

V.B. Protocol 154-115

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (200 MG DAILY) AND 14 DAYS OF ORAL CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Study Dates: 28 November 1994 - 20 March 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to clarithromycin in the treatment of subjects with acute sinusitis.

Study Design: Study 154-115 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg daily as a single dose) administered orally for 10 days versus clarithromycin (1000 mg daily as 500 mg twice daily), administered orally for 14 days for the treatment of acute sinusitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 16 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). Bacteriologic response was not assessed in this trial (i.e., no subject in either treatment group underwent trans-antral aspiration of the sinus, had a culture of an aspirate, or a blood culture during this study).

Clinical response was to be determined by the investigator and evaluated at Visit 2 (Day 4), the end of therapy (Day 15), and at the end of study (Day 28) or at the time of discontinuation from study. 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 pretreatment clinical signs of infection including post-nasal discharge, facial pain, hyposmia, jaw pain with mastication, and nasal congestion and improvement or resolution of positive sinus x-ray findings. The clinical response was to be classified as cure (resolution of signs and symptoms to the level that existed before baseline), improvement (improvement but incomplete resolution of signs and symptoms to the level that existed before baseline), or failure (lack of resolution or worsening of signs and symptoms or a need for an additional antibiotic).

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

Secondary efficacy endpoints were:

- Investigator-defined clinical response at EOT, and sponsor-defined clinical response and investigator-defined clinical response 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 5b.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 5b.1. Evaluation Groups

Evaluation Groups:	Trovafoxacin (200 mg/day)	Clarithromycin (500 mg BID)
Entered Study ^a	206	214
All Treated	203 (100%) ^b	214 (100%) ^b
Completed Study	186 (92%)	200 (93%)
Completed Treatment	158 (78%)	181 (85%)
Evaluated for Efficacy		
Clinical Intent-to-treat	193 (94%)	203 (95%)
Clinically Evaluable ^c	162 (79%)	188 (88%)
Assessed for Safety		
Adverse Events	203 (100%)	214 (100%)
Laboratory Tests	197 (97%)	211 (99%)

- a Subjects who were randomized.
- b Percentages based on treated subjects as the denominator
- c Based on End of Treatment assessment.

***Reviewer's Note:** A lower percentage of patients completed treatment and were evaluable for efficacy in the trovafoxacin arm. The difference in patients completing treatment did not reach statistical significance ($p=0.08$ using the test of equal proportions based on the normal approximation to the binomial distribution), whereas the difference in patients who were evaluable did ($p=0.025$ using the same test as above). The difference in the number of evaluable patients appears to be largely due to the greater number of patients who discontinued treatment due to an adverse event in the trovafoxacin arm (see Table 5b.2).*

Since a significantly lower percentage of trovafoxacin patients were included in the evaluable analysis, intent-to-treat efficacy results are presented below (in addition to the usual evaluable efficacy results).

Forty-six (46) of 420 randomized subjects were not clinically evaluable (31/206 [15%] subjects in the trovafoxacin group and 15/214 [7%] subjects in the clarithromycin group). The most common reasons for exclusion from the clinically evaluable efficacy analyses were insufficient therapy due to early discontinuation from treatment or study (23/206 [11%], trovafoxacin and 11/214 [5%], clarithromycin). Other reasons were randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness.

In addition, 13 randomized subjects (6%) in the trovafoxacin and 11 randomized subjects (5%) in the clarithromycin treatment groups had an inappropriate baseline diagnosis (negative baseline x-ray) and were therefore excluded from both the clinical intent-to-treat and the clinically evaluable analyses.

Discontinuations

Of the 417 treated subjects, 78 subjects were prematurely discontinued from treatment as summarized in Table 5b.2.

Table 5b.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)			
	Trovafloxacin 200 mg (N=203)	Clarithromycin 500 mg BID (N=214)	Total (N=417)
Number and Percentage (%) of Subjects			
Total Discontinued	45 (22%)	33 (15%)	78 (19%)
Discontinuations Related to Study Drug:	32 (16%)	16 (7%)	48 (12%)
Adverse Event	28 (14%)	11 (5%)	39 (9%)
Insufficient Clinical Response	4 (2%)	5 (2%)	9 (2%)
Discontinuations Unrelated to Study Drug:	13 (6%)	17 (8%)	30 (7%)
Adverse Event	4 (2%)	1 (<1%)	5 (1%)
Did Not Meet Randomization Criteria	9 (4%)	9 (4%)	18 (4%)
Laboratory Abnormality	0	1 (<1%)	1 (<1%)
Other	0	1 (<1%)	1 (<1%)
Withdrew Consent	0	5 (2%)	5 (1%)

Reviewer's Note: A significantly higher proportion of trovafloxacin patients discontinued due to adverse events (14% of trovafloxacin patients versus 5% of clarithromycin patients, $p=0.002$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Demographics

The two treatment groups were comparable with respect to age, race, weight, smoking classification and the distribution of males and females. The distribution of subjects according to smoking classification was similar between the trovafloxacin and clarithromycin groups (20% and 23% ex-smoker, 57% and 50% never smoked, and 23% and 27% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for subjects in the intent-to-treat analysis was acute sinusitis. The median (range) duration since onset of acute sinusitis was 8 days (1-29 days) for subjects in the trovafloxacin group and 7 days (1-38 days) for subjects in the clarithromycin group. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the two treatment groups with respect to medical history at baseline.

Clinical Response

A summary of clinical response for clinically evaluable subjects at EOT and EOS is presented by treatment group in Table 5b.3. Clinical response was considered therapeutically equivalent between trovafloxacin and clarithromycin at both EOT and EOS.

