CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 020759/020760

MEDICAL REVIEW(S)

Medical Officer Review of Sinusitis indication

1. Overview of requested labeling and organisms.

The proposed consolidated labeling for NDAs 20-759 and 20-760 includes the following:

◆ Under INDICATIONS AND USAGE: "**ACUTE SINUSITIS** caused by *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* or *Streptococcus pneumoniae.*"

◆ Under DOSAGE AND ADMINISTRATION: the table entitled "Dosage Guidelines" calls for the Acute Sinusitis indication to be treated with a 10 day course of trovafloxacin at a dose of 200 mg per day.

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2. Comments on IDSA guidelines for the sinusitis indication.

The sinusitis section of the IDSA guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections (Clin Infect Dis 15 [Suppl 1]: S62-88, 1992) makes specific recommendations for the design and conduct of clinical trials in support of a sinusitis indication. This includes the following recommendations:

- a small (~ 100 patient) phase 2 trial in which sinus puncture and culture is performed for all patients, with at least 20 cases of each of the three major bacterial pathogens implicated (*S. pneumoniae, H. influenzae, M. catarrhalis*). In this phase 2 study, an 'open' study design is acceptable.
- assuming a favorable result from this phase 2 study (i.e., a clinical and presumed microbiological response rate of ≥ 70%), a larger comparative phase 3 study should be conducted using an active control arm. Sinus puncture and pre-treatment radiography are desirable but not required in this study.
- assessment during course of therapy in these trials should include clinical evaluation at 2-3 and 5-7 days after initiation of antimicrobial therapy, and weekly or biweekly thereafter until resolution of all symptoms and signs. Patients should be followed clinically for at least 2 weeks after completion of antimicrobial therapy to assess relapse or recurrence, clinical complications, and adverse effects of the antimicrobial regimen.

Thus, the IDSA guidelines recommend two studies, only one of which must have a microbiologic component for study entry.

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3. Points To Consider document regarding sinusitis.

The divisional Points to Consider document addresses the acute sinusitis indication as follows:

> "One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this trial, rigorous case definitions with specific clinical and either radiographic or ultrasonic entry criteria and endpoints as the primary effectiveness parameters should be used. No sinus aspiration should be required in this study, although sinus aspiration of patients judged to be therapeutic failures should be strongly encouraged to document any bacterial pathogen(s) not adequately treated in the trial. This trial should preferably be performed in the United States for purposes of US product registration.

Also suggested would be one open study utilizing sinus aspiration. This trial should establish successful microbial, clinical, and radiographic or ultrasonic outcome in at least 90 patients. This trial should be performed by at least two investigators in geographically diverse regions, and no one center should contribute more than 55% of the evaluable patients.

4. Structure of claim

The applicant has submitted three studies in support of this indication. Overall, these studies appear to conform with the recommendations of both the IDSA document and the Divisional PTC document.

a. study 154-114: a noncomparative, open-label, phase 2 study. Consent to undergo direct aspiration of the maxillary sinus was required for study entry. At the initiation of the study, at least 150 subjects were to be enrolled, with at least 15 investigators enrolling at least 10 subjects each. The completed study included 255 subjects, who were treated with 200 mg of trovafloxacin daily for 10 days. The investigator who enrolled the largest number of patients in this study was located in Costa Rica; other investigators were located in the UK, Finland, and the US.

b. study 154-115: a double-blinded, prospective, comparative trial which randomized subjects to either trovafloxacin (200 mg QD x 10 days) or clarithromycin (500 mg BID for 14 days). The completed study enrolled 206 patients in the trovafloxacin arm and 214 in the clarithromycin arm. Although this protocol 'encouraged' collection of pre-therapy microbiology specimens, this was not a requirement for study entry. Thus, there are no microbiology data included in this study. It was conducted entirely in the US.

c. study 154-138: an open label, comparative study which randomized subjects to either trovafloxacin (200 mg BID for 10 days) or amoxicillin/clavulanate (500/125 mg TID for 10 days). This study randomized 207 patients to the trovafloxacin arm and 211 to the amox/clav arm. It was conducted entirely in Europe (UK, France, Holland, Germany, Belgium, and Finland). As in study 115, pre-randomization microbiology specimen collection was encouraged but not required; unlike study 115, there were actually 16 trovafloxacin and 14 amox/clav patients who agreed to trans-antral sinus puncture.

5. Medical officer comments:

a. Issue of endoscopically obtained microbiology specimens. Since all microbiology specimens submitted in this portion of the NDA were obtained in the standard fashion (i.e., by trans-antral puncture and aspiration of the maxillary sinus), there is no concern over the applicability of endoscopically-obtained microbiology specimens.

b. Comments on pharmacokinetics applicable to indication. The sponsor has not performed any clinical pharmacokinetic studies which specifically examine the penetration of trovafloxacin into sinus mucosal tissue. However, Study 154-020 examined the penetration of trovafloxacin into bronchial epithelium at various time points (6, 12, and 24 hours) following a single 200 mg dose, as well as 6 hours following a multiple dose (200 mg qd x 4 days) regimen. In the 9 patients studied in the multiple-dose regimen, there was a serum: epithelial tissue concentration

ratio of 1.1, indicating a slight degree of concentration of trovafloxacin in bronchial respiratory epithelium.

c. *In vitro* MIC data for important pathogens. The proposed susceptibility breakpoints for trovafloxacin as presented in the draft labeling interpret 'susceptible' as an MIC of ≤ 2 μg/mL. The reported MIC_{90} for the major pathogens of concern in sinusitis (as cited in the trovafloxacin investigator's brochure) are as follows: *Haemophilus influenzae* 0.008-0.03μg/mL; *Streptococcus pneumoniae* 0.06-0.25μg/mL; *Moraxella catarrhalis* 0.015-0.06μg/mL; and *Staphylococcus aureus* 0.03-0.12 μg/mL (for methicillin and ciprofloxacin-susceptible strains) to 1.0-8.0 μg/mL (for methicillin and ciprofloxacin-resistant strains). From these data, trovafloxacin might be anticipated to show acceptable activity against the pathogens most commonly implicated in this clinical scenario.

d. Use of approved comparators. The choice of comparators for the two comparative studies appears to be acceptable. Amoxicillin/clavulanate (Augmentin®, SmithKline Beecham) is labeled for the treatment of sinusitis due to beta-lactamase-producing strains *of Moraxella catarrhalis* and *Haemophilus influenzae* at a dose of either 250 mg or 500 mg (of the amoxicillin component) TID (the duration of therapy is not specified in the package insert). Clarithromycin (Biaxin®, Abbot) is labeled for the treatment of acute maxillary sinusitis due to *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* at a dose of 500 mg BID for 14 days.

e. Domestic vs international microbiology data. The microbiology data included in this proposed indication essentially comes from one study (114), which was conducted in both the US and elsewhere. Enrollment was predominantly (194 vs. 65) domestic, and therefore the microbiology derived from this study is generally representative of domestic resistance patterns.

