)	35	(22%)
Abdominal Pain	3	(2%)	8	(5%)
Constipation	5	(3%)	1	(<1%)
Diarrhea	2	(1%)	23	(15%)
Nausea	5	(3%)	9	(6%)
Vomiting	3	(2%)	4	(3%)
GENERAL	9	(6%)	6	(4%)
Fever	4	(3%)	0	
a ≥3% of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				

APPROVED COPY
OF ORIGINAL

Table 7c.11. Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a, b} by Body System (All Treated Subjects)		
	Trovafloxacin 200 mg (N=160)	Augmentin 500 mg TID (N=156)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	25 (16%)	36 (23%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	14 (9%)	1 (<1%)
Dizziness	8 (5%)	1 (<1%)
Headache	4 (3%)	0
GASTROINTESTINAL SYSTEM	11 (7%)	31 (20%)
Abdominal Pain	2 (1%)	8 (5%)
Constipation	3 (2%)	0
Diarrhea	1 (<1%)	22 (14%)
Nausea	4 (3%)	7 (4%)
Vomiting	2 (1%)	4 (3%)
a ≥2% of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication.		

APPEARS THIS WAY ON ORIGINAL

Twelve (12/160, 8%) subjects in the trovafloxacin group and seven (7/156, 4%) subjects in the Augmentin group had serious adverse events during this study, none of which were considered by the investigators to be related to the study drugs.

One subject in each treatment died during this study, both within 30 days of the last treatment dose. Neither of these deaths was considered to be treatment-related.

Sponsor Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 10 or 14 days of total therapy and Augmentin (1.5 g in three equally divided doses of 500 mg daily) administered orally for 10 or 14 days of total therapy were comparable for the sponsor-defined clinical success rate at the end of treatment and the end of study in the 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 (*S. aureus*, *P. aeruginosa* and *E. faecalis*).

The percentage of subjects discontinued from treatment due to adverse events was 6% in the trovafloxacin group and 10% in the Augmentin group. The overall percentage of all causality and treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the Augmentin group (34% and 16% versus 34% and 23%, respectively). The most commonly reported treatment-related adverse events in the trovafloxacin group were dizziness (5%), headache (3%) and nausea (3%). The most commonly reported treatment-related adverse events in the Augmentin group were diarrhea (14%), abdominal pain (5%) and nausea (4%).

Reviewer's Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 10 or 14 days of total therapy and Augmentin (1.5 g in three equally divided doses of 500 mg daily) administered orally for 10 or 14 days of total therapy were shown to be therapeutically equivalent in terms of sponsor-defined clinical success rate at both the end of treatment and the end of study in subjects with complicated skin and skin structure infection. These results should be interpreted with some caution, however, due to the fact that this study was not blinded.

In this study significantly more trovafloxacin patients experienced dizziness (12/160 = 8% vs. 1/156 which is < 1%, $p = 0.003$ using Fisher's exact test), while significantly more Augmentin patients experienced diarrhea (23/156 = 15% vs. 2/160 = 1%, $p < 0.001$ using Fisher's exact test).

APPEARS THIS WAY
ON ORIGINAL

VIII. CONCLUSIONS (Which May be Conveyed to the Sponsor)

1. Nosocomial Pneumonia

Overall, efficacy and safety appear acceptable for alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment in the treatment of nosocomial pneumonia.

The alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, thus if approved it will need to be labeled accordingly. In addition, it is of note that a significantly higher proportion of alatrofloxacin/trovafloxacin patients experienced adverse events and discontinued treatment due to adverse events compared to the control arm in both studies.

Conclusions from the individual protocols follow.

