Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

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Importance Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.

Objectives To establish the noninferiority of tedizolid phosphate vs linezolid in treating ABSSSIs and compare the safety of the 2 agents.

Design, Setting, and Patients The Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy (ESTABLISH-1) was a phase 3, randomized, double-blind, noninferiority trial that was conducted from August 2010 through September 2011 at 81 study centers in North America, Latin America, and Europe. The intent-to-treat analysis set consisted of data from 667 adults aged 18 years or older with ABSSSIs treated with tedizolid phosphate (n=332) or linezolid (n=335).

Interventions A 200 mg once daily dose of oral tedizolid phosphate for 6 days or 600 mg of oral linezolid every 12 hours for 10 days.

Main Outcome Measures The primary efficacy outcome was early clinical response at the 48- to 72-hour assessment (no increase in lesion surface area from baseline and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours). A 10% noninferiority margin was predefined.

Results In the intent-to-treat analysis set, the early clinical treatment response rates were 79.5% (95% CI, 74.8% to 83.7%) of 332 patients in the tedizolid phosphate group and 79.4% (95% CI, 74.7% to 83.6%) of 335 patients in the linezolid group (a treatment difference of 0.1% [95% CI, −6.1% to 6.2%]). The sustained clinical treatment response rates at the end of treatment (day 11) were 69.3% (95% CI, 64.0% to 74.2%) in the tedizolid phosphate group and 71.9% (95% CI, 66.8% to 76.7%) in the linezolid group (a treatment difference of −2.6% [95% CI, −9.6% to 4.2%]). Results of investigator-assessed clinical treatment success rates at a posttherapy evaluation visit (1-2 weeks after the end-of-treatment visit) were 85.5% (95% CI, 81.3% to 89.1%) in the tedizolid phosphate group and 86.0% (95% CI, 81.8% to 89.5%) in the linezolid group (a treatment difference of −0.5% [95% CI, −5.8% to 4.9%), and were similar for 178 patients with methicillin-resistant *Staphylococcus aureus* isolated from the primary lesion.

Conclusions and Relevance Tedizolid phosphate was a statistically noninferior treatment to linezolid in early clinical response at 48 to 72 hours after initiating therapy for an ABSSSI. Tedizolid phosphate may be a reasonable alternative to linezolid for treating ABSSSI.

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ANTIMICROBIALS AVAILABLE FOR treatment of complicated skin and skin structure infections (SSSIs) are generally efficacious, but antimicrobial resistance[1-7] and adverse effects limit their use.[1,8,9] Linezolid, an oxazolidinone, is the only oral drug approved for complicated SSSI caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Sporadic outbreaks of linezolid-resistant strains of MRSA and enterococci, including those carrying a plasmid-borne *cfr* gene encoding the chloramphenicol/florfenicol resistance protein, have been reported.[10] Significant safety concerns with linezolid have emerged since it was approved in 2000 by the US Food and Drug Administration (FDA).[11]

In 2010, the FDA issued a draft guidance for the development of systemic drugs to treat acute bacterial SSSIs (ABSSSIs) with recommendations for clinical response criteria and noninferiority trial design.[12,13] Given the time required to develop and obtain approval for a new chemical entity, trials demonstrating noninferiority to currently approved antimicrobials allow the development of new agents in advance of the selection of resistant pathogens in hospitals or in the community. Even within the same class of

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drugs, new agents may differ by their molecular mechanism of action, spectrum of activity, or pharmacokinetic, pharmacodynamic, or safety profiles.

