

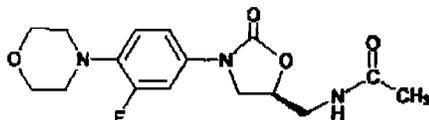
**MEDICAL OFFICER REVIEW OF ORIGINAL NDA 21-130, 21-131, AND 21-132:
Review of Uncomplicated and Complicated Skin and Skin Structure Studies and
Pediatric Clinical Studies**

Date of Submission: Oct. 18, 1999
Date Review Completed: April 21, 2000

Applicant: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001
(616) 833-8070
Regulatory Contact: Peter J. DiRoma

DRUG PRODUCT INFORMATION

Generic Name: Linezolid
Trade Name: Zyvox™
Chemical Name: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide
Chem. formula: C₁₆H₂₀FN₃O₄
Molecular weight: 337.35
Chem. structure:



Drug Category: Oxazolidinone antibiotic
Dosage Forms: Intravenous Solution, Oral Tablets, and Oral Suspension
Route of Administration: Intravenous (IV) or Oral

RESUME

Linezolid is an oxazolidinone antibiotic with activity against gram-positive bacteria. Clinical data to support the New Drug Applications for Zyvox™ were submitted in multiple volumes of IND's [REDACTED] as well as by electronic submissions as part of the original NDA's. This review addresses the studies submitted by the sponsor to support indications for both uncomplicated and complicated skin and skin structure infections (SSSI). Study M/1260/0039A is the pivotal trial for the uncomplicated SSSI indication, with data from study M/1260/0039 providing additional supportive data. Study M/1260/0055 is the pivotal trial for the complicated SSSI indication. Study M/1260/0037, a study of complicated SSSI that was terminated early, includes data on 4 additional subjects. [REDACTED]

MEDICAL OFFICER REVIEW OF ORIGINAL NDA 21-130, 21-131, AND 21-132: REVIEW OF UNCOMPLICATED AND COMPLICATED SKIN AND SKIN STRUCTURE STUDIES AND PEDIATRIC CLINICAL STUDIES 1

UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS 3

Introduction..... 3

Protocol for Studies 39/39A..... 3

Results for Study 39A 11

Results for Study 39 30

Clinical Summary: Study 39A and Study 39..... 44

Conclusions: Uncomplicated Skin and Skin Structure infections 45

COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS 46

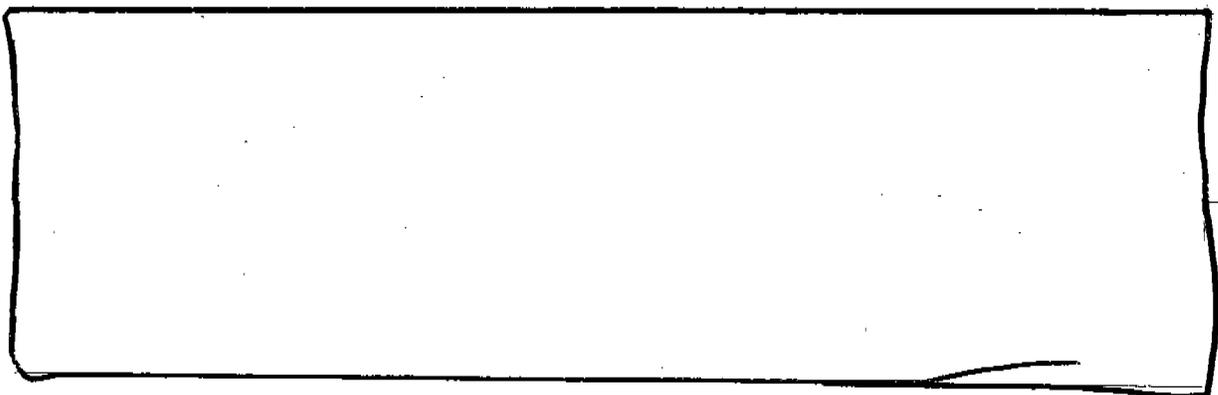
Introduction..... 46

Protocol for Study 55..... 46

Results for Study 55 56

Clinical Summary: Study 55 77

Conclusions: Complicated Skin and Skin Structure infections 78



CONCLUSIONS OF MEDICAL OFFICER REVIEW..... 93

UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

Introduction

Pharmacia & Upjohn Company has proposed the following wording for the **INDICATIONS AND USAGE** section of the package insert:

“Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-sensitive and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.”

Proposed Dosage Regimen: 400 mg taken orally every 12 hours for 10-14 days

A separate study (M/1260/0031) of infections due to methicillin-resistant strains of *Staphylococcus aureus* was performed, and reviewed by David Ross, M. D., Ph. D., elsewhere in the NDA review. This review will address the remainder of this indication.

The studies submitted to support the use of linezolid in uncomplicated skin and skin structure infections are study M/1260/0039A and study M/1260/0039. Study 39A is the pivotal trial for this indication. Originally, both of these trials were initiated as a single multi-national study under the same protocol. The protocol was amended to allow for early closure of the investigator sites from the United States (Amendment D), Canada (Amendment G), and Mexico (Amendment G); and allow separate analyses of the data from these North American sites. There were 76 U.S., 1 Mexican, and 5 Canadian sites. Study 39 continued with 45 sites in 3 South American, 1 African, 4 Asian/Pacific, and 11 European countries. In this review of these studies, the medical officer (M.O.) will provide one discussion of the protocol for both studies, since the only protocol differences should be related to protocol amendments subsequent to the administrative split or local amendments.

The following description of the study protocol is largely excerpted from the final study reports for both 39A and 39. The original protocol was reviewed concurrently with the study reports. Relevant differences between the original protocol and final study reports will be noted. The M.O. will also point out where differences in the protocol or study analyses exist between study 39 and 39A.

Financial Disclosure Statement: None of the investigators in these trials disclosed a financial interest in this product.

Protocol for Studies 39/39A

Study Title: Linezolid Versus Clarithromycin for the Treatment of Uncomplicated Skin and Superficial Skin Structure Infections

Study Objectives:

- To assess the comparative efficacy (clinical and microbiological) of linezolid versus clarithromycin in the treatment of adult patients with uncomplicated skin and superficial skin structure infections
- To assess the comparative safety and tolerance of linezolid versus clarithromycin

Study Design: These were randomized, double-blind, comparator-controlled, multicenter studies of oral linezolid and oral clarithromycin for 7 to 14 days in adult outpatients with uncomplicated skin and superficial skin structure infections. Subjects were randomized in a 1:1 ratio to receive one of the following regimens:

- 400 mg of Linezolid orally twice daily
- 250 mg of Clarithromycin orally twice daily

Study Population: For Study 39A, the first patient was enrolled on 27 March 1998, and the last patient completed the study on 09 December 1998. For study 39, the first patient was enrolled on 05 August 1998, and the last patient completed the study on 08 April 1999. The following inclusion and exclusion criteria were applied to determine eligibility for study participation:

Inclusion Criteria:

1. Suspected gram-positive uncomplicated skin and superficial skin structure infection (such as simple abscesses, impetiginous lesions, furuncles, carbuncles, cellulitis, erysipelas infections of intact skin, and mild burns) with at least 2 of the following symptoms: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, or swelling/induration

(M.O. Comment: The requirement for at least two symptoms was added to the protocol by amendment 1, dated 3 June 1998.)

2. Accessible infection site for Gram's stain and culture
3. Willingness to return for the EOT and F-U visits
4. Provision of written informed consent
5. Age of at least 18 years

(M.O. Comment: The protocol specified an upper age limit of 88 years. This upper limit was removed by amendment 1.)

Exclusion Criteria:

1. Previous antibiotic treatment for more than 24 hours within 7 days of study entry, unless the pathogen showed drug resistance, a positive infection site culture was obtained, and the treatment failed (defined as no clinical improvement after 3 days of treatment)
2. Presence of any of the following:
 - Abscesses for which surgical draining was the only therapeutic intervention required at the time of enrollment
 - A complicated skin and soft tissue infection, such as a major abscess, infected ulcer, major burn, or phlegmonous cellulitis, that involved deeper soft tissue and/or may have required significant surgical intervention in addition to antibiotic therapy
 - Diabetic foot ulcers, decubitus and ischemic ulcers, necrotizing fasciitis, gas gangrene, or burns on greater than 10% of total body surface
 - Isolated furunculosis, folliculitis, or other infection that had a high surgical incision cure rate

(M.O. Comment: This exclusion criterion will be discussed further in the results of the FDA sensitivity analyses. While it is difficult to assess the likelihood of cure by surgical incision, the medical officer has identified some subjects who most likely should have been excluded based on this criterion.)

- Superinfected eczema or other chronic medical conditions (e.g., atopic dermatitis) where inflammation could have been prominent for an extended period even after successful bacterial eradication
- Infections or conditions requiring concomitant antimicrobial or systemic corticosteroid therapy
- Infections of prosthetic materials such as those involving subcutaneous tissue in patients with central venous catheters or permanent cardiac pacemaker battery packs
- Known osteomyelitis
- Liver disease with total bilirubin >5 times upper limit of normal (ULN)

(M.O. Comment: The original protocol specified liver disease with ALT or AST >5 times ULN, total bilirubin >3 times ULN, or kidney disease with serum creatinine >2.5 times ULN. This change was made in amendment 1.)

- Neutropenia (absolute neutrophil count <500 x 10³ cells/ μ L)
- Pheochromocytoma, carcinoid syndrome, or uncontrolled hypertension
- Untreated hyperthyroidism
- Hypersensitivity to linezolid or its formulation excipients
- Hypersensitivity to clarithromycin or its formulation excipients

3. Receipt of another investigational drug within the past 30 days
4. Previous enrollment in this or another linezolid protocol
5. Females of childbearing potential who were unable to take adequate contraceptive precautions, had a positive serum pregnancy test result within 24 hours prior to study entry, were otherwise known to be pregnant, or were currently breastfeeding
6. Concomitant use of terfenadine or astemizole (Only for Canadian sites.)

(M.O. Comment: Exclusion for use of terfenadine or astemizole was added by Protocol Amendment E, dated 12 December 1997. This amendment was applicable only for sites in Canada, where the use of these drugs with clarithromycin is contraindicated.)

Removal of Patients from Therapy or Assessment: Investigators could withdraw patients from the study if in their opinion it was medically necessary, or it was the wish of the patient. The patient could voluntarily withdraw at any time. Therapy was to be withdrawn for any of the following reasons:

- Baseline laboratory assay results that documented severe neutropenia (absolute neutrophil count <500 cells/mm³)

(M.O. Comment: As with the exclusion criterion, the original protocol specified liver disease with ALT or AST >5 times ULN, total bilirubin >3 times ULN, or kidney disease with serum creatinine >2.5 times ULN. This change was made in amendment 1.)

- Lack of clinical improvement within 72 hours

- Baseline site culture pathogens were not gram-positive, and the patient was not improving clinically
- Presence of gram-negative pathogens that required gram-negative antibiotic coverage
- Suspected bacteremia

(M.O. Comment: The original protocol included blood culture at baseline and allowed bacteremic patients to remain in the trial. Patients could be discontinued for lack of microbiologic improvement, giving three consecutive positive blood cultures as an example. This criterion was changed to "clinical or laboratory evidence of bacteremia" in Amendment 1, along with changes to remove blood cultures from the protocol. This change is acceptable in a trial of uncomplicated skin infections.)

- Disease progression, such as septic shock and/or acute renal failure
- Administrative reasons, such as patient non-compliance or a major protocol violation (e.g., pregnancy)
- Request of the sponsor or regulatory agency
- Completion of the protocol-defined dosing period

Patients were to undergo a clinical and laboratory assay assessment on the day treatment with study medication was stopped, and if possible, at all scheduled follow-up visits. If a patient did not return for a scheduled visit, every effort was to be made to contact the patient, regardless of circumstance; and every effort was to be made to document patient outcome to study medication. The investigator was to document the primary reason for patient discontinuation on the CRF.

Study Visits: The study consisted of the following visits or phases:

- Baseline/screen visit – Prior to start of study drug treatment, Day 0-1.
- Patient treatment evaluation – Day 3 of study drug treatment.
- End-of-Treatment (EOT) – Within 72 hours of last dose of study drug, Days 7-14.
- Short Term Follow-up (STFU) – 7-14 days after EOT.

The following evaluations were conducted during the course of the study:

- Medical history.
- Physical examination.
- Vital signs- Body temperature was considered an efficacy measure; blood pressure, pulse, and respiration were safety measures.

(M. O. Comment: Given linezolid's potential for MAO inhibition, temperature could also be an important safety parameter.)

- Clinical observations- Objective and subjective clinical observations included the following:
 - anatomical site of infection
 - extent of infections (length, width, etc.)
 - degree of involvement (superficial or deep)
 - infected site description including erythema, swelling, tenderness, redness, extension, heat, etc.
- Adverse Events Monitoring.

The following hematologic and microbiologic evaluations were conducted during the course of the study:

- Hematology- Complete blood count (CBC) with differential, platelet count, and reticulocyte count.
 - Chemistry- AST, ALT, albumin, alkaline phosphatase, amylase, bilirubin, BUN, calcium, creatinine, creatine phosphokinase, sodium, potassium, bicarbonate, chloride, glucose, GGT, LDH, lipase, total protein and uric acid.
 - Urinalysis- with microscopic.
 - Pregnancy test for females of child-bearing potential- A urine or serum b-HCG pregnancy test had to be performed at the site to qualify the patient for study entry, and a serum b-HCG assay performed by the central laboratory at baseline and the Short Term Follow-up visit. The investigator baseline results must be available and negative before the patient takes the first dose of study medication.
 - Site culture and Gram stain- performed locally.
 - Blood culture- Two sets (each set included aerobic and anaerobic; drawn at least 5 minutes apart) obtained at baseline; single sets thereafter.
- (M.O. Comment: The blood culture requirement was removed by amendment 1.)**
- Bacterial isolate susceptibility testing- Susceptibility tests could be conducted (not required from the local investigator laboratory) to determine if pathogens were susceptible to linezolid and clarithromycin. Clarithromycin susceptibility could be determined from the microtiter plates. Minimum inhibitory concentrations were determined from a panel of antibiotics by the central laboratory.