Table 5b.3. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 200 mg (N=162)*	Clarithromycin 500 mg BID (N=188)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	161 (100%)	188 (100%)	
Success (Cure + Improvement)	136 (84%)	165 (88%)	(-10.6, 4.0)
Distribution of Clinical Response:			
Cure	67 (42%)	84 (45%)	
Improvement	69 (43%)	81 (43%)	
Failure	25 (16%)	23 (12%)	
End of Study:			
Number of Subjects Assessed	160 (100%)	184 (100%)	
Success (Cure + Improvement)	118 (74%)	138 (75%)	(-10.5, 8.0)
Distribution of Clinical Response:			
Cure	85 (53%)	112 (61%)	
Improvement	33 (21%)	26 (14%)	
Failure	25 (16%)	23 (13%)	
Relapse	17 (11%)	23 (13%)	
CI=confidence interval for the difference in rates, Trovafloxacin minus Clarithromycin a Subject 5077-0052 did not have an end of treatment assessment within the evaluable window.			

A summary of clinical response for ITT subjects at EOT and EOS is presented by treatment group in Table 5b.4. Clinical response was considered therapeutically equivalent between trovafloxacin and clarithromycin at both EOT and EOS.

Reviewer's Note: The intent-to-treat results are similar to the evaluable results, but with slightly lower success rates.

Table 5b.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Intent-to-Treat Subjects)			
	Trovafloxacin 200 mg (N=193)	Clarithromycin 500 mg BID (N=203)^a	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	193 (100%)	202 (100%)	
Success (Cure + Improvement)	154 (80%)	168 (83%)	(-11.0, 4.3)
Distribution of Clinical Response:			
Cure	72 (37%)	84 (42%)	
Improvement	82 (42%)	84 (42%)	
Failure	39 (20%)	34 (17%)	
End of Study Visit:			
Number of Subjects Assessed	193 (100%)	203 (100%)	
Success (Cure + Improvement)	135 (70%)	145 (71%)	(-10.5, 7.5)
Distribution of Clinical Response:			
Cure	94 (49%)	118 (58%)	
Improvement	41 (21%)	27 (13%)	
Failure	39 (20%)	35 (17%)	
Relapse	19 (10%)	23 (11%)	

^a Subject 5078-0238 was not assessed at the end of treatment.

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 5b.5. Tables 5b.6 and 5b.7 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 5b.5. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg (N=203)	Clarithromycin 500 mg BID (N=214)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	119 (59%)	124 (58%)
Treatment-Related Adverse Events	76 (37%)	81 (38%)
Discontinuations Due to an Adverse Event^{a, b}	32 (16%)	12 (6%)
Clinically Significant Laboratory Abnormalities	17/197 (9%)	26/211 (12%)
<p>a With the exception of four subjects in the trovafloxacin 200 mg group and one subject in the clarithromycin group who were discontinued due to unrelated adverse events, all subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.</p> <p>b One additional subject (5132-0426) in the trovafloxacin group had an unrelated adverse event (ischemic colon) for which the investigator action taken was treatment given; hospitalization for surgery; however, on the subject summary section of the case report form the investigator classified the reason for withdrawal from the study as adverse event.</p>		

For subjects in the trovafloxacin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the central and peripheral nervous system. Twenty-six subjects (26/203, 13%) in this group were discontinued due to dizziness, headache, vertigo, paresthesia, and/or hypoesthesia. Four subjects (4/214, 2%) in the clarithromycin group were discontinued due to headache, dizziness, paresthesia and/or hypertension.

For subjects in the clarithromycin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system. Nine subjects (9/214, 4%) in the clarithromycin group were discontinued due to vomiting, nausea, diarrhea, coated tongue, abdominal pain and/or blood in stool. Thirteen subjects (13/203, 6%) in the trovafloxacin group were discontinued due to nausea, vomiting, tongue edema, diarrhea, abdominal pain, and/or loose stools.

All other adverse events leading to discontinuation were reported by three or less subjects in either treatment group.

One subject in the trovafloxacin group was discontinued from treatment due to interstitial nephritis (allergic) that was considered by the investigator to be related to study drug as described in the following narrative.

Subject 5083-0108, a 61 year-old white male with a history of chronic interstitial nephritis, confirmed by biopsy, proteinuria and mild renal insufficiency and a present diagnosis of acute sinusitis was treated with trovafloxacin 200 mg for 10 days. At baseline the subject's serum creatinine value was found to be elevated

and his urine protein finding Repeat serum creatinine values on Days 3 and 10 showed further increases The subject was discontinued from treatment on Day 14 due to what the investigator defined as mild interstitial nephritis (allergic) which was not confirmed by biopsy or any other procedure. On Day 17, decreases in serum creatinine and urine protein were noted.

Treatment with prednisone was initiated on Day 18 and this event was considered to be resolved on Day 25.