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Medical officer review of Sinusitis Study 154-114

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1. Per applicant

The synopsis of the applicant's final study report for study 114 is presented below; for a more complete discussion of these results, the reader is referred to the appropriate section of the NDA.

NOTE: Medical officer text will appear as Times New Roman; applicant (aka sponsor) text will appear as **ARIAL:**

AN OPEN NONCOMPARATIVE, MULTI-CENTER TRIAL DESIGNED TO ASSESS THE EFFICACY AND SAFETY OF 10 DAYS ORAL THERAPY WITH TROVAFLOXACIN (CP-99,219) (200 MG ONCE DAILY) FOR THE TREATMENT OF ACUTE SINUSITIS.

FINAL STUDY REPORT: PROTOCOL 154-114

REPORT DATE: 12 December, 1996 (Final)

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5041	Robert Fiddes, M.D.
	5137	Richard Sterling, M.D.
	5195	Robert Ziering, M.D.
	5196	Richard Perrotta, M.D.
	5197	Trevor Goldberg, M.D.
	5198	C. Lawrence Neal, M.D.
	5218	Patrick Bianchi, M.D.
	5219	Thomas Sydnor Jr, M.D.
	5485	Peter Johnson, M.D.
United Kingdom	5105	Christopher Raine, M.D.
Finland	5388	Henrik Malmberg, M.D.
	5389	Matti Pietola, M.D.
	5391	Juhani Pukander, M.D.
	5392	Seppo Savolainen, M.D.
	5393	Heikki Kiukaanniemi, M.D.
Costa Rica	5484	Luis Arce Rodriguez, M.D.

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Study Publication: Not Applicable
Study Dates: 15 November, 1994 - 3 August, 1995
Study Objectives: The objective of this study was to evaluate the safety and efficacy of trovafloxacin administered as a 200 mg oral dose for 10 days for the treatment of subjects with acute sinusitis.
Study Design: Study 154-114 was an open, noncomparative, multicenter trial.

Evaluation Groups:	**Trovafloxacin (200 mg/day)**	
Entered Study[a]	255	(100%)
All Treated	254	(>99%)
Completed Treatment	243	(96%)
Completed Study	242	(95%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	251	(98%)
Clinically Evaluable[b]	235	(92%)
Bacteriological Intent-to-Treat	131	(51%)
Bacteriological Evaluable[b]	125	(49%)
Assessed for Safety		
Adverse Events	254	(100%)
Laboratory Tests	247	(97%)

a Subjects who were enrolled; Percentages for efficacy based on enrolled subjects as the denominator and percentages for safety based on all treated subjects.
B Based on End of Treatment assessment.

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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.
Drug Administration: Study drug was in the form of tablets and was packaged in blister packs.
Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection) and bacteriologic response (based on eradication or presumptive eradication of causative organisms isolated from trans-antral aspirations at baseline). 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).
Statistical Methods: Both intent-to-treat and evaluable subjects were analyzed in this study. For clinical efficacy (clinical success rate) and bacteriological efficacy (pathogen eradication rate), confidence intervals (95%) were calculated using the normal approximation method for success rates. No inferential statistics were presented if fewer than 15 subjects had a particular baseline pathogen for the by-pathogen analysis. Safety results including adverse events, laboratory abnormalities and vital signs were analyzed using descriptive statistics.

Efficacy Results: Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following table.

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Summary of the Sponsor's-Assessment of Clinical Response (Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=235)		Trovafloxacin 200 mg (N=227)	
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	235	(100%)	227	(100%)
Success (Cure + improvement)	213	(91%)	199	(88%)
Distribution of Clinical Response:				
Cure	110	(47%)	174	(77%)
Improvement	103	(44%)	25	(11%)
Failure	22	(9%)	22	(10%)
Relapse	NA	NA	6	(3%)
(Clinically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=251)		Trovafloxacin 200 mg (N=251)	
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	251	(100%)	251	(100%)
Success (Cure + improvement)	222	(88%)	215	(86%)
Distribution of Clinical Response:				
Cure	113	(45%)	182	(73%)
Improvement	109	(43%)	33	(13%)
Failure	29	(12%)	29	(12%)
Relapse	NA	NA	7	(3%)
Summary of Sponsor-Defined Pathogen Eradication Rates[a] (Bacteriologically Evaluable Subjects)				
	Trovafloxacin 200 mg (N=125)		Trovafloxacin 200 mg (N=121)	
	Number of Pathogens			
Pathogen[b]	End of Treatment		End of Study	
S. pneumoniae	24/25	(96%)	24/25	(96%)
H. influenzae	44/45	(98%)	43/45	(96%)
S. aureus	18/18	(100%)	16/16	(100%)
M. catarrhalis	22/23	(96%)	19/21	(90%)
(Bacteriologically Intent-to-Treat Subjects)				
	Trovafloxacin 200 mg (N=131)		Trovafloxacin 200 mg (N=131)	
	Number of Pathogens			
Pathogen[b]	End of Treatment		End of Study	
S. pneumoniae	25/26	(96%)	25/26	(96%)
H. influenzae	47/48	(98%)	44/46	(96%)
S. aureus	19/19	(100%)	17/17	(100%)
M. catarrhalis	22/23	(96%)	19/21	(90%)

a Includes subjects with presumptive eradication (subjects clinically improved or cured who did not undergo post-treatment transantral aspiration of the sinus).
b ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline
NA=Not applicable
Ref.: Tables 5.1.1, 5.1.2, 5.4.1, and 5.4.2

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

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	
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	137/254	(54%)
Treatment-Related Adverse Events	87/254	(34%)
Discontinuations Due to an Adverse Event[a]	5/254	(2%)
Clinically Significant Laboratory Abnormalities	34/247	(14%)
a With the exception of one subject who was 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. **Ref.: Tables 1.2, 6.1, 6.2, 6.3, and 7.1**		

Two subjects experienced serious adverse events unrelated to study drug. There were no subject deaths during the study.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was safe and effective in the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 2%. The overall percentage of subjects reporting adverse events was 54%; treatment-related adverse events were reported in 34% of subjects. The most commonly reported adverse events were dizziness and headache. No subjects were discontinued due to laboratory abnormalities.