All hematology, chemistry, urinalysis, and microbiological culture evaluations were performed by a central laboratory so that assay results were consistent and suitable for group analysis. At baseline the local laboratory may also have performed assays for pregnancy test, serum chemistry, hematology, and urinalysis to determine the patient's eligibility to enter the study; however, these data were not included in the study analysis.

(M.O. Comment: The following brief descriptions of study procedures are excerpted from the study protocol. Reference to blood culture was removed by the M.O. The summaries seem to provide an accurate description of study events, based on the M.O. review of a random sample of case report forms. Greater detail is provided in the sponsor's final report for studies 39A and 39. The report for study 39A was submitted under volume 8 of IND [redacted] submission N-192, dated August 27, 1999. The report for study 39 was submitted in volume 1 of IND [redacted] submission N-193, dated September 9, 1999.)

Screening Activities - After giving informed consent, eligible patients were randomized to either the linezolid or clarithromycin treatment groups and provide suitable specimens for Gram stain and infection site microbiological culture and susceptibility testing (Gram stain and culture samples must be obtained before administration of study medication). Blood was drawn for microbiological culture and laboratory assays. All patients provided a medical history (including the cause of infection, any underlying medical conditions, previous medical/surgical therapy for the infection, and an evaluation of

previous antibiotic exposure), urinalysis, and had a physical examination. Females of child-bearing potential must have had a negative pregnancy test (performed locally) prior to receiving study medication.

Treatment Period Activities - All patients could begin their study medication before the safety laboratory assay, microbiological cultures, and susceptibility results were available. Patients were allowed to receive their initial 12 hours of study medication (one dose of linezolid or clarithromycin) while the safety laboratory results were processed. If the safety laboratory criteria were not met, the patient was to be dropped from the study. Patients whose microbiological cultures grew pathogens other than gram-positive pathogens could remain in the study if they showed clinical improvement and did not require concomitant antibiotic therapy. Patients with negative site cultures (no growth) at 24 hours or who had a gram-positive pathogen other than *S. aureus*, *S. pyogenes*, *S. agalactiae*, *E. faecalis*, or *E. faecium*, but who were clinically improving, could remain in the study. Clinical observations, vital signs, hematology, serum chemistry, and urinalysis specimens were to be completed/obtained 72 hours after treatment initiation; infection site culture and susceptibility testing specimens should have been repeated 72 hours after treatment initiation (if obtainable) and/or whenever clinically indicated. Within 72 hours of treatment completion, clinical observations, vital signs, hematology, serum chemistry, and an End-of-Treatment Report were to be completed/obtained.

Post-Treatment Activities - A follow-up evaluation was completed between 7 and 14 days after treatment and was considered the test-of-cure evaluation. Clinical observations, vital signs, hematology, and serum chemistry specimens were completed/obtained. A microbiological infection site specimen was to be cultured (if obtainable), repeat pregnancy test, physical examination, and urinalysis were also to be performed/obtained at the Short Term Follow-up. The Study Completion Report form was to be completed. If any patient was noted to be a clinical failure or had any drainage from the infection site post treatment, the site was to be cultured and/or blood culture specimens obtained as clinically indicated.

Efficacy and Safety Assessments: Efficacy assessments were based on patient disposition with regard to 1) clinical signs and symptoms assessed after treatment as compared with those observed at baseline and 2) microbiological assessments after treatment compared with those conducted at baseline. Clinically evaluable patients were those who fulfilled the study entry criteria, received at least 80% of the total prescribed study medication without missing two consecutive doses during the first 7 days of treatment, and returned for a follow-up visit. Before a clinical assessment of failure could be made, patients had to be treated for at least 2 days. Before a clinical assessment of cure could be made, patients had to be treated for at least 7 days. Microbiologically evaluable patients were those who additionally had a confirmed pathogen at baseline from either the infection site and/or a blood culture. The confirmed pathogen must not be resistant to either study medication. The test-of-cure evaluation was conducted at the short term follow-up visit. Safety assessments were based on the evaluation of clinical observations, vital sign measurements, laboratory assays, and recorded adverse events.

(M.O. Comment: The protocol provides instructions for classification and reporting of adverse events in great detail. These portions of the protocol will not be repeated for this review. The criteria for clinical and microbiological evaluability above correspond roughly to criteria provided in the draft guidance for industry for skin and skin structure infections. The sponsor required at least 5 days and 10 doses of study medication before an assessment of cure or improvement could be made, and at least 2 days or 4 doses for an assessment of failure.)

At the End-of-Treatment and Short Term Follow-up (test-of-cure) visits, the investigator assessed each patient for clinical outcome according to the following criteria:

- Cured - Total resolution of all signs and symptoms of the infection, or improvement to such an extent that no further anti-microbial treatment is necessary.
- Improved - Moderate resolution of clinical symptoms (this outcome category will only be used at the End-of-Treatment evaluation).
- Failed - Persistence, incomplete resolution, or worsening of entry signs and symptoms with emergence of new disease signs or symptoms and/or requiring additional anti-microbial therapy. Patients experiencing adverse event(s) that requires study medication discontinuation will be deemed clinical failures.
- Indeterminate - Extenuating circumstances that preclude classification to one of the above outcomes.

Patient microbiological responses were based on central laboratory culture and sensitivity testing results and statistically assessed according to the following definitions:

- Documented microbiologic eradication - The absence of the original pathogen or pathogens from the culture of the original site of infection at the test-of-cure visit.
- Presumed microbiologic eradication - The patient was clinically cured at the test-of-cure visit and no appropriate material was available for culture from the original site of infection.
- Documented microbiologic persistence - The presence of at least one of the original pathogens from the culture of the original site of infection at the test-of-cure visit.
- Presumed microbiologic persistence - The patient was a clinical failure at the test-of-cure visit and no appropriate material was available for culture from the original site of infection.
- Superinfection - Any patient classified as clinically failed or clinically improved who had a pathogen isolated during therapy that was different from original pathogen(s).
- Colonization - Isolation of an organism other than one isolated at baseline in a patient classified as a clinical cure.
- Reinfection - Any patient classified as a clinical failure who had a pathogen isolated after the End-of-Treatment visit that was different than the original pathogen(s).
- Indeterminate - Any patient who was not classified into one of the above categories.

(M.O. Comment: As expected, the vast majority of patients in both studies 39 and 39A, fall into the category of presumed microbiological eradication or persistence, depending on the clinical outcome for subjects. Microbiological outcome is reported, but the M.O. analysis will focus on clinical outcomes.)

Statistical and Analytical Plan: Analyses of efficacy variables (primary and secondary) were done separately using clinically evaluable and microbiologically evaluable patients. Additionally, analyses of primary efficacy variables were done for an intent-to-treat (ITT) group of patients, and analyses of primary and secondary efficacy variables were done for a modified intent-to-treat (MITT) group of patients. The ITT population was defined as all randomized patients, while the MITT population was defined as all patients meeting entry criteria and having any organism isolated at baseline. Analyses of safety variables were done using all patients who received at least one dose of study medication.

Primary Variables - The primary efficacy variables in this study were patient clinical outcome, microbiologic outcome, and overall (combined clinical/microbiologic) outcome. The test-of-cure assessments were done at the STFU visit. Patient clinical outcome was assessed by the investigator at end-of-treatment (EOT) and short term follow-up (STFU). The proportions of patients in each clinical outcome category were compared between treatment groups at STFU using a chi-square test for homogeneity of proportions. The proportions of patients in relevant microbiologic outcome categories (as well as in the microbiologic success category) were compared between treatment groups at STFU using a chi-square test for homogeneity of proportions (microbiologic success will be defined as documented or presumed microbiologic eradication, or colonization). Patient overall outcome was measured as cure, failure, or indeterminate, with cure defined as a patient who is judged to be both a clinical cure and a microbiologic success, and failure defined as a patient who is a clinical failure and/or a microbiologic failure. The proportions of patients in these overall outcome categories were compared between treatment groups using a chi-square test for homogeneity of proportions. For all three primary efficacy variables, confidence intervals for the differences in success rates between the treatment groups were calculated. These confidence intervals were based on a normal approximation to the binomial distribution of success/failure.

Determination of Sample Size - Using a 2-sided test level of 5% and a desired statistical power of 80% under the assumption that each treatment group will yield a 90% success rate, the number of evaluable patients required per treatment group for a determination of equivalence between the two treatment groups to within 10%, is 142 patients. Assuming an evaluability rate of 45%, this translates to a requirement of 316 enrolled patients per treatment group.

(M.O. Comment: The protocol includes details of the analytical plan for secondary variables, demographic factors, adverse events, and laboratory assays. Plans for a futility (interim) analysis are also included but the planned analysis was removed by amendment 2, dated October 22, 1998. The sponsor indicated that "rapid enrollment prevents this being accomplished". The final study report indicates that the futility analysis was not performed.)

Results for Study 39A

The sponsor's results are excerpted from the final study report for Study 39A. The FDA analyses of the sponsor's data are provided together with the sponsor's results for comparison. A brief description of the methodology used by the FDA to produce these analyses is described in Appendix 1 of this document. Differences between the sponsor's results and FDA's results are discussed in the body of this section. Where the sponsor's results are provided alone, the reviewer did not perform a separate analysis or the reviewer's results are comparable.

Population Definitions

Discontinuation from Study - The first table shows the patient disposition for all randomized patients. Of the 761 patients who enrolled in the study, 383 patients were randomized to the linezolid 400 mg BID treatment group, and 378 patients to the clarithromycin 250 mg BID treatment group. 753 patients received study medication and were in the ITT group: 382 patients received linezolid, and 371 patients received clarithromycin. Comparable percentages of patients in each treatment group completed the study. Of the 382 patients in the linezolid treatment group, 323 (84.6%) subjects completed both the treatment and follow-up phases of the study; 330 (86.4%) completed treatment, and 342 (89.5%) completed the follow-up phase. Of the 371 patients in the clarithromycin treatment group, 316 (85.2%) subjects completed both the treatment and follow-up phases of the study; 331 (89.2%) completed treatment, and 325 (87.6%) completed the follow-up phase.

Sponsor: Summary of Patient Disposition for all Randomized Patients

Population	Linezolid		Clarithromycin	
	N	%	n	%
All Randomized Patients	383	-	378	-
Intent-to-Treat Patients (ITT)	382	100.0	371	100.0
Discontinued During Treatment	52	13.6	40	10.8
Completed Treatment	330	86.4	331	89.2
Discontinued During Follow-up	40	10.5	46	12.4
Completed Follow-up	342	89.5	325	87.6
Discontinued During Treatment and/or Follow-up	59	15.4	55	14.8
Completed Treatment and Follow-up	323	84.6	316	85.2

The sponsor provided reasons for discontinuation of subjects during treatment and during follow-up in the following two tables. A total of 59 (15.4 %) patients in the linezolid group and 55 (14.8%) patients in the clarithromycin group discontinued at some time during the study. The following two tables were provided by the sponsor to indicate reasons for discontinuations. Most of the subjects who discontinued are listed in both of the tables. The sponsor did not provide a table combining discontinuations during treatment and follow-up.

Sponsor: Reasons for Discontinuation During Treatment (ITT)

Reasons for Discontinuations	Linezolid N=382		Clarithromycin N=371	
	N	%	N	%
Discontinued Patients	52	13.6	40	10.8
Lack of Efficacy	7	1.8	4	1.1
Adverse Event (Serious)	5	1.3	2	0.5
Adverse Event (Non-Serious)	22	5.8	16	4.3
Ineligible, but Started Study Medication	1	0.3	0	0.0
Protocol Violation	4	1.0	1	0.3
Withdrawn Consent (Patient's Personal Request)	3	0.8	4	1.1
Lost to Follow-up	7	1.8	10	2.7
Other (reason not specified)	3	0.8	3	0.8

Sponsor: Reasons for Discontinuation During Follow-up (ITT)

Reasons for Discontinuations	Linezolid N=382		Clarithromycin N=371	
	N	%	N	%
Discontinued Patients	40	10.5	46	12.4
Lack of Efficacy	3	0.8	7	1.9
Death	1	0.3	0	0.0
Adverse Event (Serious)	4	1.0	1	0.3
Adverse Event (Non-Serious)	15	3.9	12	3.2
Withdrawn Consent (Patient's Personal Request)	2	0.5	6	1.6
Lost to Follow-up	13	3.4	14	3.8
Other (reason not specified)	2	0.5	6	1.6

Evaluable Populations - The following table provides the numbers of patients in the ITT, modified intent-to-treat (MITT), clinically evaluable, and microbiologically evaluable groups, as determined by the sponsor. The patient numbers in each group were balanced across the two treatment arms. The MITT patient population in each treatment arm consisted of all subjects with one or more organisms isolated from baseline cultures.

Sponsor: Evaluable Populations

Population	Linezolid N=382		Clarithromycin N=371	
	N	%	N	%
All Randomized Patients	383	-	378	-
Never Received Study Medication	1	-	7	-
ITT Patients	382	100.0	371	100.0
Negative Baseline Culture	172	-	156	-
MITT Patients	210	55.0	215	58.0
Clinically Evaluable Patients (CE)	314	82.2	309	83.3
Microbiologically Evaluable Patients (ME)	144	37.7	146	39.4

The number and percentage of patients in the evaluable populations as determined by the FDA analyses are shown in the following table. The ITT patient populations are the same in the FDA and sponsor analyses. The ITT group was defined as all patients who received at least one dose of study medication. The clinically evaluable population is also similar in the sponsor's and reviewer's analyses. The microbiologically evaluable population defined by the FDA is much smaller than that used by the sponsor. The sponsor included *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and other organisms in the ME population. The FDA ME population included only *Staphylococcus aureus* and *Streptococcus pyogenes*. The FDA analysis focused on these two organisms because they are likely pathogens when isolated from a culture of a skin infection site. Most of the other organisms reported by the sponsor were likely contaminants. A discussion that addresses *Staphylococcus epidermidis* in skin and skin structure infections is provided in the results of complicated SSSI trial. Some organisms included in the sponsor's ME population (e.g., *Streptococcus agalactiae*) can act as pathogens under certain circumstances. However, they are unlikely pathogens in otherwise healthy people with uncomplicated skin and skin structure infections or were isolated in too few cases to contribute greatly (e.g., *Pasteurella multocida* was isolated from one study patient). For *Streptococcus agalactiae*, 16 of 18 MITT subjects with this organism also had *Staphylococcus aureus* identified from baseline culture. *Staphylococcus aureus* was likely the pathogen in these subjects. The reviewer used the same methods to identify the ME population in supportive study 39.