Table 5b.6. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)				
	Trovafloxacin 200 mg (N=203)		Clarithromycin 500 mg BID (N=214)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event^c	119	(59%)	124	(58%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	89	(44%)	36	(17%)
Dizziness	69	(34%)	5	(2%)
Headache	29	(14%)	27	(13%)
GASTROINTESTINAL SYSTEM	39	(19%)	52	(24%)
Nausea	23	(11%)	21	(10%)
Diarrhea	8	(4%)	12	(6%)
Abdominal Pain	5	(2%)	6	(3%)
Flatulence	3	(1%)	7	(3%)
Dyspepsia	1	(<1%)	7	(3%)
PSYCHIATRIC SYSTEM	13	(6%)	10	(5%)
Insomnia	5	(2%)	6	(3%)
REPRODUCTIVE SYSTEM	5	(2%)	5	(2%)
Vaginitis ^d	4	(3%)	3	(2%)
SPECIAL SENSES	12	(6%)	48	(22%)
Taste Perversion	2	(<1%)	44	(21%)
<p>a ≥3 % of subjects in any treatment group.</p> <p>b Includes data up to 7 days after last dose of active study medication</p> <p>c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.</p> <p>d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.</p>				

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Table 5b.7. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - Treatment-Related (All Treated Subjects)

	Trovfloxacin 200 mg (N=203)		Clarithromycin 500 mg BID (N=214)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	76	(37%)	81	(38%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	60	(30%)	10	(5%)
Dizziness	54	(27%)	4	(2%)
Headache	7	(3%)	4	(2%)
Parésthésia	4	(2%)	1	(<1%)
GASTROINTESTINAL SYSTEM	30	(15%)	39	(18%)
Nausea	19	(9%)	18	(8%)
Diarrhea	4	(2%)	10	(5%)
Abdominal Pain	4	(2%)	6	(3%)
Flatulence	2	(<1%)	5	(2%)
Vomiting	3	(1%)	4	(2%)
Dyspepsia	1	(<1%)	4	(2%)
REPRODUCTIVE SYSTEM	2	(<1%)	4	(2%)
Vaginitis ^d	2	(2%)	3	(2%)
SPECIAL SENSES	5	(2%)	41	(19%)
Taste Perversion	2	(<1%)	41	(19%)

a ≥2 % of subjects in any treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.
 d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.

Two subjects in each treatment group experienced serious adverse events unrelated to study drug. The outcome of one event (presumed myocardial infarction) in the clarithromycin group was death.

Subject 5090-0129 in the trovafloxacin group and Subject 5079-0219 in the clarithromycin group were discontinued from treatment due to elevated serum glucose values attributed to the subject's underlying diabetic condition and to thrombocytopenia of unknown etiology, respectively.

Sponsor's Summary and Conclusion: Trovfloxacin 200 mg once daily for 10 days was statistically equivalent to clarithromycin 500 BID for 14 days for the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 16% in the trovafloxacin group and 6% in the clarithromycin group. The overall percentage of adverse events was 59% in the trovafloxacin group and 58% in the clarithromycin group; treatment-related adverse events were also reported at similar rates (37% and 38%, respectively). Subjects in the trovafloxacin group had a lower percentage

of adverse events associated with the special senses (6% versus 22%), and a higher percentage of adverse events associated with the central and peripheral nervous system (44% versus 17%) compared to the clarithromycin group; all other adverse events were reported at similar rates for both treatment groups. The most commonly reported adverse events were dizziness and taste perversion in the trovafloxacin and clarithromycin groups, respectively. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

Reviewer's Summary and Conclusion: 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 EQS 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 ($p<0.0001$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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V.C. Protocol 154-138

A RANDOMISED, OPEN, MULTI-CENTRE TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (200 MG ONCE DAILY) WITH ORAL AMOXYCILLIN/CLAVULANATE (AUGMENTIN, 500/125 MG TID) FOR THE TREATMENT OF ACUTE SINUSITIS.

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

Study Dates: 25 May 1995 - 11 April 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to amoxicillin/clavulanate in the treatment of subjects with acute sinusitis.

Study Design: Study 154-138 was a randomized, unblinded, comparative, multicenter trial of trovafloxacin administered orally for 10 days versus amoxicillin/clavulanate administered orally for 10 days for the treatment of acute sinusitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 18 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray, were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). Bacteriologic response was not uniformly assessed in this trial

(bacteriologic assessment was not required in the protocol, thus data were collected on only a few patients).

Clinical response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), the end of treatment (Visit 3, Day 11), and at the end of study (Visit 4, Day 24) or at the time of discontinuation from study. Clinical evaluation of 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 and compared to the pretreatment assessment. Clinical assessment was to be based upon resolution or improvement of clinical and laboratory signs of infection such as improvement in post-nasal discharge, facial pain, hyposmia, jaw pain with mastication, and nasal congestion and improvement or resolution of positive sinus x-ray findings. The clinical response was to be classified as cure (resolution of signs and symptoms of acute sinusitis to a baseline level that existed prior to the occurrence of the acute illness and improvement in x-ray findings), improvement (improvement but incomplete resolution of signs and symptoms to the level that existed before baseline and no requirement for an additional antibiotic), or failure (lack of resolution or worsening of any of the signs and symptoms of acute sinusitis or a need for an additional antibiotic).

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

Secondary efficacy endpoints were the investigator-defined clinical response at EOT, and sponsor- and investigator-defined clinical response 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:

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Analysis Groups

Table 5c.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

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Table 5c.1. Evaluation Groups

Evaluation Groups:	Trovafloracin (200 mg/day)	Amoxicillin/Clavulanate (500/125 mg TID)
Entered Study ^a	207	211
All Treated	205 (100%)	209 (100%)
Completed Study	191 (93%)	201 (96%)
Completed Treatment	189 (92%)	196 (94%)
Evaluated for Efficacy ^b		
Clinical Intent-to-treat	202 (98%)	211 (100%)
Clinically Evaluable	189 (91%)	203 (96%)
Assessed for Safety		
Adverse Events	205 (100%)	209 (100%)
Laboratory Tests	200 (98%)	206 (99%)

a Subjects who were randomized.

b Evaluability was determined at end of treatment.