2. Per medical officer

   a. Comments on study design. This open label phase 2 study was designed and conducted to comply with the divisional Points to Consider document. As such, the medical officer has no specific criticisms of this study. The inclusion and exclusion criteria were as follows:

Inclusion Criteria

1. Age ≥16 years at baseline.

2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or ≤1 year post-menopausal) were to have had a negative urine gonadotropin pregnancy test immediately prior to entry in the study and were to have used adequate contraception both during the study and for one month after the end of the study.

3. Clinically and radiologically documented acute sinusitis as defined in Section 3.1.

4. Subjects who would submit to direct aspiration of the sinus cavity.

5. Written informed consent was to be obtained. For subjects <18 years, written informed consent from the subject's parent or legal guardian was also to be obtained.

Exclusion Criteria

1. Treatment with any other systemic antibiotic for 24 hours or longer within 2 weeks prior to the baseline assessment; or subjects with infections that may have required treatment with an antibiotic other than the study drugs.

2. Subjects with a history of chronic sinusitis (three or more episodes of sinusitis within the last 6 months).

3. Subjects with evidence or history of significant gastrointestinal, hematological, renal or cardiovascular disease or immunologic compromise (i.e., neutropenia, ARC/AIDS, non-skin cancers, or malignant melanoma).

Complete details for all inclusion/exclusion criteria can be found in the Protocol (Section 5).

Criteria for the clinical diagnosis of sinusitis were as follows:

1. Post nasal purulent discharge, nasal congestion, facial pain over affected sinus, hyposmia, and jaw pain with mastication were each to be assessed at baseline (Day 1) and at every clinic visit thereafter by the investigator and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

2. A sinus x-ray (Water's view) was to be obtained at baseline (Visit 1, Day 1) and the end of therapy (Visit 3, Day 11) and at any other time point deemed necessary by the investigator. In addition, Caldwell's and lateral views were to be performed if the Water's view was inconclusive. The radiographs were to be compared to baseline using the following categories:

   - worse than at baseline;
   - same as baseline;
   - better than baseline;
   - complete resolution.

The evaluation timepoints were baseline (Day 1), during therapy (Day 4), end of therapy or EOT (Day 11), and end of study or EOS (Day 24). These timepoints are acceptable, with the caveat that the EOS evaluation should not be any sooner than day 24 but evaluations that come later than this will be considered acceptable.

The recruitment into the study was dominated by a small number of investigators. The total recruited into this study, by investigator in descending order, is as follows:

Investigator	site	N
Sydnor 5219	VA	71
Fiddes 5041	CA	32
Johnson 5485	VA	26
Savolainen 5392	Finland	21
Sterling 5137	SC	19
Rodriguez 5484	Costa Rica	16
Bianchi 5218	AL	15
Kiukaanniemi 5393	Finland	13
Goldberg 5197	NC	10
Neal 5198	LA	9
Zeiring 5195	CA	8
Pietola 5389	Finland	8
Malmberg 5388	Finland	7

Thus it can be seen that the initial goal of the study, which was to have at least 15 investigators enrolling 10 or more subjects, was not met. There were only 9 investigators who enrolled 10 or more subjects into this study.

In order to verify the results presented by the applicant above, the medical officer undertook an audit of the primary patient data as presented in the ClinView portion of the electronic submission. The data compiled on the CRFs was checked to verify that the same information was present for each patient in the electronic portion of the database, both as presented in the 'Patient Profiles' as well as the data as present in SAS-PH Clinical.

A random sample of 10% of the enrolled subjects was identified by Patient Identification Number. This randomized list was provided by the biostatistical reviewer, Dr. Silliman. These were individually reviewed in order to verify that the data as generated by the investigator had been accurately entered into the electronic database, from which all the applicant's summary tables were generated.

The following patient profiles were examined and compared to the corresponding CRF:

Patient ID number (PID)	Investigator	location	OK?	comments
11450410117	Fiddes	California, USA	✓	
11450410119	" "		✓	
11450410121	" "		✓	
11450410234	" "		✓	
11451370056	Sterling	S. Carolina, USA	✓	
11451370058	" "		✓	
11451370149	" "		✓	
11452180152	Bianchi	Alabama, USA	✓	
11452190089	Sydnor	Virginia, USA	✓	
11452190140	" "		✓	

Patient ID number (PID)	Investigator	location	OK?	comments
11452190168	Sydnor		✓	1+ nasal congestion, 3+ hyposmia at EOS; called'cure'
11452190184	" "		●	reported as clinical 'improvement' yet had EOS re-aspiration and culture + for *Strep pneumo*
11452190198	" "		✓	
11452190224	" "		✓	
11452190227	" "		✓	
11452190228	" "			
11453880006	Malmberg	Finland	✓	
11453890005	Pietola	Finland	✓	baseline x-ray on profile states 'opacification absent', but CRF calls "Right max. sinus completely shadowed"
11453890006	" "		✓	
11453920003	Savolainen	Finland	✓	
11453920005	" "		✓	
11453920011	" "		✓	
11453920012	" "		✓	
11454840002	Rodriguez	Costa Rica	✓	
11454850175	Johnson	Virginia, USA	✓	
11454850177	" "		✓	

Medical officer conclusions regarding 10% CRF audit:

In general, the data found in the Patient Profiles and that upon which the applicant's tabular results are based was found to be consistent with the information that had been collected by the investigator during the study's conduct. The only exception was the case noted above, wherein the investigator called the subject an 'improvement' even though a repeat sinus tap was performed (in which, following a negative culture at entry, was positive for Strep pneumo).