M. O.: Evaluable Populations

Population	Linezolid N=382		Clarithromycin N=371	
	N	%	N	%
ITT Patients	382	100.0	371	100.0
Clinically Evaluable Patients (CE)	320	83.8	307	82.7
Microbiologically Evaluable Patients (ME)	97	25.4	113	30.5

The first table on the following page shows the reasons that subjects were considered non-evaluable. A single subject could have multiple reasons for non-evaluability. Subjects who were not clinically evaluable fell into three main categories. These categories are insufficient therapy, non-compliance, or outcome assessment not in evaluable window. This last category included subjects lost to follow-up and subjects whose outcome assessment was earlier than 7 days after end of therapy. Most microbiologically non-evaluable patients did not have any baseline pathogens, were clinically non-evaluable, or had an organism resistant to clarithromycin. Only one baseline pathogen was noted with linezolid resistance (*Bacteroides fragilis*).

Sponsor: Reasons for Non-Evaluability

Patient Subset/Reason for Exclusion	Linezolid N=382		Clarithromycin N=371	
	N	%	N	%
Clinically Evaluable Patients	314	82.2	309	83.3
Clinically Non-evaluable Patients	68	17.8	62	16.7
Prior Antibiotic Usage	1	0.3	0	0.0
Insufficient Therapy	36	9.4	28	7.5
Non-Compliance With Therapy Regimen	46	12.0	35	9.4
Concomitant Antibiotics	1	0.3	5	1.3
Outcome Assessment not in Evaluable Window	38	9.9	40	10.8
Microbiologically Evaluable Patients	144	37.7	146	39.4
Microbiologically Non-evaluable Patients	238	62.3	225	60.6
Clinically Non-evaluable Patients	68	17.8	62	16.7
No Baseline Pathogen	172	45.0	156	42.0
Baseline Pathogen not in the Evaluable Window	1	0.3	2	0.5
All Baseline Pathogens Resistant to One or Both Study Medications	42	11.0	40	10.8

The M. O. reasons for non-evaluability were based in part on the algorithm used by the sponsor. Therefore, the reasons for non-evaluability are similar. A few patients considered non-evaluable by the sponsor are considered evaluable by the reviewer, and vice versa. This does not have a significant effect on the overall reasons for clinical non-evaluability in the FDA analysis. In the microbiologically non-evaluable population, the FDA analysis included only *Staphylococcus aureus* and *Streptococcus pyogenes* as pathogens. As a result, the number of patients who are microbiologically non-evaluable because there was no baseline pathogen increases.

**APPEARS THIS WAY
 ON ORIGINAL**

Patient Characteristics

Patient Demographics – The following table provides comparisons of age, weight, race, gender, and geographic region across the two treatment arms of the study. Demographic factors were comparable in the two treatment arms.

Sponsor: Patient Demographics (ITT)

Parameters	Linezolid N=382		Clarithromycin N=371		Statistical Test P-value
	N	%¶	N	%¶	
<i>Age (yr.)</i>					
Total Reporting	382	100.0	371	100.0	
18-44§	212	55.5	200	53.9	
45-64	109	28.5	121	32.6	
>65	61	16.0	50	13.5	
Mean ± SD	44.1 ± 17.1		43.9 ± 17.0		0.8295†
<i>Weight (kg)</i>					
Total Reporting	377	100.0	364	100.0	
Mean ± SD	83.49 ± 22.55		84.07 ± 22.26		0.7235†
<i>Race</i>					
Total Reporting	378	100.0	370	100.0	0.6834‡
White	318	84.1	322	87.0	
Black	43	11.4	31	8.4	
Asian or Pacific Islander	2	0.5	3	0.8	
Mixed	12	3.2	12	3.2	
Not allowed to ask per local regulation	3	0.8	2	0.5	
<i>Sex</i>					
Total Reporting	382	100.0	371	100.0	0.2432‡
Male	219	57.3	197	53.1	
Female	163	42.7	174	46.9	
<i>Region</i>					
Total Reporting	382	100.0	371	100.0	0.4944
North America	378	99.0	365	98.4	
Latin America (Mexico)	4	1.0	6	1.6	

¶ Percentages are based on the total number of patients reporting.

§ Patient #3910402 was included in this subset, but was later found to be only 16 years of age.

† P-value is based on a one-way Analysis of Variance.

‡ P-value is based on a chi-square test.

The sponsor also provided comparisons of the number of subjects in each treatment arm noted with abnormalities in medical history or physical examination. Comparisons of whether or not an abnormality was reported in a body system were made across treatment arms. No significant differences were noted between the two treatment arms. The sponsor compared the means of baseline vital signs across treatment arms. No differences were noted. Comparisons of mean laboratory values for chemistry, hematology, and urinalysis results were also made. Again, no differences were noted. The mean WBC counts were $7.83 \times 10^3 / \mu\text{L}$ in the linezolid group and $7.55 \times 10^3 / \mu\text{L}$ in the clarithromycin group.

Anti-microbial use (topical and systemic), prior to and during study, was compared. Roughly 9% of subjects in both treatment arms used non-investigational

antibiotics prior to the first dose of study medication. Concomitant medications other than antibiotics were used by approximately 70% of subjects in both treatment arms. Medications used by 5% or more of patients in both treatment groups prior to or during treatment were: acetaminophen, angiotensin-converting enzyme inhibitors, anti-anxiety drugs, calcium channel blocking agents, estrogens, injectable local anesthetics, narcotic analgesic combinations, non-steroidal anti-inflammatory agents, oral contraceptives, salicylates, and thyroid hormones.

Characteristics of the Skin Infection at Baseline - Clinical symptoms and signs of skin infection at baseline were compared between the two treatment arms. The investigators graded clinical symptoms and signs on a four-point scale: none, mild, moderate or severe. The clinical signs and symptoms were pain, tenderness to palpation, erythema, swelling, induration, purulent or non-purulent discharge, warmth to touch, desquamation, and chills. Non-purulent discharge was noted more often in linezolid subjects at baseline (36% vs. 30%), but the clinical signs and symptoms reported are otherwise comparable. In the ITT population, 82% of subjects had pain, 95% had tenderness, 99% had erythema, 94% had swelling, 81% had induration, and 69% had purulent drainage. Only 10% were noted with chills, and 25% with desquamation at baseline.

The following table shows the clinical diagnoses at baseline and the degree of involvement (superficial vs. deep). Results were comparable across the two treatment arms. Cellulitis, infected wounds, and skin abscesses were the most common diagnoses. However, various diagnoses typical of uncomplicated infections (e.g., carbuncle, impetigo, paronychia infection) were also included. Approximately 86% of these infections were considered superficial by the investigator.

Sponsor: Clinical Diagnosis and Degree of Involvement at Baseline (ITT)

Diagnosis	Linezolid N=382		Clarithromycin N=371	
	N	%	n	%
Infected Wound	57	14.9	39	10.5
Cellulitis	85	22.3	97	26.1
Erysipelas	2	0.5	7	1.9
Folliculitis	32	8.4	23	6.2
Carbuncle	9	2.4	8	2.2
Furuncle	28	7.3	20	5.4
Skin Ulcer	7	1.8	10	2.7
Skin Abscesses	52	13.6	68	18.3
Impetigo	16	4.2	19	5.1
Infected Bite	27	7.1	22	5.9
Infected Surgical Incision	10	2.6	11	3.0
Paronychia	26	6.8	25	6.7
Other	31	8.1	22	5.9
<i>Degree of Involvement</i>				
Superficial	332	86.9	319	86.0
Deep	50	13.1	52	14.0

The table on the following page summarizes data on the duration of infection and lesion area. Mean values were comparable across the two treatment arms.

Sponsor: Duration of Infection and Area of Lesion (ITT)

Pretreatment Variable	Results	Linezolid	Clarithromycin
Duration of Infection (Days)	No. Patients Reporting	382	371
	Mean	8.5	9.6
	Standard Deviation	11.6	18.0
Area of Lesion (cm ²)	No. Patients Reporting	381	369
	Mean	56.5	46.3
	Standard Deviation	246.8	131.4

Dosage Information – The following table shows the duration of treatment for both treatment arms using the number of days of treatment and the number of doses taken. All doses of study medication were taken orally. The majority of subjects received 14-15 days of treatment, likely representing the full 14-day treatment course. A 10-15 day course of treatment was used in 70.7% of linezolid subjects. Since the number of days treated was calculated as (stop date - start date)+1, a duration of 15 days was consistent with taking 28 doses. There were no provisions for extending the course of treatment in this trial. Subjects whose duration of treatment was greater than 15 days did not take more than 28 doses of study drug. Treatment compliance was assessed using pill counts only. Non-compliance was reported for 12% of the linezolid group and 9.4% of the clarithromycin group. These non-compliant subjects were considered clinically non-evaluable.

Sponsor: Duration of Treatment (Days) and Number of Doses (ITT)

Duration Assessment	Linezolid N=382		Clarithromycin N=371	
	N	%	n	%
Total Number of Patients Reporting	376	100.0	362	100.0
Number of Days Treated				
<5	26	6.9	17	4.7
5	6	1.6	1	0.3
6	3	0.8	5	1.4
7	28	7.4	23	6.4
8	31	8.2	30	8.3
9	16	4.3	18	5.0
10	26	6.9	26	7.2
11	30	8.0	27	7.5
12	11	2.9	7	1.9
13	5	1.3	5	1.4
14	87	23.1	95	26.2
15	91	24.2	90	24.9
>15	16	4.3	18	5.0
Mean	11.6		12.0	
SD	3.8		3.6	
Number of Doses				
Total Number of Patients Reporting	380	100.0	365	100.0
<10	31	8.2	14	3.8
10-14	45	11.8	47	12.9
15-20	75	19.7	67	18.4
21-28	229	60.3	237	64.9
Mean	21.9		23.1	
SD	7.4		6.7	

Efficacy Results – The sponsor provided multiple analyses under the heading of primary efficacy variables in the final study report. These analyses included investigator's assessment of clinical outcome, sponsor-defined clinical outcome (SDCO), sponsor-defined microbiological outcome (SDMO), and sponsor-defined overall outcome (a combination of clinical and microbiologic outcomes). The results of these analyses were consistent with one another.

(M.O. Comment: The medical officer has chosen to present the sponsor-defined clinical and microbiologic outcomes as the primary analyses by the sponsor. The sponsor-defined clinical outcome was not part of the original protocol. However, the SDCO begins with the investigator's assessment, and modifies the outcome based on rules for clinical assessment that were in the protocol. Some examples of these rules include considering a patient as a clinical failure if other antibiotics are used, and considering cures as indeterminate for noncompliance. The overall effect is to lower efficacy rates, but provide results that are more consistent with the original study design. In all populations, it appeared that the investigator's assessment provided slightly higher cure rate, but similar treatment difference and 95% confidence interval.)

The sponsor presented clinical outcomes for the modified intent-to-treat (MITT) and clinically evaluable populations in the main body of the final study report. Microbiologic outcomes are presented for the MITT, clinically evaluable (CE) and microbiologically evaluable (ME) populations. The ITT analysis was provided in the appendix. Sponsor's analyses of SDCO for the ITT, MITT, CE, and ME are provided in this review. Sponsor's analyses of SDMO for the MITT and ME populations are also provided here.

(M.O. Comment: The medical officer did not perform analyses of an MITT population. The sponsor has included in the MITT population many subjects with colonizers rather than true pathogens from site cultures. The ITT group provides a more appropriate population than the MITT group for assessment of clinical response. The goal of using an MITT population in many antibiotic trials is to assess patients with documented bacterial infection. In trials of other infections (e.g., community acquired pneumonia), the reason for selecting patients with documented infection is that subjects enrolled on the basis of clinical criteria alone could have a viral process that is unaffected by antibiotic treatment. Subjects with viral infections would tend to make the study drug and comparator appear similar. In uncomplicated skin and skin structure infections, low yields of pathogens from site cultures are expected. Most patients who fit entry criteria for the trial are felt to have bacterial infections, even when site cultures are negative. Also, isolation of bacteria is more common in certain clinical diagnoses (e.g., impetigo) than others. Therefore, the ITT and clinically evaluable populations are the primary populations used by the M.O. for assessment of clinical outcomes.)

Clinical Outcome - The tables on the following page provide the sponsor-defined clinical outcome and the FDA analysis of clinical outcome in the ITT population. The test-of-

cure assessment was made at the follow-up visit. The sponsor reported clinical cure rates of 84.5% for linezolid and 83.0% for clarithromycin at follow-up. The clinical cure rates were similar in the sponsor's and reviewer's analyses. The lower bounds of the 95% confidence intervals in the sponsor's and reviewer's analyses were -4.0% and -3.4%, respectively. The numbers of patients with indeterminate or missing outcomes were similar in the two analyses. Missing or indeterminate outcomes were noted in 11% of linezolid-treated and 13% of clarithromycin-treated patients. The number of patients assessed in each of these analyses excluded the patients with missing or indeterminate outcomes. The effect of this missing data is explored in a later section of this document (*Sensitivity Analyses*).

Sponsor: Clinical Outcome at End-of-Therapy and Follow-up (ITT)

Visit	Assessment	Linezolid		Clarithromycin		95% CI
		N	%	N	%	
End of Treatment	Number of Assessed Patients	344	100	332	100	
	Success (Cured + Improved)	303	88.1	294	88.6	
	Cured	255	74.1	241	72.6	
	Improved	48	14.0	53	16.0	
	Failed	41	11.9	38	11.4	
	Indeterminate	1	--	0	--	
Follow-Up (TOC)	Missing	37	--	39	--	
	Number of Assessed Patients	343	100	323	100	
	Cured	290	84.5	268	83.0	(-4.0, 7.2)
	Failed	53	15.5	55	17.0	
	Indeterminate	20	--	30	--	
	Missing	19	--	18	--	

M. O.: Clinical Outcome at Follow-up (ITT)

Visit	Assessment	Linezolid		Clarithromycin		95% CI
		N	%	N	%	
Follow-Up (TOC)	Number of Assessed Patients	341	100	322	100	
	Cured	293	85.9	269	83.5	(-3.4, 8.2)
	Failed	48	14.1	53	16.5	
	Indeterminate or Missing	41	--	49	--	

MITT - The following table shows the SDCO results at follow-up for the sponsor's *MITT* population. These results were comparable to those for the *ITT* population. The cure rates were slightly lower in the *MITT* population, but the treatment difference remained about the same.