Reviewer's Note: A significantly lower percentage of trovafloxacin patients were included in the evaluable efficacy analysis ($p = 0.025$ using the test of equal proportions based on the normal approximation to the binomial distribution). Intent-to-treat efficacy results will be presented below, in addition to evaluable efficacy results.

Of the 207 trovafloxacin and 211 amoxicillin/clavulanate randomized subjects, five trovafloxacin subjects (Subjects 5274-0053, 5278-0526, 5703-0338, 5723-0253, and 6462-0160) and no amoxicillin/clavulanate subject had an inappropriate baseline diagnosis (i.e., no acute sinusitis at baseline as defined by the study protocol) and were excluded from all clinical intent-to-treat and evaluable analyses.

Of the 202 trovafloxacin and 211 amoxicillin/clavulanate clinically intent-to-treat subjects, 13 in the trovafloxacin group and 8 in the amoxicillin/clavulanate were not clinically evaluable; therefore, 189 subjects in the trovafloxacin group and 203 subjects in the amoxicillin/clavulanate group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (9/207 [4%], trovafloxacin and 5/211 [2%], amoxicillin/clavulanate). Other reasons were randomized but not treated, no post-baseline clinical assessments, no post-baseline clinical response in evaluable window, prior antibiotic therapy, and concomitant antibiotic therapy for intercurrent illness.

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Discontinuations

Of the 205 trovafloxacin and 209 amoxicillin/clavulanate treated subjects, 16 trovafloxacin subjects and 13 amoxicillin/clavulanate subjects were prematurely discontinued from treatment as summarized in Table 5c.2.

Reviewer's Note: A higher percentage of trovafloxacin patients discontinued due to adverse events, although this difference did not reach statistical significance ($p = 0.09$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 5c.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)		
	Trovafloxacin 200 mg (N=205)	Amoxicillin/Clavulanate 500/125 mg TID (N=209)
	Number and Percentage (%) of Subjects	
Total Discontinued	16 (8%)	13 (6%)
Discontinuations Related to Study Drug:	15 (7%)	6 (3%)
Adverse Event	13 (6%)	6 (3%)
Insufficient Response	2 (<1%)	0
Discontinuations Unrelated to Study Drug:	1 (<1%)	7 (3%)
Adverse Event	1 (<1%)	0
Laboratory Abnormality	0	1 (<1%)
Lost To Follow-Up	0	1 (<1%)
Other	0	2 (<1%)
Withdrawn Consent	0	3 (1%)

Demographics

One hundred-two (102) of the 205 treated trovafloxacin subjects (50%) were males and 103 (50%) were females and 86 of the 209 treated amoxicillin/clavulanate subjects (41%) were males and 123 (59%) were females. The males and females in the trovafloxacin and amoxicillin/clavulanate treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and amoxicillin/clavulanate treatment groups (21% and 23% ex-smoker, 45% and 49% never smoked, and 34% and 28% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The median (range) duration since onset of sinusitis was 6 days (1-28 days) for clinically evaluable and intent-to-treat subjects in both the trovafloxacin and amoxicillin/clavulanate groups. There were no marked differences between subjects in the trovafloxacin and amoxicillin/clavulanate groups with respect to medical history at baseline.

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Clinical Response

A summary of sponsor-defined clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 5c.3. Clinical response was considered therapeutically equivalent between trovafloxacin and amoxicillin/clavulanate at both EOT and EOS.

Table 5c.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloxacin 200 mg (N=189)		Amoxicillin/Clavulanate 500/125 mg TID (N=203)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed ^a	188	(100%)	201	(100%)	
Success (Cure + Improvement)	181	(96%)	186	(93%)	(-0.8, 8.3)
Distribution of Clinical Response:					
Cure	90	(48%)	80	(40%)	
Improvement	91	(48%)	106	(53%)	
Failure	7	(4%)	15	(7%)	
End of Study:					
Number of Subjects Assessed	175	(100%)	196	(100%)	
Success (Cure + Improvement)	158	(90%)	175	(89%)	(-5.2, 7.2)
Distribution of Clinical Response:					
Cure	123	(70%)	125	(64%)	
Improvement	35	(20%)	50	(26%)	
Failure	7	(4%)	15	(8%)	
Relapse	10	(6%)	6	(3%)	
a Three subjects (1 trovafloxacin; 2 amoxicillin/clavulanate) had a missing assessment at end of treatment but were assessed at end of study.					

A summary of sponsor-defined clinical response for ITT subjects at the end of treatment and at the end of study is presented by treatment group in Table 5c.4. Clinical response was

considered therapeutically equivalent between trovafloxacin and amoxicillin/clavulanate at both EOT and EOS.

Reviewer's Note: The intent-to-treat results are similar to the evaluable results, with slightly lower success rates.

Table 5c.4. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Intent-to-Treat Subjects)

	Trovafloxacin 200 mg (N=202)		Amoxicillin/ Clavulanate 500/125 mg TID (N=211)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed ^a	202	(100%)	210	(100%)	
Success (Cure + Improvement)	191	(95%)	191	(91%)	(-1.4, 8.6)
Distribution of Clinical Response:					
Cure	93	(46%)	82	(39%)	
Improvement	98	(49%)	109	(52%)	
Failure	11	(5%)	19	(9%)	
End of Study Visit:					
Number of Subjects Assessed	202	(100%)	211	(100%)	
Success (Cure + Improvement)	180	(89%)	186	(88%)	(-5.2, 7.1)
Distribution of Clinical Response:					
Cure	136	(67%)	132	(63%)	
Improvement	44	(22%)	54	(26%)	
Failure	11	(5%)	19	(9%)	
Relapse	11	(5%)	6	(3%)	

a One subject in the amoxicillin/clavulanate group had a missing assessment at the end of treatment but was assessed at the end of study.