Medical officer comments:

1. During the course of this NDA review, the Division of Scientific Investigations notified the review division that there was reason to be concerned about the integrity of one of the investigators in this study. Investigator #5041, Dr. Fiddes, was the second-highest enrolling investigator in this study. Since this study was noncomparative, the invalidation of this portion of the data will not cause the study to

become statistically underpowered; it does, however, have the potential to decrease the numbers of pathogens to a point where their inclusion in the labeling may become problematic. The two large phase 3 studies (reviewed below) did not collect any microbiology information. (Actually, study 138 did collect microbiology data from a small proportion of the enrolled patients, but the sponsor did not present these data in the final study report. A brief glimpse of these data reveals a total of 5 subjects in study 138 who had cultures positive for *Moraxella catarrhalis* .)

Thus, the micro section of this indication is based entirely on the results of study 114.

Dr. Fiddes enrolled a total of 32 patients into this study. These 32 included 6 patients with no growth following culture of transantral sinus puncture fluid; 3 with *Strep pneumo*; 1 with *Strep pyogenes*; 1 with *Staph aureus*; 9 with *Haemophilus influenzae*; and 12 with *Moraxella catarrhalis.* If the table presented by the sponsor in the above summary, entitled "Summary of the Sponsor's Assessment of Clinical Response", is examined, the following changes would need to be made if all of investigator 5041's patients were to be considered invalid:

Summary of Sponsor-Defined Pathogen Eradication Rates
(Bacteriologically Intent-to-Treat Subjects)
Study 114

Pathogen	End of treatment (N = 125) per Sponsor	End of treatment minus investigator 5041
S. pneumoniae	25/26 (96%)	22/23 (96%)
H. influenzae	47/48 (98%)	38/39 (97%)
S. aureus	19/19 (100%)	18/18 (100%)
M. catarrhalis	22/23 (96%)	10/11 (91%)

Thus it can be seen that the number of bacteriologically evaluable (by intent-to-treat analysis) subjects is rather small. It should also be kept in mind that these data are taken from the end-of-treatment timepoint; if the end-of-study timepoint is used, there are two fewer *M. catarrhalis* subjects.

With regard to the adequacy of these numbers, the Points to Consider document states the following:

> *Also suggested would be one open study utilizing sinus aspiration. This trial should establish successful microbial, clinical, and radiographic or ultrasonic outcome in at least 100 patients. This study should establish acceptable microbial and clinical outcome in at least 25 patients with H. influenzae, in at least 25 patients with S. pneumoniae, and in at least 15 patients with M. catarrhalis. Post-therapy sinus aspiration is strongly encouraged in those patients judged to be therapeutic failures so that bacterial persistence or superinfection could be determined. In this trial, outcomes on all patients enrolled should be reported, not just those patients with the bacterial pathogens mentioned previously in this paragraph. This trial should be performed by at least two investigators in geographically diverse regions, and no one center should contribute more than 55% of the evaluable patients.*

When the Fiddes subjects are removed from the analysis, the numbers of *M. catarrhalis* subjects drops to a point where this organism cannot be approved for inclusion in the labeling. As noted, there were some patients in Study 138 who had microbiology data collected; however, of the 5 who had cultures positive for *M. catarrhalis*, only three randomized to the trovafloxacin arm. (One of these three isolates did not have any susceptibilities reported, but all three were assessed as 'cure' by both the investigator and sponsor at the end-of-study [EOS] timepoint.) Thus, even if these subjects are added to the totals for Study 114 (minus Fiddes), the total number of *M. catarrhalis* patients is 14.

Study 138 also contributes five trovafloxacin-treated subjects with cultures positive for *S. pneumoniae*. As can be seen above, the organism-specific results for study 114 (minus Fiddes) show a total of 23 such patients, which again does not meet the PTC criteria. Of these five patients derived from study 138, four (56950439, 57240271, 57240355, 57250205) are considered to be clinically evaluable; three of the 4 were assessed as 'cure' and one was assessed as 'improvement' at the EOS visit. If these subjects are permitted to be grouped with those of study 114, the result is a total of 25/27 *S. pneumoniae* subjects who had satisfactory outcomes.

These numbers do not preclude approval of this indication for all three of the major pathogens; they do, however, indicate that the results of the AECB and CAP studies, additional indications in which these same three pathogens play important roles, will be looked at for confirmation of trovafloxacin's efficacy in infections caused by these organisms.

2. Listing of *Staphylococcus aureus* as a pathogen in sinusitis.

The sponsor has requested that *S. aureus* be granted as a pathogen in this indication. The precise role of this organism in the pathogenesis of this disease is somewhat controversial, in large part due to the fact that anywhere from of normal healthy adults will harbor *S. aureus* in their nasal cavities.

On 6 September 1997, the following electronic communication was sent by this reviewer to the sponsor:

> "I have a request for some further data synthesis regarding the sinusitis indication, specifically regarding the inclusion of *Staph aureus* in the listed organisms.
>
> As you may know, the Division has not to this date approved the acute sinusitis indication for *Staph aureus*. The role of this organism in this disease has been of some controversy, mainly because this bug is considered to be part of the normal nasal flora in some proportion of the population. As stated in the IDSA Guidelines, "*S. aureus* is a common nasal contaminant and an infrequent cause of acute sinusitis." It is necessary to differentiate between persons with nasal carriage with *S. aureus* and persons who truly have an infected maxillary sinus with this bug.
>
> To be an evaluable *Staphylococcus aureus* subject in an acute sinusitis study, the following criteria have all been used in the review of other sinusitis applications:
>
> 1. A specimen obtained by antral puncture and NOT by endoscopic cannulation and irrigation. (Not an issue with study 114.)
>
> 2. A Gram's stain of the aspirated material that shows Gram positive cocci in clusters.
> 3. A culture which is ONLY *Staph aureus*, not polymicrobic.
> 4. A quantitative culture result showing greater than 10^4 organisms in the cultured material.
>
> Although no information of this nature was presented in tabular form (or otherwise) in the study report of study 114, the Case Record Forms appear to include such information. Would it be possible to tabulate these results so that I can efficiently review the information?"