Sponsor: Clinical Outcome at Follow-up (MITT)

Visit	Assessment	Linezolid N=210		Clarithromycin N=215		95% CI
		N	%	N	%	
Follow-Up (TOC)	Number of Assessed Patients	190	100.0	188	100.0	
	Cured	159	83.7	152	80.9	(-4.9, 10.5)
	Failed	31	16.3	36	19.1	
	Indeterminate	10	-	16	-	
	Missing	10	-	11	-	

Clinically Evaluable -The SDCO in the sponsor's clinically evaluable population is shown in the table below. The clinical cure rates at follow-up were 91.3% for linezolid and 87.0% for clarithromycin. These cure rates were higher than those reported for the ITT population. The treatment difference and 95% confidence interval were consistent with the analysis in the ITT population.

Sponsor: Clinical Outcome at End-of-Therapy and Follow-up (CE)

Visit	Assessment	Linezolid N=314		Clarithromycin N=309		95% CI
		N	%	N	%	
End of Treatment	Number of Assessed Patients	296	100.0	289	100.0	
	Success (Cured + Improved)	280	94.6	265	91.7	
	Cured	235	79.4	216	74.7	
	Improved	45	15.2	49	17.0	
	Failed	16	5.4	24	8.3	
	Indeterminate	1	-	0	-	
Follow-Up (Test-of-Cure)	Missing	17	-	20	-	
	Number of Assessed Patients	310	100.0	301	100.0	
	Cured	283	91.3	262	87.0	(-0.7, 9.2)
	Failed	27	8.7	39	13.0	
	Indeterminate	4	-	8	-	

The FDA analysis of clinical outcome at follow-up for the clinically evaluable population is shown in the table below. The clinical cure rates at follow-up were 88.4% for linezolid and 85.3% for clarithromycin. The number of clinically evaluable subjects that were considered to be cured was the same in the sponsor's and reviewer's analyses. There were more subjects considered to be clinical failures in the FDA analysis, providing cure rates much closer to those seen in the ITT population. In the FDA analysis, indeterminate outcomes were treated the same as missing data. The patients with indeterminate outcomes in the sponsor's analysis would have been considered non-evaluable in the FDA analysis, unless some other factor led to their inclusion as failures. The lower bounds of the 95% confidence interval was -0.7% in the sponsor's analysis and -2.5% in the FDA analysis.

M. O.: Clinical Outcome at Follow-up (CE)

Visit	Assessment	Linezolid N=320		Clarithromycin N=307		95% CI
		N	%	N	%	
Follow-Up (Test-of-Cure)	Number of Assessed Patients	320	100	307	100	
	Cured	283	88.4	262	85.3	(-2.5, 8.7)
	Failed	37	11.6	45	14.7	

Microbiologically Evaluable – Unlike the clinically evaluable population, there are large differences between the sponsor and FDA reviewer in the size of the microbiologically evaluable groups. These differences are related to the organisms included as pathogens by the M. O. and the sponsor. The M.O. included only patients with *Staphylococcus aureus* or *Streptococcus pyogenes* at baseline in the microbiologically evaluable

population. Despite the differences in population analyzed, the results appear fairly similar.

The following table provides the SDCO for the sponsor's microbiologically evaluable population. The clinical cure rates at follow-up were 88.1% for linezolid and 86.5% for clarithromycin. As with the ITT and CE groups, linezolid had a slightly higher clinical cure rate than clarithromycin.

Sponsor: Clinical Outcome at EOT and Follow-up (ME)

Visit	Assessment	Linezolid N=144		Clarithromycin N=146		95% CI
		N	%	N	%	
End of Treatment	Number of Assessed Patients	138	100	139	100	
	Success (Cured + Improved)	131	94.9	126	90.6	
	Cured	115	83.3	100	71.9	
	Improved	16	11.6	26	18.7	
	Failed	7	5.1	13	9.4	
	Indeterminate	1	--	0	--	
Follow-Up (Test-of-Cure)	Missing	5	--	7	--	
	Number of Assessed Patients	143	100	141	100	
	Cured	126	88.1	122	86.5	(-6.2, 9.3)
	Failed	17	11.9	19	13.5	
	Indeterminate	1	--	5	--	

The FDA analysis of clinical outcome at follow-up for the microbiologically evaluable population is shown in the table below. The clinical cure rates at follow-up were 86.6% for linezolid and 85.8% for clarithromycin. The differences in definition of the ME population make direct comparisons of cures and failures difficult at best. However, it is reassuring that a similar treatment difference (favoring linezolid) was seen. The lower bounds of the 95% confidence interval were -6.2% in the sponsor's analysis and -9.5% in the FDA analysis. The wider 95% confidence interval in the FDA analysis reflects the smaller ME population defined by the M. O.

M. O.: Clinical Outcome at Follow-up (ME)

Visit	Assessment	Linezolid N=97		Clarithromycin N=113		95% CI
		N	%	N	%	
Follow-Up (Test-of-Cure)	Number of Assessed Patients	97		113		
	Cured	84	86.6	97	85.8	(-9.5, 11.0)
	Failed	13	13.4	16	14.2	

A similar treatment difference of roughly 1-3% (favoring linezolid) was seen in the primary analyses of clinical outcome, despite differences in the methodology of the FDA and the sponsor and differences in study population. This consistency indicates a fairly robust result, and supports the sponsor's contention that this study demonstrates equivalence of linezolid and clarithromycin in uncomplicated skin and skin structure infections.

Microbiological Outcome – The following table shows the SDMO for the MITT, CE, and ME population. Microbiological success included subjects in one of the following categories: documented eradication of the baseline pathogen, presumed eradication, or colonization. Microbiological success rates were higher than clinical cure rates in the same population. SDMO in these populations generally showed larger treatment differences (favoring linezolid) than seen in clinical outcome results. It should be noted that roughly 45% of the clinically evaluable population did not have a baseline pathogen. Another factor of note is that the number of patients assessed in the clinically evaluable population is higher than for the ME population. This difference reflects the fact that inclusion in the ME population required not only isolation of an baseline organism, but also excluded resistant pathogens.

(M.O. Comment: The majority of microbiological successes were subjects with presumed eradication of the baseline pathogen in subjects who were clinical cures. However, the likely explanation for higher microbiological success rates is that subjects who were considered clinical failures or indeterminate could be considered microbiological successes if the baseline pathogen was not present on test-of-cure culture. Similarly, some subjects could be considered microbiological failures if cultures demonstrated continued growth of an organism (documented persistence) in a subject with cure or indeterminate as the clinical outcome. The M. O. focused on clinical outcome rather than microbiological outcome results.)

Sponsor: Microbiological Outcome at Follow-Up (MITT, CE, ME)

Assessment	Linezolid		Clarithromycin		95% CI
	n	%	n	%	
<i>MITT Population</i>					
Total Number of Patients	210	-	215	-	
Number of Assessed Patients	190	100.0	193	100.0	
Microbiological Success	163	85.8	152	78.8	(-0.6, 14.6)
<i>Clinically Evaluable Population</i>					
Total Number of Patients	314		309		
Number of Assessed Patients	173	100.0	178	100.0	
Microbiological Success	160	92.5	149	83.7	(2.1, 15.5)
<i>Microbiological Evaluable Population</i>					
Total Number of Patients	144		146		
Number of Assessed Patients	143	100.0	145	100.0	
Microbiological Success	130	90.9	122	84.1	(-0.8, 14.4)

Patient Overall Outcome – The sponsor has also provided a table of patient overall outcome in the clinically evaluable population. This analysis involves a combination of the clinical and microbiological outcome data. The results of these analyses are consistent with the clinical and microbiological outcome results already presented. They will not be repeated here, but are available in the sponsor’s final study report and appendix tables.

Subgroup Analyses

Pathogen – The sponsor included a number of organisms in the microbiologically evaluable population. The following tables show the SDMO and SDCO for selected organisms. The reviewer chose to focus on clinical outcome in these selected pathogens. There is a tendency to overestimate or underestimate microbiological success, as noted in the discussion of microbiological outcome. Comparing SDMO and SDCO in *S. aureus*, these differences were seen. In the linezolid arm, two subjects with *S. aureus* were clinical failures, but microbiological successes. In the clarithromycin arm, 4 subjects were microbiological failures, but their clinical outcomes were indeterminate.

Sponsor: Microbiological Success Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Microbiological Success Rate			
	Linezolid		Clarithromycin	
	n/N	%	n/N	%
<i>E faecalis</i>	8/8	100.0	8/12	66.7
<i>S aureus</i>	82/91	90.1	89/108	82.4
<i>S epidermidis</i>	28/31	90.3	21/23	91.3
<i>S lugdunensis</i>	8/8	100.0	7/8	87.5
<i>S agalactiae</i>	10/10	100.0	4/5	80.0
<i>S pyogenes</i>	5/5	100.0	10/12	83.3

Sponsor: Clinical Cure Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Clinical Cure Rate			
	Linezolid		Clarithromycin	
	n/N	%	n/N	%
<i>E faecalis</i>	8/8	100.0	8/12	66.7
<i>S aureus</i>	80/91	87.9	89/104	85.6
<i>S epidermidis</i>	26/31	83.9	21/23	91.3
<i>S lugdunensis</i>	8/8	100.0	7/8	87.5
<i>S agalactiae</i>	10/10	100.0	4/5	80.0
<i>S pyogenes</i>	5/5	100.0	10/11	90.9

The sponsor has requested an indication for uncomplicated SSSI that includes *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*.

Staphylococcus lugdunensis, *Staphylococcus epidermidis*, and *Enterococcus faecalis* were not included in the requested indication. *S. epidermidis* is widely recognized as normal skin flora in humans. The medical literature includes case series reports of subjects with infection due to *S. lugdunensis*. However, these same reports also note that the organism occurs as a skin colonizer. Enterococci can cause skin infections as well, though usually associated with complicated infections or compromised hosts (e.g., peri-rectal abscess, wound infection in hospitalized patients). *Enterococcus faecalis* is also a commensal organism that is usually found in the gastrointestinal tract, but can be isolated from intact skin. In this trial of uncomplicated SSSI, isolation of these organisms most likely represents colonization. These organisms will not be discussed further.

The FDA analysis of clinical outcome at follow-up by pathogen for the microbiologically evaluable population is shown in the table below. The FDA analysis included only *Staphylococcus aureus* and *Streptococcus pyogenes* as pathogenic organisms. There were 3 additional microbiologically evaluable subjects (2 linezolid, 1 clarithromycin) with *Staphylococcus aureus* in the FDA analysis. All were considered clinical failures. However, the clinical cure rates for these individual pathogens were consistent with the clinical cure rates in the primary analyses. The number of subjects with *S. pyogenes* in this trial was small, but additional subjects with this pathogen were included in Study 39. Although not shown, FDA clinical cure rates for patients with *Streptococcus agalactiae* on baseline cultures were the same as the sponsor's results.

M. O.: Clinical Cure Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Clinical Cure Rate			
	Linezolid		Clarithromycin	
	n/N	%	n/N	%
<i>S aureus</i>	80/93	86.0	89/105	84.8
<i>S pyogenes</i>	5/5	100	10/11	90.9

Streptococcus agalactiae and *Staphylococcus epidermidis* were considered likely colonizers by the M. O. in most cases where obtained. *S. agalactiae* is known to cause cases of skin and skin structure infections. However, cases described in the literature are usually in neonates, post-partum women, the immunocompromised, or diabetic patients. The M. O. reviewed the cases of *Streptococcus agalactiae* in this study. Of 18 subjects in the ITT population identified with *S. agalactiae* at baseline, 16 subjects had *S. aureus* on the same culture. In these cases, the contribution of *S. agalactiae* as a pathogen can not be determined. In only two cases, pilonidal abscess and left arm surgical infection, was *S. agalactiae* identified in pure culture. Even in the subject with pilonidal abscess, *S. agalactiae* may be from the vaginal tract flora. Only one subject in study 39 had *S. agalactiae* on baseline culture.

(M. O. Comment: Based on these data, the medical reviewer would not recommend inclusion of *S. agalactiae* in the indication for skin and skin structure infections. It should be noted that some of the subjects with *S. pyogenes* had *S. aureus* as a co-pathogen. However, *S. pyogenes* is recognized as a common cause of skin infections in otherwise healthy individuals. Thus, clinical cure in *S. pyogenes* and *S. aureus* co-infection does provide sufficient information on the effectiveness of the test agent against *S. pyogenes*. For *S. agalactiae*, the same level of evidence is not present.)

Clinical diagnosis – The tables on the following pages provide subgroup analyses of the clinical cure rates by clinical diagnosis produced by the sponsor and the FDA review. The results shown were obtained in the clinically evaluable population. These results were generally consistent between the sponsor and FDA analyses, and also consistent with the primary analyses of clinical outcome. Clinical cure rates <80% were seen for some diagnoses, but these were diagnoses with very few patients.