*Protocol 154-113: Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ciprofloxacin at both EOT and EOS in terms of clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional aztreonam or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.*

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced adverse events, 95% versus 81% for ciprofloxacin patients, and discontinued treatment due to adverse events, 15% versus 7% for ciprofloxacin patients ($p < 0.001$ and $p = 0.047$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

APPEARS THIS WAY
ON ORIGINAL

*Protocol 154-137: Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ceftazidime/ciprofloxacin at both EOT and EOS in terms of the clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional gentamycin or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.*

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced treatment-related adverse events, 12% versus 4% for ceftazidime/ciprofloxacin patients, discontinued treatment due to an adverse event, 12% versus 4% for ceftazidime/ciprofloxacin patients, and discontinued treatment due to a treatment-related adverse event, 5% versus < 1% for ceftazidime/ciprofloxacin patients ($p = 0.01$, 0.02 and 0.03 , respectively, using the test of equal proportions based on the normal approximation to the binomial distribution for the first two comparisons and Fisher's exact test for the third comparison).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment for the treatment of nosocomial pneumonia. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, if approved it should be labeled accordingly.

APPEARS THIS WAY
ON ORIGINAL

2. Community-Acquired Pneumonia

Overall, efficacy and safety appear acceptable for both (1) trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and (2) alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy in the treatment of community-acquired pneumonia.

Conclusions from the individual protocols follow.

Protocol 154-102: This was an exploratory study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 200 mg, trovafloxacin 300 mg, and cefaclor appeared similar at both EOT and EOS. However, sample sizes were too small to allow for any definitive conclusions about equivalence.

A significantly higher proportion of trovafloxacin 300 mg patients experienced adverse events, both all causality and treatment-related ($p=0.01$ and $p<0.001$, respectively, using the Chi-square test). A higher proportion of trovafloxacin 300 mg patients also discontinued treatment due to an adverse event (this was marginally significant; $p=0.07$ using Fisher's exact test).

Protocol 154-110: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy was considered therapeutically equivalent to intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy at both EOT and EOS.

The most common adverse events in the alatrofloxacin/trovafloxacin arm were headache (16%), insomnia (11%), constipation (9%), and nausea (9%). The most common adverse events in the ciprofloxacin/ampicillin/amoxicillin arm were insomnia (12%), headache (11%), constipation (10%), and nausea (10%).

Protocol 154-111: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.

Alatrofloxacin/trovafloxacin patients experienced a significantly higher percentage of the following adverse events than did ceftriaxone/cefepodoxime patients: central and peripheral nervous system events (overall), dizziness, headache, and constipation ($p < 0.001$, $p < 0.001$, $p = 0.046$, and $p = 0.01$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Protocol 154-112: Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxicillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were considered therapeutically equivalent in terms of clinical response in clinically evaluable patients at both EOT and EOS.

The proportion of trovafloxacin patients experiencing central and peripheral nervous system events (all causalities) was marginally significantly higher than that in the amoxicillin group ($p = 0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Protocol 154-134: Trovafloxacin 200 mg once daily for 7 or 10 days and clarithromycin 500 mg BID for 7 or 10 days were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.

Overall, a higher proportion of clarithromycin patients experienced adverse events ($p = 0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution). In terms of individual adverse events, a higher proportion of trovafloxacin patients experienced dizziness ($p = 0.003$ using the test of equal proportions based on the normal approximation to the binomial distribution), while a higher proportion of clarithromycin patients experienced diarrhea and taste perversion ($p = 0.01$ and $p < 0.001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of both (1) trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and (2) alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy for the treatment of community-acquired pneumonia.

3. Acute Exacerbation of Chronic Bronchitis

Overall, efficacy and safety appear acceptable for trovafloxacin 100 mg given once daily for 7 days in the treatment of acute bacterial exacerbation of chronic bronchitis.

Conclusions from the individual protocols follow.

Protocol 154-101: This was a Phase II study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 100 mg, trovafloxacin 300 mg, and ofloxacin appeared similar at both EOT and EOS (perhaps more

APPEARS THIS WAY
ON ORIGINAL

similar at EOT), but sample sizes were too small to allow for any definitive conclusions about equivalence.

The percent of patients experiencing adverse events regardless of relationship to study drug, treatment-related adverse events, and discontinuations due to an adverse event were all significantly different across treatment groups (rates were higher in the trovafloxacin 300 mg arm; p-values <0.0001, <0.0001, and =0.001, respectively, using the chi-square test). In addition, the rate of dizziness in the trovafloxacin 300 mg arm was rather high (40% of patients experienced dizziness; 37% of patients experienced dizziness that was considered treatment related).