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Bacteriologic Response

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Sixteen (16) trovafloxacin and 14 amoxicillin/clavulanate clinically intent-to-treat subjects had trans-antral aspiration of the sinus performed at baseline. All 16 trovafloxacin subjects with pathogens isolated at baseline had a sponsor-defined clinical response of cure or improved at EOT. At EOS, 12 of the 16 subjects were designated as clinically cured or improved and four subjects had a clinical response of relapse. These four subjects had one or more of the following pathogens isolated at baseline: *Staphylococcus aureus*, *H. influenzae*, *Acinetobacter sp.*, *Fusobacterium nucleatum*, *Prevotella sp.*, and/or *Streptococcus anginosus*. The baseline pathogen was not present on repeat culture in three of the four subjects; in the remaining subject *Prevotella sp.* was still present. In the amoxicillin/clavulanate group, ten of the 14 subjects with pathogens isolated at baseline had a sponsor-defined clinical response of cure or improved at EOT and EOS and four subjects were designated as clinical failures at both EOT and EOS. These four subjects had one or more of the following pathogens isolated at baseline: *Fusobacterium sp.*, *Veillonella sp.*, *Acinetobacter sp.*, *E. agglomerans*, *Peptostreptococcus sp.* and/or *K. pneumoniae*. None of the four subjects designated as a clinical failure had a repeat culture.

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 5c.5. Tables 5c.6 and 5c.7 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 5c.5. Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg	Amoxicillin/ Clavulanate 500/125 mg TID
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	77/205 (38%)	62/209 (30%)
Treatment-Related Adverse Events	52/205 (25%)	48/209 (23%)
Discontinuations From Treatment Due to an Adverse Event	15/205 (7%)	7/209 (3%)
Clinically Significant Laboratory Abnormalities	38/200 (19%)	56/206 (27%)

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Reviewer's Note: Trovafloxacin patients reported a higher number of adverse events (all causalities) than did amoxicillin/clavulanate patients, although this difference did not reach statistical significance ($p = 0.09$ using the test of equal proportions based on the normal approximation to the binomial distribution). Amoxicillin/clavulanate patients experienced a significantly higher number of clinically significant laboratory abnormalities ($p = 0.05$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 5c.6. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)		
	Trovafloxacin (N=205)	Amoxicillin/ Clavulanate (N=209)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	77 (38%)	62 (30%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	46 (22%)	9 (4%)
Dizziness	34 (17%)	2 (<1%)
Headache	15 (7%)	4 (2%)
GASTROINTESTINAL SYSTEM	19 (9%)	43 (21%)
Diarrhea	1 (<1%)	19 (9%)
Dyspepsia	0	6 (3%)
Nausea	9 (4%)	9 (4%)
REPRODUCTIVE SYSTEM	1 (<1%)	6 (3%)
Vaginitis ^c	1 (<1%)	5 (4%)

a ≥3% of subjects in either treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Preferred term is gender-specific; the percentages are based on the number of males and females, appropriately.

Table 5c.7. Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - Treatment-Related (All Treated Subjects)		
	Trovafloxacin (N=205)	Amoxicillin/ Clavulanate (N=209)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	52 (25%)	48 (23%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		
Dizziness	36 (18%)	4 (2%)
Headache	30 (15%)	2 (<1%)
	9 (4%)	1 (<1%)
GASTROINTESTINAL SYSTEM	11 (5%)	39 (19%)
Diarrhea	1 (<1%)	19 (9%)
Dyspepsia	0	6 (3%)
Nausea	6 (3%)	9 (4%)
REPRODUCTIVE SYSTEM	1 (<1%)	6 (3%)
Vaginitis ^c	1 (<1%)	5 (4%)
<p>a ≥2% of subjects in either treatment group.</p> <p>b Includes data up to 7 days after last dose of active study medication.</p> <p>c Preferred term is gender-specific and the percentages are based on the number of males and females, appropriately.</p>		

No deaths were reported during this study. One subject in the trovafloxacin group had a serious adverse event (intentional overdose with Co-proxamol), which occurred ten days after the last treatment dose and led to hospitalization. This serious adverse event was attributed to reactive depression and was noted as having resolved. No serious adverse events were reported during this study for any subject in the amoxicillin/clavulanate group.

Sponsor’s Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was statistically equivalent to amoxicillin/clavulanate 500/125 mg three times daily for 10 days for clinical success rates at the end of treatment in subjects with acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 7% in the trovafloxacin group and 3% in the amoxicillin/clavulanate group. The overall percentage of all and treatment-related adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the amoxicillin/clavulanate group (38% and 25% versus 30% and 23%, respectively). The most commonly reported treatment-related adverse events were dizziness in the trovafloxacin group and diarrhea in the amoxicillin/clavulanate group.

Reviewer’s Summary and Conclusion: 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).

VI. UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

The efficacy and safety of oral trovafloxacin in the treatment of uncomplicated skin infections was assessed in two double-blind, comparative trials. The comparator agents were flucloxacillin (154-129) and cefpodoxime (154-130).

Reviewer's Note: The sponsor assessed whether efficacy differed in various subgroups in the uncomplicated skin and skin structure 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.