Sponsor: Clinical Outcome at Follow-Up by Clinical Diagnosis (CE)

Diagnosis	Sponsor-Defined Clinical Outcome			
	Linezolid		Clarithromycin	
	n/N	%	n/N	%
Erysipelas	1/1	100.0	7/7	100.0
Furuncle	26/26	100.0	17/19	89.5
Infected surgical incision	6/6	100.0	7/8	87.5
Infected bite	21/22	95.5	18/18	100.0
Infected wound	44/47	93.6	28/30	93.3
Skin abscesses	42/46	91.3	53/58	91.4
Cellulitis	60/66	90.9	65/77	84.4
Impetigo	10/11	90.9	12/16	75.0
Folliculitis	23/26	88.5	14/17	82.4
Paronychia	22/25	88.0	16/18	88.9
Carbuncle	6/8	75.0	5/7	71.4
Skin ulcer	3/4	75.0	3/6	50.0
Other	19/22	86.4	17/20	85.0

M. O.: Clinical Outcome at Follow-Up by Clinical Diagnosis (CE)

Diagnosis	FDA Clinical Outcome			
	Linezolid		Clarithromycin	
	n/N	%	N/N	%
Erysipelas	1/1	100	7/7	100
Furuncle	26/26	100	17/19	89.5
Infected surgical incision	6/8	75.0	7/8	87.5
Infected bite	21/23	91.3	18/19	94.7
Infected wound	44/47	93.6	28/30	93.3
Skin abscesses	42/47	89.4	53/60	88.3
Cellulitis	60/70	85.7	65/79	82.3
Impetigo	10/12	83.3	12/16	75.0
Folliculitis	23/26	88.5	14/17	82.4
Paronychia	22/25	88.0	16/18	88.9
Carbuncle	6/8	75.0	5/7	71.4
Skin ulcer	3/5	60.0	3/6	50.0
Other	19/22	86.4	17/21	81.0

Age – The following table provides clinical cure rates in the ITT population, grouped by age. The subjects who are ≥ 65 years show lower clinical cure rates in both treatment arms. The treatment difference widens in the older age group, but the number of patients in the ≥ 65 years age group is small. The results suggest that the treatment difference favoring linezolid is not adversely affected by older age.

(M. O. Comment: In the following subgroup analyses of the ITT population, the patients with missing outcomes are excluded from the analyses. A total of 341 linezolid-treated patients and 322 clarithromycin-treated patients had non-missing outcomes.)

M. O.: Clinical Cure Rates at Follow-Up by Age Category (ITT)

Age Category	Clinical Cure Rate			
	Linezolid		Clarithromycin	
	N	%	N	%
≥ 65 years	51	82.4	45	66.7
< 65 years	290	86.6	277	86.3

Gender – The effect of gender on efficacy of linezolid was also investigated by looking at clinical cure rates in males and females separately. The following table shows clinical cure rates in the ITT population by gender. The treatment difference between linezolid and clarithromycin was smaller in females compared to males, but no gender differences in treatment effect were established.

M. O.: Clinical Cure Rates at Follow-Up by Gender (ITT)

Gender	Clinical Cure Rate			
	Linezolid		Clarithromycin	
	N	%	N	%
Female	145	84.1	150	83.3
Male	196	87.2	172	83.7

Lesion Size – The size of lesions (in cm²) was calculated by the sponsor based on the width and length of lesions recorded in the case report forms. The subjects with a clinical diagnosis of skin abscess, folliculitis, carbuncle, or furuncle and who had a lesion size of ≤ 1 cm² were considered likely to have resolution of infection with incision and drainage (I&D). I&D for bacterial culture was a part of the protocol for all patients. Thirty-six subjects in each treatment arm fell into this category. The treatment effect favoring linezolid remained without a significant change in clinical cure rates.

M. O.: Clinical Cure Rates at Follow-Up by Lesion Size (ITT)

Lesion Size	Clinical Cure Rate			
	Linezolid		Clarithromycin	
	N	%	N	%
> 1 cm ²	304	86.2	284	83.8
≤ 1 cm ²	36	83.3	36	83.3
Missing	1	100	2	50

Sensitivity Analyses

Effect of Missing Data – The effect of missing data was investigated by looking at changes in clinical cure rates when missing outcomes are changed to failures. The following table shows the clinical cure rates in the ITT population when missing outcome was considered failure. As expected the clinical cure rates decreased, but the treatment difference favoring linezolid was similar to the results of the primary analysis.

M. O.: Clinical Outcome at Follow-up with Missing Outcome as Failure (ITT)

Visit	Assessment	Linezolid		Clarithromycin		95% CI
		N	%	N	%	
Follow-Up (TOC)	Number of Assessed Patients	382	100	371	100	(-2.3, 10.7)
	Cured	293	76.7	269	72.5	
	Failed, Indeterminate, or Missing	89	23.3	102	27.5	

Safety Results – The safety results are excerpted from the sponsor’s final study report. The following table provides an overall summary of the treatment emergent adverse events (AE) reported in the ITT population. AE were reported more frequently in the linezolid arm vs. the clarithromycin arm. The same result was seen in the comparison of drug-related AE. There were only a few subjects reported with serious AE in either treatment arm.

Sponsor: Summary of Adverse Events (ITT)

Parameter	Linezolid N=382		Clarithromycin N=371		Statistical Test P-value
	n	%‡	n	%	
Total Number of Patients Reporting	382	100.0	371	100.0	
Patients with >1 AE Reported	206	53.9	170	45.8	0.0262*
Patients with >1 Drug-related AE Reported	113	29.6	80	21.6	0.0118*
Patients with >1 AE Resulting in D/C of Study Medication	28	7.3	18	4.9	0.1557
Patients with >1 Drug-related AE Resulting in D/C of Study Medication	17	4.5	11	3.0	0.2815
Patients with >1 Serious AE Reported	9	2.4	5	1.3	0.3058
Patients Who Died	2	0.5	0	0.0	0.1628

Deaths - There were two deaths in protocol 0039A, both in subjects who received linezolid. A 34 year-old obese, diabetic male (#3910811) had cellulitis of the thigh, which progressed to necrotizing fasciitis after three days of oral linezolid. The subject was admitted to the hospital and underwent surgery. He was started on clindamycin and aztreonam. He died in the operating room, on the evening of hospital admission. The culture report included *Proteus mirabilis*, *Klebsiella pneumoniae*, *Escherichia coli*, viridans group Streptococci, and *Staphylococcus epidermidis*.

The second subject (#3910615) was a 76 year-old diabetic female with a history of vascular disease. She was a clinical failure who started ciprofloxacin between the end-of-treatment and follow-up visits due to continued clinical symptoms of infection. Adverse events reported for this subject included “coronary artery disease” on the third day of therapy, and “transient ischemic attacks” and “bladder infection” between the EOT and follow-up visits. The subject died during cardiac bypass graft surgery 6 days after the follow-up visit and 13 days after the last dose of linezolid. The adverse event report indicated that the surgeons were unable to restart the patient’s heart during surgery.

All Adverse Events - The treatment emergent adverse events occurring in >1% of patients in either treatment arm are shown in the table on the following page. The most common adverse events were headache, diarrhea, and nausea. These same events were also common in other studies with linezolid. Tongue discoloration, reported in healthy volunteers in phase 1 studies, was also seen in this trial. Reports of fungal infections were more common in the linezolid treatment arm.

Uncomplicated Skin and Skin Structure Infections
Study 39A Results
Pivotal Study

Sponsor: Study-Emergent AE Occurring in >1% of Patients (ITT)

COSTART Body System /MET	Linezolid N=382		Clarithromycin N=371	
	n	%	n	%
Patients With None	176	46.1	201	54.2
Patients With at Least One	206	53.9	170	45.8
BODY				
Headache	43	11.3	38	10.2
Infection Fungal NOS	8	2.1	1	0.3
Trauma	10	2.6	9	2.4
Fatigue	5	1.3	7	1.9
Upper Respiratory Infection	6	1.6	4	1.1
DIGESTIVE				
Appetite Decreased	0	0	5	1.3
Diarrhea	38	9.9	28	7.5
Dry Mouth	5	1.	4	1.1
Dyspepsia	8	2.1	4	1.1
Nausea	22	5.8	22	5.9
Tongue Discoloration	6	1.6	0	0
Tongue Disorder	5	1.3	0	0
Vomiting	8	2.1	7	1.9
METABOLIC AND NUTRITIONAL				
Serum Creatinine Phosphokinase Increased	5	1.3	5	1.3
SGPT Increased	2	0.5	5	1.3
NERVOUS				
Dizziness	11	2.9	10	2.7
Insomnia	6	1.6	2	0.5
RESPIRATORY				
Rhinitis	0	0	5	1.3
SKIN				
Skin Disorder	3	0.8	4	1.1
Pruritis (Non-Application Site)	5	1.3	4	1.1
Rash	6	1.6	5	1.3
SPECIAL SENSES				
Taste Perversion	8	2.1	9	2.4
UROGENITAL				
Moniliasis Vaginal	10	2.6	7	1.9

Drug Related AE – The table on the following page shows the AE that were considered drug-related and occurring in >2% of patients in either treatment arm. The leading drug-related AE were similar to those noted in the table of all adverse events.

Uncomplicated Skin and Skin Structure Infections
Study 39A Results
Pivotal Study

Sponsor: Study-Emergent Drug-Related AE Occurring in >2% of Patients (ITT)

	Linezolid N=382		Clarithromycin N=371	
	n	%	N	%
COSTART Body System/MET				
Patients With None	269	70.4	291	78.4
Patients With at Least One	113	29.6	80	21.6
BODY				
Headache	13	3.4	11	3.0
Infection Fungal NOS	8	2.1	1	0.3
DIGESTIVE				
Diarrhea	27	7.1	22	5.9
Nausea	14	3.7	17	4.6
SPECIAL SENSES				
Taste Perversion	8	2.1	9	2.4
UROGENITAL				
Moniliasis Vaginal	9	2.4	7	1.9

Serious AE – All serious AE noted in this study are listed in the following table. None were considered drug-related by the reporter. Several AE (abscess, cellulitis, and fasciitis) are likely related to the underlying disease under study. Coronary artery disease and transient ischemic attack were both noted in the same patient. This patient was one of the two deaths described earlier in this review.

Sponsor: Study-Emergent Serious Adverse Events (ITT)

	Linezolid N=382		Clarithromycin N=371	
	n	%†	N	%†
COSTART Body System/MET				
Patients With None	373	97.6	366	98.7
Patients With at Least One	9	2.4	5	1.3
BODY				
Abscess	3	0.8	-	-
Cellulitis	1	0.3	2	0.5
Sepsis	-	-	1	0.3
Trauma	-	-	1	0.3
CARDIOVASCULAR				
Coronary artery disease	1	0.3	-	-
Palpitation	-	-	1	0.3
MUSCULO-SKELETAL				
Fasciitis	1	0.3	-	-
NERVOUS				
Disorder bipolar affective	1	0.3	-	-
Dizziness	-	-	1	0.3
Transient ischemic attacks	1	0.3	-	-
SKIN				
Skin infection	1	0.3	-	-
UROGENITAL				
Abortion, spontaneous	1	0.3	-	-

An 18 y.o. subject had a spontaneous abortion on the eighth post-treatment day. She was first noted with a positive pregnancy test on the third post-treatment day. Her baseline urine pregnancy test was negative.

Results for Study 39 (Non-North American, Supportive Trial)

The sponsor's results are excerpted from the final study report for Study 39. The FDA analyses of the sponsor's data are provided together with the sponsor's results for comparison.

(M. O. Comment: The results of this trial were provided as supportive information for the indication of uncomplicated skin and skin structure infection. The same differences in methodology and overall results seen with study 39A also apply here. As such, an abbreviated description of the primary efficacy and safety results will be provided, but the detailed subgroup and sensitivity analyses presented for study 39A will not be included in this review.)

Population Definitions

Discontinuation from Study - The first table shows the patient disposition for all randomized patients. Of the 241 patients who enrolled in the study, 170 patients were randomized to the linezolid 400 mg BID treatment group, and 171 patients to the clarithromycin 250 mg BID treatment group. 332 patients received study medication and were in the ITT group: 166 patients received linezolid, and 166 patients received clarithromycin. Comparable percentages of patients in each treatment group completed the study. Of the 166 patients in the linezolid treatment group, 141 (84.9%) subjects completed both the treatment and follow-up phases of the study; 146 (88.0%) completed treatment, and 147 (88.6%) completed the follow-up phase. Of the 166 patients in the clarithromycin treatment group, 148 (89.2%) subjects completed both the treatment and follow-up phases of the study; 153 (92.2%) completed treatment, and 154 (92.8%) completed the follow-up phase.

Sponsor: Summary of Patient Disposition for all Randomized Patients

Population	Linezolid		Clarithromycin	
	N	%	N	%
All Randomized Patients	170	-	171	-
Intent-To-Treat Patients (ITT)	166	100.0	166	100.0
Discontinued During Treatment	20	12.0	13	7.8
Completed Treatment	146	88.0	153	92.2
Discontinued During Follow-Up	19	11.4	12	7.2
Completed Follow-Up	147	88.6	154	92.8
Discontinued During Treatment and/or Follow-Up	25	15.1	18	10.8
Completed Treatment and Follow-Up	141	84.9	148	89.2

The sponsor provided reasons for discontinuation of subjects during treatment and during follow-up in the following two tables. A total of 25 (15.1%) patients in the linezolid group and 18 (10.8%) patients in the clarithromycin group discontinued at some time during the study. The following two tables were provided by the sponsor to indicate reasons for discontinuations. Most of the subjects who discontinued are listed in both of the tables. The sponsor did not provide a table combining discontinuations during treatment and follow-up.

Uncomplicated Skin and Skin Structure Infections
Study 39 Results
Supportive Study

Sponsor: Reasons for Discontinuation During Treatment (ITT)

Reasons for Discontinuations	Linezolid N=166		Clarithromycin N=166	
	n	%	n	%
Discontinued Patients	20	12.0	13	7.8
Lack of Efficacy	2	1.2	3	1.8
Adverse Event (Non-Serious)	4	2.4	2	1.2
Ineligible, but Started Study Medication	4	2.4	0	-
Protocol Non-Compliance	2	1.2	2	1.2
Subject's Personal Request	1	0.6	3	1.8
Lost to Follow-Up	5	3.0	2	1.2
Other	2	1.2	1	0.6

Sponsor: Reasons for Discontinuation During Follow-up (ITT)

Reasons for Discontinuations	Linezolid N=166		Clarithromycin N=166	
	n	%	n	%
Discontinued Patients	19	11.4	12	7.2
Lack of Efficacy	2	1.2	2	1.2
Adverse Event (Non-Serious)	2	1.2	0	-
Ineligible, but Started Study Medication	2	1.2	0	-
Protocol Non-Compliance	1	0.6	1	0.6
Subject's Personal Request	2	1.2	2	1.2
Lost to Follow-up	10	6.0	6	3.6
Other (Reason not Specified)	0	-	1	0.6

Evaluable Populations - The following table provides the numbers of patients in the ITT, MITT, clinically evaluable, and microbiologically evaluable groups, as determined by the sponsor. The patient numbers in each group were balanced across the two treatment arms. The MITT patient population in each treatment arm consisted of all subjects with one or more organisms isolated from baseline cultures.