The following information was compiled by the sponsor:

A total of 19 subjects in study 114 had *Staph aureus* in cultures of trans-antral aspirates. All of these reports were from the local, rather than the centralized (Scicor) laboratory. These 19 cases can be sorted as follows:

Of the 19, 7 were mixed cultures with other pathogens:

Staph aureus and *Haemophilus influenzae*	3
Staph aureus and *Enterobacter cloacae*	1
Staph aureus and *Escherichia coli*	1
Staph aureus and *Strep pneumoniae*	1
Staph aureus, *Serratia marcescens*, and *Pseudomonas aeruginosa*	1

Of the 12 remaining, 6 had no Gram stain reported.
Of the 6 with Gram stains, 3 showed Gram positive cocci.

Of these 3, only one had quantification of the growth in culture (expressed as "Many, Profuse").

Medical officer conclusions regarding study 114:

1. This open, bacteriologically-driven study appears to demonstrate the clinical and bacteriologic efficacy of trovafloxacin in the treatment of acute bacterial maxillary sinusitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae*.
2. Because of concerns over the integrity of one of the major contributing investigators in this study, the number of evaluable subjects with culture-confirmed *Moraxella catarrhalis* sinusitis is less than the number recommended by the divisional Points To Consider document.
3. The eventual recommendation regarding inclusion of *M. catarrhalis* in the product labeling will hinge upon the efficacy of trovafloxacin in other respiratory infections in which this organism plays an acknowledged role. If the drug appears efficacious in these settings, in adequate numbers to warrant inclusion of *M. catarrhalis* as a listed pathogen, then it would seem reasonable to include this organism in the labeling for acute bacterial sinusitis.
4. The data presented in this study are inadequate to support the inclusion of *Staphylococcus aureus* as a pathogen for this indication.

Medical officer review of Study 154-115

1. Introduction

The applicant conducted two phase 3 studies following the completion of study 114 (reviewed above). Both of these were prospective, randomized, studies using FDA-approved active comparators.

Study 115 was a double-blinded, double-dummy, multicenter study conducted exclusively in the US, using clarithromycin as the comparator agent. The choice of this agent and the dosage used (500 mg BID for 14 days) constitute an FDA-approved regimen for the treatment of acute sinusitis.

2. Results per applicant

The applicant's synopsis of study 115 follows:

PROTOCOL 154-115: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (CP-99,219) (200 MG DAILY) AND 14 DAYS OF ORAL CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Principal Investigators:

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Study Publication: Not Applicable

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.

Evaluation Groups:

	Trovafloxacin (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				
Intent-to-treat	193	(94%)	203	(95%)
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.

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.

Drug Administration: Study drug was in the form of tablets and was packaged in blister cards, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). 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).

Statistical Methods: Both intent-to-treat and evaluable subjects were analyzed in this study. For clinical efficacy, confidence intervals (95%) for each pairwise difference in success rates between treatments were calculated. Treatment groups were compared by a 2 degree of freedom (d.f.) chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment to account for investigator differences. Safety results including adverse events, laboratory abnormalities and vital signs were analyzed using descriptive statistics.

Efficacy Results:

Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -10.6, 4.0 and -11.0, 4.3, respectively) and at the end of study (95% CI: -10.5, 8.0 and -10.5, 7.5, respectively). Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects are presented in the following tables.

A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinically Evaluable Subjects)

	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=162)[a]	Clarithromycin 500 mg BID (N=188)	Trovafloxacin 200 mg (N=160)	Clarithromycin 500 mg BID (N=184)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	161 (100%)	188 (100%)	160 (100%)	184 (100%)
Success (Cure + improvement)	136 (84%)	165 (88%)	118 (74%)	138 (75%)
Distribution of Clinical Response:				
Cure	67 (42%)	84 (45%)	85 (53%)	112 (61%)
Improvement	69 (43%)	81 (43%)	33 (21%)	26 (14%)
Failure	25 (16%)	23 (12%)	25 (16%)	23 (13%)
Relapse	NA	NA	17 (11%)	23 (13%)

NA=Not applicable
a Subject 5077-0052 did not have an end of treatment assessment within the evaluable window.
Ref.: Table 5.1.1

A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinical Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=193)	Clarithromycin 500 mg BID (N=203)[a]	Trovafloxacin 200 mg (N=193)	Clarithromycin 500 mg BID (N=203)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	193 (100%)	202 (100%)	193 (100%)	203 (100%)
Success (Cure + improvement)	154 (80%)	168 (83%)	135 (70%)	145 (71%)
Distribution of Clinical Response:				
Cure	72 (37%)	84 (42%)	94 (49%)	118 (58%)
Improvement	82 (42%)	84 (42%)	41 (21%)	27 (13%)
Failure	39 (20%)	34 (17%)	39 (20%)	35 (17%)
Relapse	NA	NA	19 (10%)	23 (11%)

NA=Not applicable
a Subject 5078-0238 was not assessed at the end of treatment.
Ref.: Table 5.1.2

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 the following table.

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%)

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.
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 (Table 6.1); however, on the subject summary section of the case report form the investigator classified the reason for withdrawal from the study as adverse event (Table 4.2).
Ref.: Tables 1.2, 6.1, 6.2, 6.3, and 7.1

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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.

Summary and Conclusion: Trovafloxacin 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.

3. Results per Medical Officer

a. Comments on study design: This phase 3 study was designed and conducted to comply with the divisional Points to Consider document. As such, the medical officer has no specific criticisms of this study. The entry criteria, evaluability criteria, and timepoints for post-therapy follow-up are acceptable (and are identical to those enumerated for study 114, above). Although subjects were to be encouraged (but not required) to submit to pre-therapy collection of a sinus aspirate, there were apparently no willing enrollees as there is no microbiology information whatsoever submitted in the final study report.

A total of 36 investigators recruited subjects into this study. The following 20 investigators, presented in descending number of randomized subjects, recruited ten or more subjects into this study:

Investigator	site	location	N
Allen	5141	AL	32
De Abate	5078	LA	32
Durden	5143	AL	28
Bruya	5076	WA	26
Nielsen	5146	UT	24
Adelglass	5096	TX	20
McAdoo	5132	TN	20
Ellison	5079	SC	17
Wolff	5103	NC	16
Bateman	5142	ID	16
VanZandt	5151	NC	13
Garamy	5080	KY	12
Ziering	5092	CA	12
Ruoff	5149	MI	12
Serfer	5102	FL	11
Stoltz	5138	IN	11
Caldwell	5077	FL	10
Handley	5099	AL	10
Hill	5100	FL	10
Stoker	5216	UT	10

In looking at the geographic distribution of the leading enrolling centers in this study, the absence of any site in the Northeastern US is somewhat surprising. Aside from this observation, the geographic distribution of the study sites is certainly acceptable.