Protocol 154-109: Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to clarithromycin 500 mg twice daily for 7 days in terms of clinical-success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.

There was a higher incidence of both adverse events, regardless of relationship to study drug, and treatment-related adverse events in the clarithromycin arm ($p=0.04$ and $p<0.0001$, respectively). The most commonly reported adverse events in the trovafloxacin group were headache (10%), dizziness (6%), and nausea (6%) and the most commonly reported adverse events in the clarithromycin group were taste perversion (16%), nausea (10%), diarrhea (7%), and insomnia (7%).

Protocol 154-141: Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to ciprofloxacin 500 mg twice daily for 7 days in terms of clinical success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.

The most commonly reported adverse events in the trovafloxacin group were nausea (8%), dizziness (4%), headache (4%), and insomnia (4%) and the most commonly reported adverse events in the ciprofloxacin group were nausea (10%), dizziness (6%), diarrhea (5%), and insomnia (4%).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of trovafloxacin 100 mg given once daily for 7 days in the treatment of acute bacterial exacerbation of chronic bronchitis.

APPROVED THIS WAY
ORIGINAL

4. Acute Sinusitis

Overall, efficacy and safety appear acceptable for trovafloxacin 200 mg given once daily for 10 days in the treatment of acute sinusitis. There is some concern about the high rate of dizziness (and patients discontinuing treatment due to dizziness), however this can probably be taken care of with appropriate labeling.

Conclusions from the individual protocols follow.

Protocol 154-114: Trovafloxacin 200 mg once daily for 10 days appears to have been effective in the treatment of acute sinusitis in this trial. Caution should be taken in interpreting results, however, due to the fact that this was an uncontrolled trial. Eighteen percent of trovafloxacin patients reported dizziness that was considered treatment related. Eleven percent of trovafloxacin patients reported nausea that was considered treatment related.

One of the investigators involved in this trial, Dr. Fiddes, has plead guilty to violations of FDA regulations. Results are fairly robust when patients from Dr. Fiddes' center are excluded. The number of evaluable patients with M. catarrhalis drops to 11 (slightly below the number of 15 recommended in the Division of Anti-Infective Drug Products 1992 "Points to Consider" document), however eradication rates still appear acceptable (10/11 = 91% patients are eradicated at EOT; 9/11 = 82% patients are eradicated at EOS).

Protocol 154-115: A greater number of patients in the trovafloxacin arm were excluded from the evaluable efficacy analysis ($p=0.025$), due largely to the greater number of patients who discontinued treatment due to an adverse event in the trovafloxacin arm ($p=0.002$). However, clinical response for trovafloxacin 200 mg once daily for 10 days was therapeutically equivalent to clarithromycin 500 mg BID for 14 days at both EOT and EOS for both the clinically evaluable and ITT patient group.

Central and peripheral nervous system adverse events were the most frequently occurring adverse events that led to discontinuation from treatment with trovafloxacin. Twenty-six trovafloxacin subjects (26/203, 13%) were discontinued due to dizziness, headache, vertigo, paresthesia, and/or hypoesthesia, compared to only four clarithromycin subjects (4/214, 2%) who discontinued due to headache, dizziness, paresthesia and/or hypertonia ($p<0.0001$).

Protocol 154-138: Trovafloxacin 200 mg once daily for 10 days was therapeutically equivalent to amoxicillin/clavulanate 500/125 mg three times daily for 10 days in terms of clinical-success rates at both EOT (the primary efficacy endpoint) and EOS. This was true for both the evaluable and ITT patient group (recall that a significantly higher number of trovafloxacin patients were excluded from the evaluable efficacy analysis, $p=0.025$).

Safety appears acceptable, although dizziness was noted in a number of patients (17%, regardless of relationship to treatment).

RECOMMENDED REGULATORY ACTION:

APPEARS THIS WAY
ON ORIGINAL

The data provided by the sponsor in this submission support the approval of trovafloxacin 200 mg given once daily for 10 days in the treatment of acute sinusitis. There is some concern about the high rate of dizziness observed in the three sinusitis trials for patients on the trovafloxacin regimen (rates were 17% in study 154-138, 20% in study 154-114, and 34% in study 154-115). Thus, if approved it might be useful to include this information in the label.