Sponsor: Evaluable Populations

Population	Linezolid N=170		Clarithromycin N=171	
	n	%†	N	%†
All Randomized Patients	170	-	171	-
Never Received Study Medication	4	-	5	-
ITT Patients	166	100.0	166	100.0
No Baseline Pathogen	81	48.8	70	42.2
MITT Patients	85	51.2	96	57.8
Clinically Evaluable Patients (CE)	127	76.5	124	74.7
Microbiologically Evaluable Patients (ME)	55	33.1	68	41.0

The number and percentage of patients in the evaluable populations as determined by the FDA analyses are shown in the table on the following page. The FDA methods for determining these populations were described with the results for study 39A. The ITT population was the same as that of the sponsor. The clinically evaluable populations

were comparable. The ME population defined by the M. O. is smaller than that of the sponsor, since only *Staphylococcus aureus* and *Streptococcus pyogenes* were included by the M. O.

M. O.: Evaluable Populations

Population	Linezolid N=166		Clarithromycin N=166	
	N	%	N	%
ITT Patients	166	100.0	166	100.0
Clinically Evaluable Patients (CE)	128	77.1	127	76.5
Microbiologically Evaluable Patients (ME)	41	24.7	58	34.9

The following table shows the reasons that subjects were considered non-evaluable. A single subject could have multiple reasons for non-evaluability. As in study 39A, clinically non-evaluable subjects fell into three main categories: insufficient therapy, non-compliance, or outcome assessment not in evaluable window. Most microbiologically non-evaluable patients did not have any baseline pathogens, were clinically non-evaluable, or had an organism resistant to clarithromycin. There were no reported pathogens resistant to linezolid at baseline.

Sponsor: Reasons for Non-Evaluability

Patient Subset/Reason for Exclusion	Linezolid N=166		Clarithromycin N=166	
	n	%	n	%
Clinically Evaluable Patients	127	76.5	124	74.7
Clinically Not Evaluable Patients	39	23.5	42	25.3
Insufficient Therapy	17	10.2	6	3.6
Non-Compliance With Therapy Regimen	30	18.1	30	18.1
Concomitant Antibiotics	2	1.2	2	1.2
No Post-Baseline Clinical Outcome in Evaluable Window	14	8.4	17	10.2
Sponsor Override*	3	1.8	3	1.8
MITT Patients	85	51.2	96	57.8
Not MITT Patients (No Baseline Pathogen)	81	48.8	70	42.2
Microbiologically Evaluable Patients	55	33.1	68	41.0
Microbiologically Not Evaluable Patients	111	66.9	98	59.0
Clinically Not Evaluable Patients	39	23.5	42	25.3
No Baseline Pathogen	83	50.0	70	42.2
All Baseline Pathogens Resistant to Study Medication	8	4.8	6	3.6

*2 patients with non-qualifying diagnosis, 3 patients in whom compliance could not be assessed, and 1 patient non-evaluable for erythromycin use

The M. O. reasons for non-evaluability were based in part on the algorithm used by the sponsor. Therefore, the reasons for non-evaluability are similar. A few patients considered non-evaluable by the sponsor are considered evaluable by the reviewer, and vice versa. This does not have a significant effect on the overall reasons for non-evaluability in the FDA analysis. As with study 39A the microbiologically non-evaluable group with no baseline pathogen is increased in the FDA analysis.

Patient Characteristics

Patient Demographics – The following table provides comparisons of age, weight, race, gender, and geographic region across the two treatment arms of the study. Demographic factors were comparable in the two treatment arms. Patients from 45 sites in 1 African, 3 South American, 11 European, and 4 Asian/Pacific countries were included in this trial.

Sponsor: Patient Demographics (ITT)

Parameters	Linezolid N = 166		Clarithromycin N = 166		P-Value
	n	%	n	%	
Age (yr.)					
Total Reporting	166	100.0	166	100.0	
18-44†	99	59.6	103	62.0	
45-64	48	28.9	50	30.1	
>65	19	11.4	13	7.8	
Mean ± SD	41.7 ± 16.3		41.1 ± 16.9		0.7212‡
Weight (kg)					
Total Reporting	155	93.4	161	97.0	
Not Reported	11	6.6	5	3.0	
Mean ± SD	69.99 ± 18.88		71.16 ± 9.31		0.5860‡
Race					
Total Reporting	166	100.0	166	100.0	0.9979§
White	88	53.0	85	51.2	
Black	10	6.0	11	6.6	
Asian or Pacific Islander	45	27.1	46	27.7	
Mixed	22	13.3	23	13.9	
Not Allowed to Ask Per Local Regulation	1	0.6	1	0.6	
Sex					
Total Reporting	166	100.0	166	100.0	0.5806§
Male	95	57.2	90	54.2	
Female	71	42.8	76	45.8	
Region					
Total Reporting	166	100.0	166	100.0	0.9903§
Latin America	36	21.7	37	22.3	
Europe	86	51.8	85	51.2	
Other	44	26.5	44	26.5	

† Patient No. 3912061 was 17 years old.

‡ P-value is based on a one-way Analysis of Variance.

§ P-value is based on a chi-square test.

As with Study 39A, the baseline medical history, baseline physical examination, baseline vital signs, and mean values for baseline laboratory data were compared across treatment arms for any differences. No significant differences at baseline were reported by the sponsor for any of these parameters. The mean WBC was $8.37 \times 10^3/\text{mm}^3$ for linezolid-treated patients and $8.21 \times 10^3/\text{mm}^3$ for clarithromycin-treated patients.

Anti-microbial use (topical and systemic), prior to and during study, was compared. Comparable percentages of ITT patients in each treatment group (15.7% of linezolid-treated patients and 12.0% of clarithromycin-treated patients) took a non-investigational antibiotic prior to the first dose of study medication. Concomitant medications other than

antibiotics were used by approximately 52% of subjects in both treatment arms. The list of medications used was similar to that described for study 39A.

Characteristics of the Skin Infection at Baseline - Clinical symptoms and signs of skin infection at baseline were compared between the two treatment arms. The investigators graded clinical symptoms and signs on a four-point scale: none, mild, moderate or severe. The clinical signs and symptoms were pain, tenderness to palpation, erythema, swelling, induration, purulent or non-purulent discharge, warmth to touch, desquamation, and chills. All the clinical signs and symptoms reported were comparable across the two treatment arms. In the ITT population, 84.3% (140/166) of linezolid-treated patients and 85.5% (142/166) of clarithromycin-treated patients had pain, and 92.2% (153/166) of linezolid-treated patients and 95.2% (158/166) of clarithromycin-treated patients had tenderness.

The following table shows the clinical diagnoses at baseline and the degree of involvement (superficial vs. deep). Results were comparable across the two treatment arms. The only statistically significant difference reported was for cellulitis in the ITT population; a higher percentage of patients in the linezolid group had this diagnosis compared to the clarithromycin group ($p = 0.0148$). Cellulitis, skin abscesses and furuncles were the most common diagnoses. However, a variety of diagnoses typical of uncomplicated infections (e.g., carbuncle, impetigo, paronychia infection) were also included. Approximately 82% of these infections were considered superficial by the investigator.

Sponsor: Clinical Diagnosis and Degree of Involvement at Baseline (CE)

Diagnosis	Linezolid N = 127		Clarithromycin N = 124	
	n	%	n	%
<i>Diagnosis</i>				
Infected Wound	9	7.1	12	9.7
Cellulitis	43	33.9	30	24.2
Erysipelas	9	7.1	12	9.7
Folliculitis	2	1.6	3	2.4
Carbuncle	2	1.6	3	2.4
Furuncle	17	13.4	11	8.9
Skin Ulcer	2	1.6	3	2.4
Skin Abscesses	19	15.0	23	18.5
Impetigo	4	3.1	7	5.6
Infected Bite	3	2.4	0	-
Infected Surgical Incision	6	4.7	2	1.6
Paronychia	2	1.6	5	4.0
Other	9	7.1	13	10.5
<i>Degree of Involvement</i>				
Superficial	102	80.3	105	84.7
Deep	25	19.7	19	15.3

The table on the following page summarizes data on the duration of infection and lesion area. Mean values were comparable across the two treatment arms.

Sponsor: Duration of Infection and Area of Lesion (ITT)

Pretreatment Variable	Results	Linezolid	Clarithromycin
Duration of Infection (Days)	No. Patients Reporting	166	166
	Mean	9.1	8.7
	Standard Deviation	19.9	16.3
Area of Lesion (cm ²)	No. Patients Reporting	165	164
	Mean	150.3	123.4
	Standard Deviation	383.1	318.6

Dosage Information – The following table shows the duration of treatment for both treatment arms using the number of days of treatment and the number of doses taken. All doses of study medication were taken orally. The findings shown will not be discussed in any detail except to say that duration of treatment, and treatment compliance are comparable in the two treatment arms, and these results are similar to those described for Study 39A.

Sponsor: Duration of Treatment (Days) and Number of Doses (ITT)

Duration Assessment	Linezolid N = 166		Clarithromycin N = 166	
	n	%	n	%
<i>Total Number of Patients Reporting</i>	161	97.0	163	98.2
Number of Days Treated				
<5	9	5.6	4	2.5
5	2	1.2	0	-
6	3	1.9	1	0.6
7	8	5.0	12	7.4
8	26	16.1	23	14.1
9	11	6.8	18	11.0
10	13	8.1	12	7.4
11	11	6.8	14	8.6
12	16	9.9	11	6.7
13	5	3.1	12	7.4
14	25	15.5	24	14.7
15	23	14.3	25	15.3
>15	9	5.6	7	4.3
Mean		11.0		11.3
SD		3.7		3.2
Number of Doses				
<i>Total Number of Patients Reporting</i>	164	98.8	164	98.8
<10	8	4.9	4	2.4
10-14	28	17.1	33	20.1
15-20	39	23.8	33	20.1
21-28	77	47.0	86	52.4
>28	12	7.3	8	4.9
Mean		21.1		21.4
SD		7.2		6.6

Efficacy Results – The sponsor provided multiple analyses under the heading of primary efficacy variables in the final study report. These analyses included investigator’s assessment of clinical outcome, sponsor-defined clinical outcome (SDCO), sponsor-defined microbiological outcome (SDMO), and sponsor-defined overall outcome (a combination of clinical and microbiologic outcomes). The results of these analyses were consistent with one another.

(M. O. Comment: The discussion in Study 39A provides the rationale for the selection of analyses and populations presented here. The reader is referred to the results section of Study 39A for that rationale.)

Clinical Outcome - The following tables provide the sponsor-defined clinical outcome and the FDA analysis of clinical outcome in the ITT population. The test-of-cure assessment was made at the follow-up visit. The sponsor reported clinical cure rates of 87.2% for linezolid and 90.6% for clarithromycin at follow-up. The clinical cure rates were similar in the sponsor’s and reviewer’s analyses. As opposed to study 39A, this study showed a treatment difference that favors clarithromycin. That, along with the smaller number of patients in this trial, results in wider and more negative confidence intervals. The lower bounds of the 95% confidence intervals in the sponsor’s and reviewer’s analyses were –10.5% and –11.1%, respectively. The numbers of patients with indeterminate or missing outcomes were similar in the two analyses. Missing or indeterminate outcomes were noted in 12% of linezolid-treated and 11% of clarithromycin-treated patients. The number of patients assessed in each of these analyses excluded the patients with missing or indeterminate outcomes.

Sponsor: Clinical Outcome at End-of-Therapy and Follow-up (ITT)

Visit	Assessment	Linezolid N=166		Clarithromycin N=166		95% CI
		n	%	n	%	
EOT	Number of Assessed Patients	148	100.0	155	100.0	
	Success (Cured + Improved)	136	91.9	146	94.2	
	Cured	111	75.0	119	76.8	
	Improved	25	16.9	27	17.4	
	Failed	12	8.1	9	5.8	
	Missing	18	-	11	-	
Follow-Up (TOC)	Number of Assessed Patients	149	100.0	149	100.0	
	Cured	130	87.2	135	90.6	(-10.5, 3.8)
	Failed	19	12.8	14	9.4	
	Indeterminate	6	-	11	-	
	Missing	11	-	6	-	

M. O.: Clinical Outcome at Follow-up (ITT)

Visit	Assessment	Linezolid		Clarithromycin		95% CI
		n	%	N	%	
Follow-Up (TOC)	Number of Assessed Patients	148		149		
	Cured	130	87.8	136	91.3	(-11.1, 4.2)
	Failed	18	12.2	13	8.7	
	Indeterminate or Missing	18	12.1	17	11.4	

MITT – The MITT analysis was not addressed in the final study report, but was included in the appendix tables. The smaller number of patients in this population resulted in a wider confidence interval (-11.2, 7.8). The clinical cure rates at follow-up reported by the sponsor were 68/87 (88.3%) for linezolid treated patients and 81/90 (90.0%) for clarithromycin-treated patients. The results are consistent with the ITT results.

Clinically Evaluable -The SDCO in the sponsor's clinically evaluable population is shown in the table below. The clinical cure rates at follow-up were 91.1% for linezolid and 92.7% for clarithromycin. These cure rates were higher than those reported for the ITT population. The treatment difference and 95% confidence interval were consistent with the analysis in the ITT population.

Sponsor: Clinical Outcome at End-of-Therapy and Follow-up (CE)

Visit	Assessment	Linezolid N=127		Clarithromycin N=124		95% CI
		n	%	n	%	
EOT	Number of Assessed Patients	120	100.0	120	100.0	
	Success (Cured + Improved)	116	96.7	116	96.7	
	Cured	92	76.7	91	75.8	
	Improved	24	20.0	25	20.8	
	Failed	4	3.3	4	3.3	
	Missing	7	-	4	-	
F-U (TOC)	Number of Assessed Patients	124	100.0	123	100.0	
	Cured	113	91.1	114	92.7	(-8.4, 5.2)
	Failed	11	8.9	9	7.3	
	Indeterminate	3	-	1	-	

The FDA analysis of clinical outcome at follow-up for the clinically evaluable population is shown in the table below. The clinical cure rates at follow-up were 88.% for linezolid and 89.8% for clarithromycin. The number of clinically evaluable subjects that were considered to be cured was the same in the sponsor's and reviewer's analyses. There were more subjects considered to be clinical failures in the FDA analysis, providing cure rates much closer to those seen in the ITT population. In the FDA analysis, indeterminate outcomes were treated the same as missing data. The patients with indeterminate outcomes in the sponsor's analysis would have been considered non-evaluable in the FDA analysis, unless some other factor led to their inclusion as failures. The lower bounds of the 95% confidence interval was -8.4% in the sponsor's analysis and -9.9% in the FDA analysis.