In order to verify the results presented by the applicant above, the medical officer undertook an audit of the primary patient data as presented in the ClinView portion of the electronic submission. The data compiled on the CRFs was checked to verify that the same information was present for each patient in the electronic portion of the database, both as presented in the 'Patient Profiles' as well as the data as present in SAS-PH Clinical.

A random sample of 10% of the enrolled subjects was identified by Patient Identification Number. This randomized list was provided by the biostatistical reviewer, Dr. Silliman. These were individually reviewed in order to verify that the data as generated by the investigator had been accurately entered into the electronic database, from which all the applicant's summary tables were generated. They were also scrutinized to determine whether the medical officer was in agreement with the sponsor's interpretation of whether the subject was evaluable or not, and a cure/improve/fail/relapse.

The following patient profiles were examined and compared to the corresponding CRF:

Clarithromycin patients

Patient ID (PID)	Investigator	location	OK?	comments
50760043	Bruya	WA	✓	no post-Rx labs
50760045	" "		✓	
50760248	" "		✓	
50760522	" "		✓	
50780065	DeAbate	LA	✓	
50790007	Ellison	SC	✓	
50960353	Adelglass	TX	✓	
50960358	" "		●	

Comment: this patient was called an 'improvement' by both the investigator and sponsor at EOS (day 32), yet was started on Keflex from day 32 to 36 for 'yellow sputum'. This, technically, does not violate the protocol but nonetheless might have been changed to 'relapse' by the sponsor.

50990090	Handley	AL	✓	
51000100	Hill	FL	✓	
51020124	Serfer	FL	✓	
51020125	" "		✓	
51410338	Allen	AL	✓	
51420350	Bateman	ID	●	

Comment: patient called 'cure' at EOS but was rated as having 3 symptoms (purulent nasal discharge, nasal congestion, and facial pain) as 1 out of 3 (on a zero to 3 rating scale); would probably be more accurately termed 'improvement', as x-ray interpreted as 'better'.

51420480	" "		✓	

Clarithromycin patients (con't)

Patient ID (PID)	Investigator	location	OK?	comments
51430459	Durden	AL	✓	
51430498	" "		✓	
51460496	Nielsen	UT	✓	
51490312	Ruoff	MI	✓	
51510394	VanZandt	NC	✓	
52160300	Stoker	CA	✓	
52160390	" "		✓	

Trovafloxacin patients

Patient ID (PID)	Investigator	location	OK?	comments
50760047	Bruya	WA	✓	
50760241	" "		✓	
50920159	Ziering	CA	✓	
50960414	Adelglass	TX	●	

Comment: patient took one dose, had severe dizziness and nausea, and was promptly switched to cefuroxime for 10 days, resulting in clinical cure. Called clinically unevaluable (appropriately) but called a trovafloxacin 'cure' by intent-to-treat. Although this conforms to the stated criteria for inclusion in the ITT analysis, it points out a potential weakness of such an analysis. (Of course, if the patient had not responded to cefuroxime, the same rules would require that this be a trovafloxacin failure.)

50980082	Grossman	AZ	✓	
50990089	Handley	AL	✓	
50990096	" "		✓	
51000101	Hill	FL	✓	
51000226	" "		✓	
51010114	Rudolph	NM	✓	
51240266	Anthony	TX	✓	
51320388	McAdoo	TN	✓	
51410340	Allen	AL	✓	
51420479	Bateman	ID	✓	

Trovafloxacin patients (con't)

Patient ID (PID)	Investigator	location	OK?	comments
51430330	Durden	AL	✓	
51430331	" "		✓	
51490492	Ruoff	MI	✓	
51510395	VanZandt	NC	✓	
52050022	Bock	PA	✓	
52160389	Stoker	CA	✓	

Medical officer conclusions regarding audit:

With the minor exception of the noted comments, the data as presented in the Patient Profiles was an accurate representation of the information in the actual case report forms. In general, the interpretations of the sponsor were conservative; that is, the sponsor's categorization of cure/improve/fail was the most conservative one, based on the information at hand.

The interpretations of the sponsor were made prior to the breaking of the blind, as detailed in section H.3.A of the NDA. This audit did not detect any indication that the blind was in any way compromised.

Medical officer comments:

1. As noted in the summary tables, the end-of-study (EOS) Success rates for the two interventions (i.e., cure + improvement) were equivalent: 135/193 or 70% for trovafloxacin, and 145/203 or 71% for clarithromycin in the ITT subset; and 118/160 or 74% for trovafloxacin and 138/184 or 75% for clarithromycin in the Clin Eval subset. If one looks only at the end-of-study clinical cures in the two arms, however, one sees that the cure rates were 94/193 or 49% for trovafloxacin, vs. 118/203 or 58% for clarithromycin (ITT subset); and 85/160 or 53% for trovafloxacin and 112/184 or 61% for clarithromycin (Clin Eval subset). As there were no microbiology data for this study, there is no way to examine these results by specific pathogen. [For the EOS cure in the ITT subset, the 95% confidence iterval for the difference between trovafloxacin and clarithromycin is (119.7%, 0.9%) with a corresponding p-value of 0.06. For EOS cure in the Clin Eval subset, the 95% CI for the difference is (-18.8%, 3.3%) , with a p-value of 0.15. Thus, the two arms of this study meet the criteria for equivalence when just the 'cures' are evaluated.]
2. Comparatively, the EOS clinical cure rates for study 114, an open noncomparative study, was 77% for the clinically evaluable subset and 73% for the ITT subset.
3. The IDSA guidelines (page S76) call for the differentiation of clinical response into dichotomous variables of clinical cure (defined as the complete resolution of signs and symptoms at the conclusion of antimicrobial therapy and at follow-up) and clinical failure, along with categories such as early and late relapse. No provision is made for the clinical response category of 'improvement'. These are guidelines, however, and FDA medical reviewers are not bound by these general recommendations.
4. Previous medical officer reviews of this indication have defined 'cure' as the resolution of all baseline signs and symptoms (although it is generally agreed that radiographic cure is not necessary). A category of 'improvement' has not previously been utilized.