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VI.A. Protocol 154-129

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND FLUCLOXACILLIN (500 MG QID) FOR THE TREATMENT OF UNCOMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE

Study Dates: 10 July 1995 - 10 January 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to that of flucloxacillin in the treatment of subjects with uncomplicated infections of the skin and skin structure.

Study Design: Study 154-129 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg daily as a single dose) administered orally for 7 days versus flucloxacillin (2000 mg daily as 500 mg every 6 hours), administered orally for 7 days for the treatment of uncomplicated infections of the skin and skin structure.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 16 years of age at the baseline assessment, with clinically documented uncomplicated 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 (individual pathogen response).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment visit (Visit 2, Day 8), and at the end of study (Day 30) or at the time of discontinuation from study. 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 including erythema, pain, induration or swelling and general condition. The clinical response was to be classified as cure (resolution of signs and symptoms to the level that existed before baseline), improvement (incomplete resolution of signs and symptoms to the level that existed before baseline and no

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requirement for additional antibiotics), or failure (lack of resolution and or a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment visit (Visit 2, Day 8), and the end of study (Day 30) or at the time of discontinuation from 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 or relapse.

For all infections except cellulitis, culturable material was to be obtained at Visit 1. For simple abscesses and minor wound infections, the exudate was to be cultured. For impetiginous lesions, a swab was adequate. For cellulitis, an attempt was to be made to aspirate from the margin of the infected area if no other culturable material (e.g., an exudate from a vesicle) was present. If the location and type of uncomplicated skin or skin structure infection consistent with a possible anaerobic infection, e.g., a perianal abscess, anaerobic cultures were to be performed.

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

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Table 6a.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg/day)	Flucloxacillin (500 mg QID)
Entered Study ^a	141 (100%)	139 (100%)
All Treated	140 (>99%)	138 (>99%)
Completed Treatment	128 (91%)	133 (96%)
Completed Study	135 (96%)	135 (98%)
Evaluated for Efficacy		
Clinical Intent-to-treat	141 (100%)	139 (100%)
Clinically Evaluable ^b	130 (92%)	133 (96%)
Bacteriological Intent-to-Treat	81 (57%)	86 (62%)
Bacteriologically Evaluable ^b	76 (54%)	83 (60%)
Assessed for Safety		
Adverse Events	140 (100%)	138 (100%)
Laboratory Tests	128 (91%)	132 (96%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Of the 141 trovafloxacin and 139 flucloxacillin clinical ITT subjects, 11 subjects in the trovafloxacin group and six subjects in the flucloxacillin group were not clinically evaluable; therefore, 130 trovafloxacin and 133 flucloxacillin subjects were clinically evaluable. The most common reason for exclusion from the clinically evaluable efficacy analyses was insufficient therapy (8/141 [6%], trovafloxacin and 4/139 [3%], flucloxacillin). Other reasons were randomized but not treated, 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 141 trovafloxacin and 139 flucloxacillin clinical ITT subjects, 60 subjects in the trovafloxacin group and 53 subjects in the flucloxacillin group had negative baseline cultures; therefore, 81 trovafloxacin and 86 flucloxacillin subjects were included in the bacteriological ITT analyses.

Of the 130 trovafloxacin and 133 flucloxacillin clinically evaluable subjects, 54 subjects in the trovafloxacin group and 50 subjects in the flucloxacillin group were not included in the bacteriologically evaluable analyses; therefore, 76 trovafloxacin subjects and 83 flucloxacillin subjects were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (54/141 [38%], trovafloxacin and 50/139 [36%], flucloxacillin). Other reasons were no post-baseline culture or baseline culture outside the evaluability window.

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Discontinuations

Of the 140 trovafloxacin and 138 flucloxacillin treated subjects, 12 trovafloxacin and five flucloxacillin subjects were prematurely discontinued from treatment as summarized in Table 6a.2.

Table 6a.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloxacin 100 mg (N=140)		Flucloxacillin 500 mg QID (N=138)	
Number and Percentage (%) of Subjects				
Total Discontinued	12	(9%)	5	(4%)
Discontinuations Related to Study Drug:	9	(6%)	4	(3%)
Adverse Event	8	(6%)	3	(2%)
Insufficient Clinical Response	1	(<1%)	1	(<1%)
Discontinuations Unrelated to Study Drug:	3	(2%)	1	(<1%)
Adverse Event	2	(1%)	0	
Lost to Follow-up	1	(<1%)	1	(<1%)

Reviewer's Note: A marginally higher number of trovafloxacin patients discontinued treatment prematurely (p=0.09 using the test of equal proportions based on the normal approximation to the binomial distribution).

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Demographics

Sixty-nine (69) of the 140 treated trovafloxacin subjects (49%) were males and 71 were females (51%) and 70 of the 138 treated flucloxacillin subjects (51%) were males and 68 were females (49%). The males and females in the trovafloxacin and flucloxacillin 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 flucloxacillin groups was 44.1 years and 47.3 years, respectively. Sixteen percent of subjects in the trovafloxacin group and 25% of subjects in the flucloxacillin group were ≥65 years of age.

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The primary diagnosis for clinical ITT subjects was uncomplicated skin and skin structure infection. The median duration since onset of infection was 4 days in each treatment group. Subject 5278-0178 in the flucloxacillin group had a reported duration since onset of infection (cellulitis) of 227 days; however, this included multiple episodes of infection. The subject's actual duration for the most recent onset of cellulitis was 46 days.