M. O.: Clinical Outcome at Follow-up (CE)

Visit	Assessment	Linezolid		Clarithromycin		95% CI
		n	%	N	%	
Follow-Up (Test-of-Cure)	Number of Assessed Patients	128	100	127	100	
	Cured	113	88.3	114	89.8	(-9.9, 7.0)
	Failed	15	11.7	13	10.2	

Microbiologically Evaluable –The following table provides the SDCO for the sponsor’s microbiologically evaluable population. The clinical cure rates at follow-up were 98.1% for linezolid and 98.5% for clarithromycin. As with the ITT and CE groups, linezolid had a slightly lower clinical cure rate than clarithromycin.

Sponsor: Clinical Outcome at EOT and Follow-up (ME)

Visit	Assessment	Linezolid N=55		Clarithromycin N=68		95% CI
		n	%	n	%	
EOT	Number of Assessed Patients	53	100.0	66	100.0	
	Success (Cured + Improved)	52	98.1	65	98.5	
	Cured	46	86.8	54	81.8	
	Improved	6	11.3	11	16.7	
	Failed	1	1.9	1	1.5	
	Missing	2	-	2	-	
F-U (TOC)	Number of Assessed Patients	54	100.0	68	100.0	
	Cured	53	98.1	67	98.5	(-5.0, 4.2)
	Failed	1	1.9	1	1.5	
	Indeterminate	1	-	0	-	

The FDA analysis of clinical outcome at follow-up for the microbiologically evaluable population is shown in the table below. The clinical cure rates at follow-up were 95.3% for linezolid and 96.7% for clarithromycin. The factors that resulted in a different ME population between the sponsor and the reviewer were the same as those described with Study 39A. Despite the differences in population analyzed, the results appear fairly similar. The differences in definition of the ME population make direct comparisons of cures and failures difficult at best. The lower bounds of the 95% confidence interval were -5.0% in the sponsor’s analysis and -11.1% in the FDA analysis. The wider 95% confidence interval in the FDA analysis reflects the smaller ME population defined by the M. O.

M. O.: Clinical Outcome at Follow-up (ME)

Visit	Assessment	Linezolid N=43		Clarithromycin N=60		95% CI
		n	%	N	%	
Follow-Up (Test-of-Cure)	Number of Assessed Patients	43	100	60	100	
	Cured	41	95.3	58	96.7	(-11.1, 8.4)
	Failed	2	4.7	2	3.3	

A similar treatment difference of roughly 1-4% (favoring clarithromycin) was seen in the primary analyses of clinical outcome, despite differences in the methodology of the FDA and the sponsor and differences in study population. The smaller number of subjects in this trial and the treatment difference favoring clarithromycin result in wider confidence intervals. However, these findings are not inconsistent with the results of the pivotal trial, study 39A.

Microbiological Outcome – The following table shows the SDMO for the MITT and ME population. The results for the CE population are not shown, but are similar to the ME population results. Microbiological outcome favors linezolid in both the CE and Me population in this trial. These results are presented for completeness. The limitations of the microbiological analysis were discussed with the SDMO results for Study 39A. The M. O. will focus on the clinical outcome analyses.

Sponsor: Microbiological Outcome at Follow-Up (MITT and ME)

Assessment	Linezolid		Clarithromycin		95% CI
	n	%	n	%	
MITT Population					
Total Number of Patients	85	-	96	-	
Number of Assessed Patients	77	100.0	90	100.0	
Micro Success	67	87.0	79	87.8	(-10.9, 9.3)
Microbiologically Evaluable Population					
Total Number of Patients	55	-	68	-	
Number of Assessed Patients	54	100.0	68	100.0	
Micro Success	53	98.1	66	97.1	(-4.3, 6.5)

Patient Overall Outcome –As with Study 39A, the sponsor provided an analysis of the overall outcome. They will not be repeated here, but are available in the sponsor’s final study report and appendix tables. The results were consistent with the clinical outcome analyses by the sponsor.

Subgroup Analyses

Pathogen –The following tables shows the SDMO and SDCO for selected organisms. The clinical and microbiological outcomes for these pathogen groups are the same. *Staphylococcus epidermidis* was most likely a contaminant of the baseline culture for the otherwise healthy subjects with uncomplicated skin infections in this trial. There was only one subject in this trial who was identified with *Streptococcus agalactiae* (a clinical cure treated with linezolid) at baseline.

Sponsor: Microbiological Success Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Linezolid		Clarithromycin	
	n/N	%	n/N	%
<i>S aureus</i>	38/39	97.4%	51/53	96.2%
<i>S epidermidis</i>	8/8	100.0%	7/7	100.0%
<i>S pyogenes</i>	6/6	100.0%	7/7	100.0%

Sponsor: Clinical Cure Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Linezolid		Clarithromycin	
	n/N	%	n/N	%
<i>S aureus</i>	38/39	97.4	52/53	98.1
<i>S epidermidis</i>	8/8	100.0	7/7	100.0
<i>S pyogenes</i>	6/6	100.0	7/7	100.0

The FDA analysis of clinical outcome at follow-up by pathogen for the microbiologically evaluable population is shown in the table below. The FDA analysis included only *Staphylococcus aureus* and *Streptococcus pyogenes* as pathogenic organisms. The results of the FDA analysis are the same as the results of the sponsor's analysis, except for one additional failure in each treatment arm. The clinical cure rates in the pathogen specific groups are high compared to the clinical outcomes in the CE or ITT population. There were a small number of subjects with *Streptococcus pyogenes* in this trial. There were also 5 subjects in this trial with methicillin resistant *Staphylococcus aureus* (1 linezolid, 4 clarithromycin). All were considered clinical cures.

M. O.: Clinical Cure Rates at Follow-Up for Selected Pathogens (ME)

Pathogen	Clinical Cure Rate			
	Linezolid		Clarithromycin	
	n/N	%	n/N	%
<i>S aureus</i>	38/39	97.4	52/54	96.3
<i>S pyogenes</i>	6/7	85.7	7/7	100

Clinical diagnosis – The following table provides subgroup analyses of the clinical cure rates by clinical diagnosis produced by the sponsor. The results shown were obtained in the clinically evaluable population.

Sponsor: Clinical Outcome at Follow-Up by Clinical Diagnosis (CE)

Diagnosis	Sponsor-Defined Clinical Outcome			
	Linezolid		Clarithromycin	
	n/N	%	N/N	%
Erysipelas	9/9	100	10/12	83.3
Furuncle	16/17	94.1	11/11	100
Infected surgical incision	3/6	50.0	2/2	100
Infected bite	3/3	100	0	0
Infected wound	9/9	100	11/12	91.7
Skin abscesses	15/16	88.9	23/23	100
Cellulitis	38/41	92.7	28/29	96.6
Impetigo	4/4	100	7/7	100
Folliculitis	2/2	100	2/3	66.7
Paronychia	2/2	100	4/5	80.0
Carbuncle	2/2	100	0/3	0
Skin ulcer	1/2	50.0	3/3	100
Other	8/9	88.9	13/13	100

The table on the following page provides the FDA assessment of clinical outcome by clinical diagnosis. These results were generally similar to those presented in the sponsor's table. There were a few changes in percentages, usually due to the addition of one or two subjects in each category. In most of these subgroups, the numbers of subjects were too small to draw any clear conclusions. For the most common diagnoses (cellulitis, skin abscess, and furuncle), the results are consistent with the clinical outcome in all CE patients.

M. O.: Clinical Outcome at Follow-Up by Clinical Diagnosis (CE)

Diagnosis	FDA Clinical Outcome			
	Linezolid		Clarithromycin	
	n/N	%	N/N	%
Erysipelas	9/10	90.0	10/13	76.9
Furuncle	16/17	94.1	11/11	100
Infected surgical incision	3/6	50.0	2/4	50.0
Infected bite	3/3	100	0	0
Infected wound	9/9	100	11/12	91.7
Skin abscesses	17/18	88.9	23/24	95.8
Cellulitis	38/42	90.5	28/29	96.6
Impetigo	4/4	100	7/7	100
Folliculitis	2/2	100	2/3	66.7
Paronychia	2/2	100	4/5	80.0
Carbuncle	2/2	100	0/3	0
Skin ulcer	1/2	50.0	3/3	100
Other	8/10	80.0	13/13	100

Age – The effect of age on clinical cure rates was investigated. The following table shows the clinical cure rates in the ITT population by age. Subjects ≥ 65 years are noted with lower cure rates than those younger than 65 in both treatment arms. While the treatment difference favors clarithromycin in the older age group, the number of patients in this age group is small. These results are different from those of Study 39A, where the treatment difference still favored linezolid and a greater number of patients were studied.

M. O.: Clinical Cure Rates at Follow-Up by Age Group (ITT)

Age Group	Linezolid		Clarithromycin	
	N	Cure Rate %	N	Cure Rate %
Age ≥ 65 years	16	62.5	9	77.8
Age < 65 years	111	92.8	118	90.7

Other Subgroup Analyses – Gender and lesion size were investigated by subgroup analyses similar to those shown for Study 39A. A sensitivity analysis of the effect of missing data was also performed. The results of these analyses are consistent with the analyses of Study 39A.

Safety Results – The safety results are excerpted from the sponsor’s final study report. The following table provides an overall summary of the treatment emergent adverse events (AE) reported in the ITT population. The number of patients reporting AE was balanced across the two treatment arms. It should be noted that fewer subjects in this trial reported adverse events, compared to the results of Study 39A. In general, fewer AE are reported in non-U.S. studies compared to U.S. studies. There were only a few subjects reported with serious AE in either treatment arm. There were no deaths reported in study patients for this trial.

Sponsor: Summary of Adverse Events (ITT)

Parameter	Linezolid N = 166		Clarithromycin N = 166		Statistical Test P-Value
	n	%	n	%	
Total Number of Patients Reporting	166	100.0	166	100.0	
Patients With >1 AE Reported	53	31.9	51	30.7	0.8129
Patients With >1 Drug-Related AE Reported	26	15.7	25	15.1	0.8790
Patients With >1 AE Resulting in D/C of Study Medication	5	3.0	3	1.8	0.4741
Patients With >1 Drug-Related AE Resulting in D/C of Study Medication	2	1.2	2	1.2	1.0000
Patients With >1 SAE Reported	3	1.8	4	2.4	0.7025

All Adverse Events - The treatment emergent adverse events occurring in >2% of patients in either treatment arm are shown in the table on the following page. The most common adverse events were headache, diarrhea, nausea, and abdominal pain. These same events were also common in other studies with linezolid.

(M. O. Comment: This table differs from the analogous table in the Study 39A results in that a threshold of 2% is used for inclusion of an adverse event. This is appropriate for this smaller trial, since any AE reported in 2 subjects per treatment group would be included using the 1% threshold. Again, the common AE are the same as with Study 39A and the other pivotal trials.)

Sponsor: Study-Emergent AE Occurring in >2% of Patients (ITT)

COSTART Body System /MET	Linezolid N=166		Clarithromycin N=166	
	n	%	n	%
Patients With None	113	68.1	115	69.3
Patients With at Least One	53	31.9	51	30.7
BODY				
Abdominal Pain Localized	5	3.0	0	--
Headache	5	3.0	7	4.2
DIGESTIVE				
Constipation	4	2.4	0	-
Diarrhea	7	4.2	5	3.0
Nausea	6	5.6	2	1.2
NERVOUS				
Dizziness	3	1.8	6	3.6

Drug Related AE - Only two categories of AE were considered drug-related and occurred in >2% of patients in either treatment arm. Drug-related nausea was reported in 5 (3.0%) linezolid patients and 2 (1.2%) clarithromycin patients. Drug-related diarrhea was reported in 2 (1.2%) linezolid patients and 4 (2.4%) clarithromycin patients.

Serious AE – All serious AE noted in this study are listed in the following table. None were considered drug-related by the reporter. Several AE (abscess, cellulitis) are likely related to the underlying disease under study. None of the serious AE were seen in more than one patient under study.

Sponsor: Study-Emergent Serious Adverse Events (ITT)

	Linezolid N = 166		Clarithromycin N = 166	
	n	%	n	%
COSTART Body System/MET				
Patients With at Least One	3	1.8	4	2.4
BODY				
Abscess	-	-	1	0.6
Cellulitis	1	0.6	-	-
Localized Pain	-	-	1	0.6
CARDIOVASCULAR				
Cardiopulmonary Arrest	1	0.6	-	-
METABOLIC AND NUTRITIONAL				
Healing Abnormal	-	-	1	0.6
Hyperglycemia	-	-	1	0.6
MUSCULO-SKELETAL				
Bursitis	1	0.6	-	-
SKIN				
Necrosis Skin	1	0.6	-	-
UROGENITAL				
Infection Urinary Tract	1	0.6	-	-

**APPEARS THIS WAY
 ON ORIGINAL**

Clinical Summary: Study 39A and Study 39

Subjects with uncomplicated skin and skin structure infections were studied in two randomized, double-blind, comparative trials of linezolid 400 mg PO twice daily and clarithromycin 250 mg PO twice daily. The clinical outcomes in these trials are summarized in the table below. The larger, pivotal trial for this indication (study 39A) showed clinical cure rates for linezolid slightly higher than for the comparator. The smaller, supportive trial showed clinical cure rates that were slightly lower than clarithromycin. These results, with the support of the results in complicated SSSI, provide substantial evidence of effectiveness in uncomplicated SSSI.