Medical officer conclusions regarding efficacy results, study 115:

1. This double-blinded study supports the clinical efficacy of trovafloxacin in the treatment of acute bacterial sinusitis, both when the clinical endpoint is 'success' and when analysis is restricted to the clinical endpoint of 'cure'.
2. The clinical cure rates in this double-blinded study were substantially lower than the rates reported in the open-label, uncontrolled study 114 (77% vs 53% at EOS in the Clin Eval subset). This may reflect the extremely conservative approach taken by the applicant in evaluating the outcomes of subjects prior to the breaking of the blind, as well as some degree of investigator bias in favor of the drug in the open-label phase 2 study 114.

Medical officer review of sinusitis study 154-138

1. Introduction

The applicant conducted two phase 3 studies following the completion of study 114 (reviewed above). Both of these were prospective, randomized, studies using FDA-approved active comparators.

Study 138 was a open-label, comparative, multicenter study conducted exclusively outside of the US, using amoxacillin/clavulanate as the comparator agent. The choice of this agent and the dosage used (500 mg TID for 10 days) constitute an FDA-approved regimen for the treatment of acute sinusitis. (It should, however, be mentioned that although the precise duration of therapy for acute sinusitis is not specified in the approved product labeling, a ten-day course of amoxicillin/clavulanate would be considered the shortest acceptable duration of therapy by most Infectious Disease experts).

2. Results per applicant

The applicant's study synopsis for study 138 follows:

PROTOCOL 154-138: A RANDOMISED, OPEN, MULTI-CENTRE TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (CP-99,219) (200 MG ONCE DAILY) WITH ORAL AMOXYCILLIN/CLAVULANATE (AUGMENTIN, 500/125 MG TID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Principal Investigators:

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Dr. Perrin	Dr. J. K. Agarwala	Dr. M. Schiffmann
Dr. P. Corlieu	Dr. S. A. Ahmed	Dr. I. Senftleber
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Professor Stoll	Dr. M. C. Brown	Dr. W. Motzko
Professor Pignat	Dr. J. B. Frazer	Dr. L. Capiau
Professor Chabolle	Dr. Safi U. Khan	Dr. Clarysse
Professor Bernard Meyer	Dr. P. Marazzi	Dr. H. Flore
Dr. Andre Coste	Dr. N. H. Patel	Dr. Lousbergh
Professor Legent	Dr. R. S. Paton	Dr. E. Schatteman
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Dr. G. Amsellem	Dr. C. Marshall	Dr. Hannu Markkanen
Dr. J. Danon	Dr. M. L. Mairs	Dr. Juhani Nuutinen
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Dr. A. Q. D. N'Guyen	Dr. A. Djamchidi	Dr. H. Mulder
Dr. B. Passerat	Dr. Reinhold Eichler	Dr. J. C. Ehrlich
Dr. R. Jacquelin	Dr. J. Horn	

Study Publication: None
Study Dates: 25 May 1995 - 11 April 1996
Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin and amoxycillin/clavulanate in the treatment of subjects with acute sinusitis.
Study Design: Study 154-138 was a randomized, open, comparative, multicenter trial.

Evaluation Groups:

	Trovafloxacin (200 mg/day)		Amoxycillin/ Clavulanate (500/125 mg TID)	
Rrandomized	207		211	
All Treated	205	(100%)	209	(100%)
Completed Study	191	(93%)	201	(96%)
Completed Treatment	189	(92%)	196	(94%)
Evaluated for Efficacy[b]				
Intent-to-treat	202	(98%)	211	(100%)
Evaluable	189	(91%)	203	(96%)
Assessed for Safety				
Adverse Events	205	(100%)	209	(100%)
Laboratory Tests	200	(98%)	206	(99%)

a_ Evaluability was determined at end of treatment.

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.

Drug Administration: Study drug was in the form of trovafloxacin tablets and amoxycillin/clavulanate tablets packaged in bottles or blister packs.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). 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).

Statistical Methods: Treatment groups were compared using the confidence interval approach. Confidence intervals (95%) were produced for the difference in success rates between treatments using the normal approximation method. Additionally, a chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment was used to account for investigator differences. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy: Comparisons of the difference between the two treatment groups in sponsor -defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -0.8, 8.3 and -1.4, 8.6, respectively) and at the end of study (95% CI: -5.2, 7.2 and -5.2, 7.1, respectively). Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects are presented in the following tables.

Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinically Evaluable Subjects)								
	End of Treatment				End of Study			
	Trovafloxacin 200 mg (N=189)		Amoxycillin/ Clavulanate 500/125 mg TID (N=203)		Trovafloxacin 200 mg (N=189)		Amoxycillin/ Clavulanate 500/125 mg TID (N=203)	
	Number and Percentage (%) of Subjects							
Number of Subjects Assessed	188	(100%)	201	(100%)	175	(100%)	196	(100%)
Success (Cure + improvement)	181	(96%)	186	(93%)	158	(90%)	175	(89%)
Distribution of Clinical Response:								
Cure	90	(48%)	80	(40%)	123	(70%)	125	(64%)
Improvement	91	(48%)	106	(53%)	35	(20%)	50	(26%)
Failure	7	(4%)	15	(7%)	7	(4%)	15	(8%)
Relapse					10	(6%)	6	(3%)

NA=Not applicable
Ref.: Table 5.1.1

Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinically Intent-to-Treat Subjects)								
	End of Treatment				End of Study			
	Trovafloxacin 200 mg (N=202)		Amoxycillin/ Clavulanate 500/125 mg TID (N=211)		Trovafloxacin 200 mg (N=202)		Amoxycillin/ Clavulanate 500/125 mg TID (N=211)	
	Number and Percentage (%) of Subjects							
Number of Subjects Assessed[a]	202	(100%)	210	(100%)	202	(100%)	211	(100%)
Success (Cure + improvement)	191	(95%)	191	(91%)	180	(89%)	186	(88%)
Distribution of Clinical Response:								
Cure	93	(46%)	82	(39%)	136	(67%)	132	(63%)
Improvement	98	(49%)	109	(52%)	44	(22%)	54	(26%)
Failure	11	(5%)	19	(9%)	11	(5%)	19	(9%)
Relapse					11	(5%)	6	(3%)

NA=Not applicable
a One subject in the amoxycillin/clavulanate group had a missing assessment at the end of treatment but was assessed at the end of study.
Ref.: Table 5.1.2

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 the following table.