The most commonly reported type of infection reported among clinical ITT subjects in both treatment groups was simple abscess (28, trovafloxacin and 24, flucloxacillin). Other types of infections included impetiginous lesion, minor wound infection, otitis externa, cellulitis with and without a baseline pathogen, paronychia, leg ulcers and others (including infected burn, ingrown toenail, insect bite, superficial ulcers, dyshidrosis, erysipelas, pyodermal vegetans, infected serbareous cyst or bedsores). 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. Fourteen (14) trovafloxacin subjects and nine flucloxacillin subjects had skin infections that required surgical intervention at baseline and five trovafloxacin subjects and four flucloxacillin subjects had skin infections that required surgical intervention post-baseline. Subject 6080-0239 in the flucloxacillin group had a surgical procedure done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report form. Subject 6141-0267 in the trovafloxacin group had a skin infection that required surgical intervention both at baseline and post-baseline. The most commonly reported type of skin infection for subjects requiring surgical intervention in both treatment groups was simple abscess (11/18 [61%], trovafloxacin and 6/13 [60%], flucloxacillin).

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 6a.3.

Table 6a.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT Subjects)		
	Trovafloxacin 100 mg (N=141)	Flucloxacillin 500 mg QID (N=139)
Type of Infection^a	Number and Percentage (%) of Subjects	
Simple Abscess	28 (20%)	24 (17%)
Impetiginous Lesion	23 (16%)	24 (17%)
Minor Wound	17 (12%)	21 (15%)
Cellulitis with a Baseline Pathogen	12 (9%)	19 (14%)
Cellulitis without a Baseline Pathogen	19 (13%)	19 (14%)
Otitis Externa	19 (13%)	19 (14%)
Paronychia	16 (11%)	11 (8%)
Leg Ulcers	8 (6%)	3 (2%)
Other	11 (8%)	12 (9%)
Subjects Requiring Surgical Intervention	18 (12%)	13 ^b (9%)
At Baseline	14 (9%)	9 (6%)
Post-Baseline	5 (3%)	3 (2%)
Before the EOT Assessment	4 (2%)	2 (1%)
After the EOT Assessment	1 (<1%)	1 (<1%)

a A subject may have had more than one type of infection.
 b Subject 6080-0239 had a surgical procedure done post-baseline. The type and timing of the procedure was not listed on the subject's case report form.

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There were no marked differences between subjects in the trovafloxacin and flucloxacillin groups with respect to medical history at baseline. A small percentage of subjects in each treatment group (3%, trovafloxacin; 2%, flucloxacillin) had diabetes mellitus without reported complication at baseline.

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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 6a.4. Trovafloxacin was considered therapeutically equivalent to flucloxacillin at both EOT and EOS.

Table 6a.4. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 100 mg (N=130)	Flucloxacillin 500 mg QID (N=133)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment			
Number of Subjects Assessed ^a	129 (100%)	133 (100%)	
Success (Cure + Improvement)	117 (91%)	115 (86%)	(-3.4, 11.9)
Distribution of Clinical Response:			
Cure	72 (56%)	60 (45%)	
Improvement	45 (35%)	55 (41%)	
Failure	12 (9%)	18 (14%)	
End of Study			
Number of Subjects Assessed	125 (100%)	123 (100%)	
Success (Cure + Improvement)	106 (85%)	97 (79%)	(-3.6, 15.5)
Distribution of Clinical Response:			
Cure	97 (78%)	92 (75%)	
Improvement	9 (7%)	5 (4%)	
Failure	12 (10%)	18 (15%)	
Relapse	7 (6%)	8 (7%)	

a Subject 5895-0252 in the trovafloxacin group was not assessed at the end of treatment visit.

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogen (*S. aureus*) among clinically evaluable subjects is presented by treatment group in Table 6a.5.

Table 6a.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)				
	Trovafloxacin 100 mg (N=130)	Flucloxacillin 500 mg QID (N=133)	Trovafloxacin 100 mg (N=125)	Flucloxacillin 500 mg QID (N=123)
Number of Subjects				
Pathogen	End of Treatment		End of Study	
<i>S. aureus</i>	39/42 (93%)	42/47 (89%)	34/40 (85%)	33/42 (79%)

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

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, otitis externa, paronychia, leg ulcers, or other) in clinical ITT subjects, a trend towards a higher (≥10 percentage points) clinical success rate at EOT and EOS was observed among subjects with a simple abscess in the trovafloxacin group (26/28, 93% and 25/28, 89%, respectively) compared to the flucloxacillin group (19/24, 79% and 19/24, 79%, respectively). In subjects with impetiginous lesion, similar results were observed between the

two treatment groups at the end of treatment (trovafloxacin: 22/23, 96%; flucloxacillin: 22/24, 92%), but a higher clinical success rate was observed in the trovafloxacin group at the end of study (trovafloxacin: 22/23, 96%; flucloxacillin: 19/24, 79%). Similar clinical success rates were observed between the two treatment groups for subjects with the other types of infection (minor wound infection, cellulitis with and without a baseline pathogen, otitis externa, paronychia, leg ulcers, or other); however, due to the small number of subjects in each treatment group no definitive conclusions can be drawn.

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 6a.6.