5. Uncomplicated Skin and Skin Structure Infections

Overall, efficacy and safety appear acceptable for trovafloxacin 100 mg given once daily for 7-10 days in the treatment of uncomplicated skin and skin structure infections.

Conclusions from the individual protocols follow.

Protocol 154-129: 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).

Protocol 154-130: 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).

RECOMMENDED REGULATORY ACTION:

APPEARS THIS WAY
ON ORIGINAL

The data provided by the sponsor in this submission support the approval of trovafloxacin 100 mg given once daily for 7-10 days in the treatment of uncomplicated skin and skin structure infections.

6. Complicated Skin and Skin Structure Infections

Overall, efficacy and safety appear acceptable for alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg daily) for 10 or 14 days of total therapy in the treatment of complicated skin and skin structure infections. This conclusion is based on results from study 154-131.

It is harder to come to a conclusion regarding the regimen of trovafloxacin 200 mg once daily for 10 or 14 days in the treatment of complicated skin and skin structure infections. Two studies, 154-132 and 154-139, were conducted using this regimen. Results regarding efficacy and safety appear acceptable in these two studies, however study 154-132 was uncontrolled and study 154-139, while controlled, was unblinded. Since the primary outcome in both studies was clinical success (not an entirely objective outcome measure), caution needs to be exercised in interpreting results from both studies.

Conclusions from the individual protocols follow.

Protocol 154-131: *Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (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/trovafloxacin 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/trovafloxacin 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/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). 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).

Protocol 154-132: *Clinical success rates for trovafloxacin 200 mg once daily for 10 or 14 days were 195/209=93% at EOT and 179/206=87% at EOS. However, since this trial had no control group it is difficult to know how to interpret these results.*

The most common adverse events experienced by patients in this trial were dizziness (9%) and nausea (4%).

Protocol 154-139: *Trovafloxacin (200 mg once daily) administered orally for 10 or 14 days of total therapy and Augmentin (1.5 g in three equally divided doses of 500 mg daily) administered orally for 10 or 14 days of total therapy were shown to be therapeutically equivalent in terms of sponsor-defined clinical success rate at both the end of treatment and the end of study in subjects with complicated skin and skin structure infection. These results should be interpreted with some caution, however, due to the fact that this study was not blinded.*

In this study significantly more trovafloxacin patients experienced dizziness (12/160 = 8% vs. 1/156 which is < 1%, $p = 0.003$ using Fisher's exact test), while significantly more Augmentin patients experienced diarrhea (23/156 = 15% vs. 2/160 = 1%, $p < 0.001$ using Fisher's exact test).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg daily) for 10 or 14 days of total therapy for the treatment of complicated skin and skin structure infections.

It is harder to come to a conclusion regarding the regimen of trovafloxacin 200 mg once daily for 10 or 14 days in the treatment of complicated skin and skin structure infections. Two studies, 154-132 and 154-139, were conducted using this regimen. Results regarding efficacy and safety appear acceptable in these two studies, however study 154-132 was uncontrolled and study 154-139, while controlled, was unblinded. Since the primary outcome in both studies was clinical success (not an entirely objective outcome measure), the reviewing medical officer will have to determine whether results from these two trials are reasonable.

/S/

11/18/97

Nancy Paul Silliman, Ph.D.
Mathematical Statistician, Division of Biometrics IV

/S/

11/29/97

Concur: Mohammad Huque, Ph.D.
Acting Director, Division of Biometrics IV

cc:
Orig. NDA #20-759
Orig. NDA #20-760
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Dr. Albrecht
HFD-590/Dr. Leissa
HFD-590/Dr. Alivisatos
HFD-590/Dr. Coyne
HFD-590/Dr. Roca
HFD-590/Ms. Fogarty
HFD-725/Dr. Huque
HFD-725/Dr. Silliman
HFD-725/Dr. Jiang
HFD-725/Dr. Lin
HFD-725/Ms. Shores
HFD-344/Dr. Thomas
This review contains 197 pages.