Clinical Outcomes (%) and 95% Confidence Intervals for Uncomplicated SSSI

Study Population	Linezolid	Clarithromycin	95% Confidence Interval
Study 39A (North American Pivotal Trial)			
ITT	85.9%	83.5%	(-3.4, 8.2)
Clinically Evaluable	88.4%	85.3%	(-2.5, 8.7)
Study 39 (Non-North American Supportive Trial)			
ITT	87.8%	91.3%	(-11.1, 4.2)
Clinically Evaluable	88.3%	89.8%	(-9.9, 7.0)

Several subgroup analyses were performed. Clinical outcomes in subgroups identified with specific pathogens at baseline are summarized in the following table. The two major pathogens for this indication, *Staphylococcus aureus* and *Streptococcus pyogenes*, were each identified in more than 10 linezolid-treated subjects with acceptable clinical outcomes. These results support the inclusion of both methicillin-susceptible strains of *S. aureus* and *S. pyogenes* within the indication for uncomplicated SSSI.

Clinical Outcome by Pathogen for Uncomplicated SSSI

Study/Pathogen	Linezolid	Clarithromycin
Study 39A		
<i>S. aureus</i>	80/93	89/105
<i>S. pyogenes</i>	5/5	10/11
Study 39		
<i>S. aureus</i>	38/39	52/54
<i>S. pyogenes</i>	6/7	7/7

Other subgroup analyses were based on age, gender, clinical diagnosis, and lesion size. In the pivotal trial, no differences in treatment effect based on gender or age over 65 were noted. The subgroup analysis of lesion size showed results consistent with the

primary analyses, despite exclusion of small lesion likely to resolve without antibiotics. There was no evidence of differences in treatment effect for specific clinical diagnoses.

The safety analysis demonstrated a higher rate of adverse events in linezolid-treated patients compared to clarithromycin treated patients. The common adverse events seen in these two clinical trials are similar to those reported in other phase 3 studies of linezolid. Diarrhea, nausea, headache, and fungal infections were the most common AE reported, and were reported in both trials. Since these are the only phase 3 trials that use a dosage regimen of 400 mg every 12 hours, the **ADVERSE REACTIONS** section of the package insert should provide the adverse event tables that distinguish the safety results of these studies from the other clinical trials where 600 mg every 12 hours was used.

Conclusions: Uncomplicated Skin and Skin Structure infections

The medical officer has concluded that there is sufficient information provided to recommend approval of the indication of uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains) or *Streptococcus pyogenes*. Only 1 linezolid-treated subject in the two trials was noted with methicillin-resistant *Staphylococcus aureus* (MRSA). There is not sufficient evidence to approve the use of linezolid for uncomplicated SSSI in subjects with MRSA. The dose regimen studied in these trials was 400 mg PO every 12 hours for 10 to 14 days. This should be the dosage regimen recommended for this indication in the **DOSAGE AND ADMINISTRATION** section of the product label.

**APPEARS THIS WAY
ON ORIGINAL**

COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

Introduction

Pharmacia & Upjohn Company has proposed the following wording for the **INDICATIONS AND USAGE** section of the package insert:

“Complicated skin and skin structure infections, including cases with concurrent bacteremia, caused by *Staphylococcus aureus* (methicillin-sensitive and -resistant strains), *Staphylococcus epidermidis* (including methicillin-sensitive and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Zyvox has not been studied in the treatment of diabetic foot and decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms.”

A separate study of infections due to methicillin-resistant strains of *Staphylococcus aureus* was performed, and is the subject of another medical officer review. This review will address the remainder of this indication.

The study submitted to support the use of linezolid in complicated skin and skin structure infections is study M/1260/0055, the pivotal trial for this indication. The following description of the study protocol is largely excerpted from the final study report for study 55. The original protocol was reviewed concurrently with the study report. Relevant differences between the original protocol and final study reports were noted. A total of 200 investigators in Argentina, Australia, Austria, Brazil, Canada, Chile, Czech Republic, France, Germany, Hungary, Indonesia, Israel, Mexico, Norway, Pakistan, Peru, the Philippines, Poland, Russia, Slovak Republic, South Africa, Taiwan, the United States, and Venezuela were recruited to perform the study and received study medication supplies. Of these 200 centers, 133 enrolled patients into the study.

Study M/1260/0037, comparing linezolid IV/PO with nafcillin IV/dicloxacillin PO, was initiated by the sponsor, but halted after only 4 patients (2 linezolid, 2 comparator) had been enrolled. The sponsor reported that all four subjects were considered clinical cures. Both linezolid patients reported adverse events. One subject was noted with “superficial phlebitis”. The other subject reported nausea, diarrhea, yeast vaginitis, and sore throat. This study will not be discussed further.

Financial Disclosure Statement: Only one investigator in these studies, Dr. Thomas Nigra, disclosed a financial interest in this product. This investigator participated in Study 55, randomized 3 subjects, and had 2 subjects who received study medication. This level of enrollment is insufficient to significantly bias the overall study results.

Protocol for Study 55

Study Title: Linezolid versus Oxacillin Sodium/Dicloxacillin Sodium for the Treatment of Complicated Skin and Soft Tissue Infections

Study Objectives:

- To assess the comparative efficacy (clinical and microbiological) of linezolid versus oxacillin sodium (oxacillin)/dicloxacillin sodium (dicloxacillin) in the treatment of adults with complicated skin and soft tissue infections
- To assess the comparative safety and tolerance of linezolid versus oxacillin/dicloxacillin
- To determine the direct medical resource use required to achieve an acceptable clinical outcome

(M. O. Comment: Medical resource utilization was recorded in the case report forms, but the sponsor indicated that this last objective would be addressed in a separate report. Medical resource utilization was not addressed in the final study report of this trial. This is acceptable since the concerns of the FDA medical review are the first two study objectives.)

Study Design: This was a randomized, double-blind, comparator-controlled, multicenter, multi-national study of IV/PO linezolid and IV oxacillin/PO dicloxacillin for 10 to 21 days in hospitalized adults with complicated skin and skin structure infections. All subjects began with IV study medication, and could be switched, when clinically indicated, to oral medication. The IV dosing period was every 6 hours. At least one dose of intravenous study medication was required before a switch to oral therapy. Subjects were randomized in a 1:1 ratio to receive one of the following regimens:

- 600 mg IV linezolid at the first and third dosing period alternated with IV oxacillin placebo at the second and fourth dosing period; followed by switch to 600 mg oral linezolid tablets every 12 hours and oral dicloxacillin placebo every 6 hours
- 2 g IV oxacillin at all dosing periods, the infusion bags at the first and third dosing period were identical to the linezolid infusion bag; followed by switch to 500 mg dicloxacillin sodium every 6 hours and oral linezolid placebo every 12 hours.

(M. O. Comment: The blinding scheme worked differently for the IV and oral phases of treatment. In the IV phase, a total of four infusions per day were given to all subjects. In the oral phase, six tablets per day are given. Both should be successful at maintaining the study blind, if executed properly.)

Subjects in either treatment arm could receive IV aztreonam 1-2 g three or four times daily (not to exceed 8 g/day). Use of aztreonam was not blinded in any way.

(M. O. Comment: The protocol indicated that "intravenous aztreonam could be administered until cultures confirm that the cause of the infection is gram-positive". This was suggested as a maximum of 2-3 days. However, the use of aztreonam was not limited. Subjects could continue in the trial on aztreonam for longer periods. The results section includes a subgroup analysis of subjects receiving aztreonam.)

Study Population: Subjects were enrolled from 19 November 1998 to 21 June 1999. Hospitalized adults (male and female) with complicated skin and soft tissue infections were enrolled in the trial. The following inclusion and exclusion criteria were applied to determine eligibility for study participation:

Inclusion Criteria:

1. A suspected gram-positive complicated skin and soft tissue infection caused by susceptible organisms that involves deeper soft tissue, may require significant surgical intervention (such as a major abscess, infected ulcer, major burn, or deep and extensive cellulitis), and with at least two of the following:
 - drainage/discharge
 - erythema
 - fluctuance
 - heat/localized warmth
 - pain/tenderness to palpation
 - swelling/induration
2. An accessible infection site for Gram stain and culture.
3. At least one of the following conditions considered to be pathogen related:
 - fever, defined as body temperature $>37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ (axillary); $>38^{\circ}\text{C}/100.4^{\circ}\text{F}$ (orally); $>38.5^{\circ}\text{C}/101.3^{\circ}\text{F}$ (tympanically); or $>39^{\circ}\text{C}/102.2^{\circ}\text{F}$ (rectally).
 - elevated total peripheral white blood cell count $>10,000/\text{mm}^3$.
 - $>15\%$ immature neutrophils (bands) regardless of total peripheral white count.
4. Be at least 18 years of age.
5. Able to take intravenous and oral medications.
6. Willing to return for the End-of-Treatment and Long Term Follow-up visits.

(M.O. Comment: A reference to a protocol appendix is given with the first criterion. This appendix was supposed to provide a "expanded definition" of complicated skin and skin structure infections. In fact, it only provided a brief expansion of criteria 1 and 3. It also listed specific diagnoses; major abscesses, infected ulcers, wounds, major burns, and extensive cellulitis. Criterion 3 is used as a means of selecting subjects with evidence of systemic inflammatory response, and is used as an integral part of their definition of complicated SSSI. However, a small proportion of subjects did not meet this criterion. This issue is discussed further with the results of the primary analyses.)

Exclusion Criteria:

1. Previous antibiotic treatment received for more than 24 hours within 7 days of study entry unless the pathogen showed drug resistance or the treatment failed (defined as no clinical improvement after 3 days of treatment).
2. An uncomplicated skin and superficial skin structure infection such as a simple abscess, impetiginous lesion, furuncle, or superficial cellulitis.
3. Abscesses that only need surgical draining at the time of patient enrollment.
4. Self limited infections such as isolated folliculitis or other infection that has a high surgical incision cure rate or furunculosis or carbunculosis that is not associated with a cellulitis at least 1 cm in radius.
5. Diabetic foot, decubitus, and ischemic ulcers, necrotizing fasciitis, gas gangrene, or burns greater than 20% of total body surface.

6. Superinfected eczema or other chronic medical conditions (i.e., atopic dermatitis) where inflammation may be prominent for an extended period even after successful bacterial eradication.
7. Infections or conditions requiring concomitant antimicrobial (with the exception of aztreonam) or systemic corticosteroid treatment.
8. Infections complicated by the presence of prosthetic materials such central venous catheters, permanent cardiac pacemaker battery packs, or those involving joint replacement prostheses, etc.
9. Known osteomyelitis.
10. Females of child-bearing potential who are unable to take adequate contraceptive precautions, have a positive serum pregnancy test result within 24 hours prior to study entry, are otherwise known to be pregnant, or are currently breastfeeding an infant.
11. Known liver disease with total bilirubin >5 times Upper Limit of Normal.
12. Known neutropenia (absolute neutrophil count <500 cells/mm³).
13. Pheochromocytoma, carcinoid syndrome, or uncontrolled hypertension.
14. Untreated hyperthyroidism.
15. Unlikely to survive through the treatment period and evaluation (< 60 days).
16. Hypersensitivity to linezolid or its formulation excipients.
17. Hypersensitivity to penicillins or their formulation excipients.
18. Another investigational medication received within the past 30 days.
19. Previous enrollment in this or another linezolid protocol.

(M. O. Comment: Exclusion criterion #8 made it unlikely that any subjects with true infection due to Staphylococcus epidermidis would be enrolled. This organism is discussed further with the results of efficacy by pathogen. Other exclusion criteria for allergy or diseases that can cause hypertension were for protection of subjects. Patients with diabetic foot ulcers or decubitus ulcers were excluded from the study, and should be so labeled. The exclusion of these infections from the study is noted in the sponsor's proposed indication for cSSSI. Exclusion of subjects with necrotizing fasciitis, gas gangrene, and infected eczema are consistent with the draft guidance for industry on developing antimicrobials for uncomplicated and complicated SSSI. While exclusion of these disease entities are not required, they are acceptable.)

Patient Discontinuation from Study: Patients should have been withdrawn from the study if, in the opinion of the investigator, it was medically necessary or if it was the wish of the patient. In addition, a patient should also have been withdrawn from study medication for any of the following:

- Laboratory assay results documented severe neutropenia (absolute neutrophil count <500 cells/mm³).
- Lack of clinical improvement within 72 hours.
- Baseline site culture pathogens were not gram-positive and the patient was not improving clinically.
- Presence of gram-negative pathogens that required gram-negative antibiotic coverage other than aztreonam.

- Lack of microbiological improvement (e.g., three consecutive positive blood cultures).
- Disease progression such as septic shock and/or acute renal failure.
- Administrative reasons, such as patient non-compliance or a major protocol violation (e.g., pregnancy).
- Upon request of the sponsor or regulatory agency.
- Completion of the protocol-defined dosing period (without an approved extension).

If a patient did not return for a scheduled visit, every effort was to be made to contact the patient and to document patient outcome to study medication. The investigator was to document the reason for discontinuation on the patient's case report form.

(M. O. Comment: These criteria are similar to those provided for Protocol 39A. Criteria for early discontinuation of the study were also outlined in the protocol. These criteria will not be repeated here, since the study was completed.)

Study Visits: The study consisted of the following visits or phases:

- Baseline/screen visit (first day of treatment)
- Hospitalization (1 day minimum). If necessary, patients were hospitalized for the entire study. (CRF data were recorded every three days while hospitalized)
- Outpatient treatment (after discharge, CRF data recorded every 6 days).
- End-of-Treatment (at least 10 days, up to 21 days from baseline)
- Long Term Follow-up (15-20 days after final dose of study medication).

Clinical and Health Economics Evaluations: The following evaluations were conducted during the course of the study:

- Medical history.
- Physical examination.
- Vital signs. Body temperature was considered an efficacy measure; blood pressure, pulse, and respiration were considered safety measures.
- Electrocardiogram (ECG). 12-lead, at baseline and subsequently only as needed for routine care of the patient.
- Clinical observations. Objective and subjective clinical observations were made by the investigator and included the following:
 - anatomical site of infection
 - extent of infections (length, width, etc.)
 - degree of involvement (superficial or deep)
 - infected site description, which included drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness, and swelling/induration.
 - Medical resources used to achieve an acceptable clinical outcome.
 - Adverse Events.

Laboratory Evaluations: The following hematology and microbiological culture evaluations were conducted during the course of the study:

- Hematology- Complete blood count (CBC) with differential, platelet count, and reticulocyte count.