	Trovafloxacin 100 mg (N=141)		Flucloxacillin 500 mg QID (N=139)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection ^a	EOT	EOS	EOT	EOS
Simple Abscess	26/28 (93%)	25/28 (89%)	19/24 (79%)	19/24 (79%)
Impetiginous Lesion	22/23 (96%)	22/23 (96%)	22/24 (92%)	19/24 (79%)
Minor Wound Infection	14/15 (93%)	15/17 (88%)	20/21 (95%)	19/21 (90%)
Cellulitis Without a Baseline Pathogen	16/19 (84%)	16/19 (84%)	16/19 (84%)	15/19 (79%)
Cellulitis With a Baseline Pathogen	11/12 (92%)	10/12 (83%)	17/19 (89%)	16/19 (84%)
Otitis Externa	15/19 (79%)	14/19 (74%)	16/19 (84%)	13/19 (68%)
Paronychia	15/15 (100%)	14/16 (88%)	10/11 (91%)	10/11 (91%)
Leg Ulcers	3/8 (38%)	1/8 (13%)	2/3 (67%)	2/3 (67%)
Other	9/11 (82%)	8/11 (73%)	8/12 (67%)	7/12 (58%)

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

Reviewer's Note: Although the numbers are small, trovafloxacin did not appear very effective against leg ulcers. Only 1 of 8 patients (13%) was considered a clinical success at EOS.

When sponsor-defined clinical response was subset by timing of surgical intervention in clinical ITT subjects, similar success rates were observed between treatment groups at both the end of treatment and at the end of study, for subjects with no surgical intervention. Among subjects with surgical intervention at baseline or 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 6a.7.

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

	Trovafloxacin 100 mg (N=141)		Flucloxacillin 500 mg QID (N=139)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention ^a	EOT		EOS	
No Surgical Intervention	106/120 (88%)	102/123 (83%)	109/126 (87%)	102/126 (81%)
Surgical Intervention at Baseline	13/14 (93%)	13/14 (93%)	8/9 (89%)	7/9 (78%)
Surgical Intervention Post Baseline				
Before the EOT Assessment	1/4 (25%)	1/4 (25%)	1/2 (50%)	1/2 (50%)
After the EOT Assessment	1/1 (100%)	1/1 (100%)	1/1 (100%)	0

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

Bacteriologic Response

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

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

	Trovafloxacin 100 mg (N=76)	Flucloxacillin 500 mg QID (N=83)	95% CI	Trovafloxacin 100 mg (N=69)	Flucloxacillin 500 mg QID (N=76)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>S. aureus</i>	26/42 (62%)	31/46 (67%)	-25.5, 14.5	32/38 (84%)	33/42 (79%)	-11.3, 22.6

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
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), discontinuations from treatment due to adverse events and clinically significant laboratory values is presented in Table 6a.9. Tables 6a.10 and 6a.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

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Table 6a.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 (N=140)	Flucloxacillin 500 mg QID (N=138)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	31/140 (22%)	27/138 (20%)
Treatment-Related Adverse Events	13/140 (9%)	18/138 (13%)
Discontinuations from Treatment Due to an Adverse Event	12/140 (9%)	3/138 (2%)
Discontinuations Due to a Treatment-Related Adverse Event	8/140 (6%)	3/138 (2%)
Clinically Significant Laboratory Abnormalities	21/128 (16%)	16/132 (12%)

Reviewer's Note: 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).

Table 6a.10. A Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - All Causalities (All Treated Subjects)		
	Trovafloxacin 100 mg (N=140)	Flucloxacillin 500 mg QID (N=138)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	31 (22%)	27 (20%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	9 (6%)	3 (2%)
Dizziness	4 (3%)	1 (<1%)
Headache	5 (4%)	2 (1%)
GASTROINTESTINAL SYSTEM	11 (8%)	16 (12%)
Dyspepsia	1 (<1%)	7 (5%)
Nausea	4 (3%)	4 (3%)
Vomiting	4 (3%)	2 (1%)
URINARY SYSTEM	2 (1%)	5 (4%)
Urinary Tract Infection	0 (0%)	4 (3%)

a ≥ 3 % of subjects in any treatment group.
 b Includes data up to 7 days after last dose of active study medication

Reviewer's Note: 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).

Table 6a.11. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)		
	Trovafloxacin 100 mg (N=140)	Flucloxacillin 500 mg QID (N=138)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	13 (9%)	18 (13%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	7 (5%)	0
Dizziness	3 (2%)	0
Headache	4 (3%)	0
GASTROINTESTINAL SYSTEM	7 (5%)	15 (11%)
Dyspepsia	1 (<1%)	7 (5%)
Nausea	2 (1%)	3 (2%)
Vomiting	3 (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.		

Four subjects, (3 subjects in the trovafloxacin group and 1 subject in the flucloxacillin group) had serious adverse events. All serious adverse events were attributed to other illnesses or the disease under study.

One subject in the trovafloxacin group had acute renal failure during this study as summarized in the following narrative.

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Trovafloxacin 100 mg

Subject 5884-0040, an 82-year-old white male with a history of cerebrovascular disease, asthma, Parkinson's Disease, and Paget's disease, and a primary diagnosis of uncomplicated skin and skin structure infection of the left great toe, received trovafloxacin (100 mg) once daily for 7 days. On Day 8, the subject had elevated creatinine and urea

values; baseline creatinine and urea values were unavailable for this subject. On Day 11, the subject was diagnosed with acute renal failure, which was considered by the investigator to be mild in intensity and not related to study drug. On Day 29, this subject had a repeat creatinine value that was within the normal range and a urea value that had decreased but was still above the normal range. This adverse event (acute renal failure) was listed as still present at the end of study.

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There were no deaths reported during the study.

Sponsor Summary and Conclusion: Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to flucloxacillin 500 mg every six hours for 7 days for clinical success rates at the end of treatment and the end of study for both intent-to-treat and evaluable subjects in subjects with uncomplicated skin and skin structure infection. Pathogen eradication rates were comparable for the most frequently isolated pathogen of (*S. aureus*) between treatment groups at the end of treatment and the end of study.