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg	Amoxycillin/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%)
Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.2, 6.3, 7.1, and Appendix I, Table 3.1.		

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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 amoxycillin/clavulanate group.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was statistically equivalent to amoxycillin/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 amoxycillin/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 amoxycillin/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 amoxycillin/clavulanate group.

3. Results per Medical Officer

a. Comments on study design: This phase 3 study was designed and conducted in compliance with the IDSA Guidelines for the Evaluation of Anti-Infective Drug Products and the Divisional Points To Consider document. The entry criteria, evaluability criteria, and timepoints for post-therapy follow-up are acceptable (and are identical to those enumerated for studies 114 and 115, above). Although subjects were to be encouraged (but not required) to submit to pre-therapy collection of a sinus aspirate, there were very few enrollees willing to do so, as no microbiology information was presented in the study report. (A total of 8 subjects had microbiology data collected, which appears in table 16, Appendix V of the complete study report for study 154-138.)

The choice of duration of therapy should also be mentioned. Since this study was an open label comparison, there would seem to be no reason (from a study design standpoint) that a 14-day regimen for amoxicillin/clavulanate could not have been selected. (In other words, since the study was not double-blinded, it would have been logistically quite easy to design the study in this way.) The previously reviewed study (115) was designed to be double-blinded despite the discrepancy in durations of therapy between the two arms (10 days for trovafloxacin and 14 days for clarithromycin).

Of the 68 principal investigators listed at the beginning of this study report, 42 of them actually enrolled subjects. The greatest number of subjects were enrolled from the UK (149), followed by Germany (99) and France (64). The ten leading investigators in this study were:

Center	Investigator	Location	# randomized
5695	Kivisaari	Finland	39
5722	Brunswig	Germany	31
5274	Cranfield	UK	31
5674	Ahmed	UK	30
5730	Senftleber	Germany	20
5701	Clarysse	Belgium	19
5727	Jenner	Germany	18
5675	Allin	UK	17
6397	Tlili	France	16
5724	Eichler	Germany	16

It would thus appear that enrollment in this study was not dominated by investigators from one particular country, but was relatively well distributed throughout Western Europe.

b. Results of Case report form audit: As was done with the previously reviewed studies in this indication, a random sample of 10% of the subjects was selected by the reviewing biostatistician, Dr. Nancy Silliman. The case record forms of this sample were carefully reviewed to ascertain the consistency of the information therein contained, compared to the data as it appears on the corresponding Patient Profile for that patient. The investigator's and applicant's interpretation of the results for that patient, with regard to whether that patient was considered clinically evaluable or not, and what the final outcome was determined to be, were reviewed for discrepancies from the protocol.

Trovafloxacin subjects

Patient ID (PID)	Investigator	Location	OK?	Comments
52740075	Cranfield	UK	✓	EOT eval < 14 days post Rx
52740085	"—"		✓	
52780513	Khong	UK	✓	
54690321	Vandewalle	Holland	✓	
56890022	Patel	UK	●	No CRFs present
56950403	Kivisaari	Finland	✓	
56950408	"—"		✓	
56950424	"—"		✓	
56950432	"—"		✓	
56950439	"—"		✓	
56990442	Valkeinen	Finland	✓	
Comment: called NOT clinically evaluable but called an ITT cure. Patient received one dose of trovafloxacin, then d/c'ed due to rash. Was assessed as a 'cure' by ITT 18 days later; no other antibiotics listed as being administered. Single dose therapy for sinusitis?				
57000309	Capiau	Belgium	●	
Comment: day 23 x-ray called 'better' on Patient Profile; no mention of x-ray at day 23 on CRF. Also, EOS visit was < 14 days post end of therapy.				
57000311	"—"		✓	
57060299	Schatteman	Belgium	✓	
57070617	DeVlieger	Belgium	✓	
57220350	Pitschner	Germany	✓	
57270267	Jenner	Germany	✓	
57300212	Senftleber	Germany	✓	
63200445	Marshall	UK	✓	
63970163	Tlili	France	●	
Comment: EOS visit 11 days post-completion of therapy. Still had 2 symptoms listed as 2/3, and one symptom as 1/3 yet considered 'improvement' and therefore a 'successful clinical outcome'.				
65040172	Passerat	France	✓	

Amoxicilln/clavulanate subjects

Patient ID (PID)	Investigator	Location	OK?	Comments
52740073	Cranfield	UK	●	EOS eval 10 days post-Rx
52740573	"—"		✓	
52770523	James	UK	✓	
56750066	Allin	UK	✓	
56950430	Kivisaari	Finland	✓	
56950433	"—"		✓	
56990441	Valkeinen	Finland	●	EOS eval day 12 post-Rx
57010288	Clarysse	Belgium	✓	
57010301	"—"		●	

Comment: Patient listed in CRF as being clinically cured at both EOT and EOS visits; sponsor lists EOT visit as day 3 (of 10 day course of therapy) and then carries this forward to EOS (day 27) as an evaluable failure.

57220352	Pitschner	Germany	✓	
57240251	Eichler	Germany	✓	
57240272	"—"		✓	
57240353	"—"		✓	
57270268	Jenner	Germany	●	EOS eval 12 days post-Rx
57300239	Senftleber	Germany	●	EOS eval 11 days post-Rx
63210457	Mairs	UK	✓	
63220531	Langdon	UK	✓	
63230539	Horsfield	UK	✓	
63970162	Tlili	France	✓	
64620159	N'Guyen	France	●	

Comment: called clinically evaluable failure by sponsor after day 4 called EOT failure then carried forward. EOT was actually day 9, called improved by investigator, then seen at day 28 and still improved. Should actually be nonevaluable due to protocol violation (patient 17 years old, and no written consent was obtained from parents).

65040171	Passerat	France	●	EOS eval 11 days post-Rx