Tedizolid phosphate (also known as TR-701) is a novel, potent oxazolidinone prodrug rapidly converted in vivo to microbiologically active tedizolid (TR-700). Tedizolid interacts with the bacterial 23S ribosome initiation complex to inhibit translation, and is active against all clinically relevant gram-positive pathogens, including linezolid-resistant *S aureus*.[14] Both tedizolid phosphate and linezolid can be administered orally or intravenously. Linezolid is administered twice daily for 10 to 14 days.[11] In a phase 2, dose-ranging trial of patients with complicated SSSIs, 200 mg of oral tedizolid phosphate administered once daily for 5 to 7 days was the lowest effective dose.[15]

METHODS

Study Design

The Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy (ESTABLISH-1) was a randomized, double-blind, double-dummy, multicenter, multinational, phase 3 noninferiority trial. The study was designed to examine the efficacy and safety of 200 mg of oral tedizolid phosphate administered once daily for 6 days vs 600 mg of oral linezolid administered twice daily for 10 days for the treatment of adults with ABSSSIs (cellulitis/erysipelas, major cutaneous abscesses, or wound infections).

Patients

Adults aged 18 years or older could be eligible for enrollment if the patient had cellulitis/erysipelas, major cutaneous abscess, or wound infection surrounded by erythema with a minimum total lesion surface area of 75 cm^2 (measured head to toe, length × width),[16] accompanied by at least 1 local and 1 regional (lymphadenopathy) or 1 systemic (oral temperature ≥38°C, white blood cell count ≥10 000/μL or <4000/μL, or >10% of immature neutrophils) sign of infection, and a gram-positive pathogen was suspected or documented.

Patients were ineligible if the ABSSSI was uncomplicated or associated with a vascular catheter site, thrombophlebitis, or surgery other than clean surgery. A patient also was ineligible if a gram-negative pathogen was suspected or documented, unless the ABSSSI was a wound infection. Additional criteria excluded patients receiving systemic or topical antibiotics with gram-positive activity within 96 hours before the first dose of study drug or those with previous treatment failure of the same infection site.

The institutional review board, or equivalent, at each study center approved the trial and all patients provided written informed consent. A data and safety monitoring board reviewed safety data during the conduct of the study.

Patients were recruited from 81 study centers, enrolled at 54 of those sites, and randomized on a 1:1 basis to study treatment using an interactive voice response system, and assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. Randomization was stratified by presence or absence of fever at baseline, study center geographic region (North America, Latin America, Europe), and type of ABSSSI (cellulitis/erysipelas, major cutaneous abscess [maximum of 30% of the total study population], or wound infection) using block randomization via the interactive voice response system. The first patient was enrolled on August 12, 2010, and the last patient had his/her last visit on September 30, 2011. A list of study centers, primary investigators, and number of patients enrolled at each center appears in eTable 1 at http://www.jama.com.

Interventions

Patients received 200 mg of tedizolid phosphate once daily for 6 days or 600 mg of linezolid twice daily for 10 days. To maintain the blinding, tedizolid phosphate and linezolid tablets were packaged in individual daily blister packs that contained active drug and placebo, and each patient took 3 tablets daily. Patients in the tedizolid phosphate group took 1 tablet of tedizolid phosphate plus 1 tablet of placebo followed 12 hours later by 1 tablet of placebo on days 1 through 6, and 3 tablets of placebo on days 7 through 10.

Patients in the linezolid group took 1 tablet of linezolid plus 1 tablet of placebo followed 12 hours later by 1 tablet of linezolid on days 1 through 10. Adjunctive aztreonam and/or metronidazole could have been initiated up to day 3 in patients with wound infections for whom gram-negative aerobes/anaerobes were suspected or confirmed. Nonsteroidal anti-inflammatory drugs were prohibited before the 48- to 72-hour assessment. Medications with antipyretic activity were to be considered only if the patient's temperature was higher than 38°C.

Time Points and Analysis Sets

Response to treatment was assessed at the 48- to 72-hour visit after the first dose of study drug, at the end-of-treatment (EOT; day 11 relative to the first dose of either study drug on day 1) visit, and at the posttherapy evaluation (PTE; 7-14 days after the EOT) visit. The last day of active therapy was day 6 for patients in the tedizolid phosphate group and day 10 for those in the linezolid group.

The intent-to-treat (ITT) analysis set included all randomized patients. The safety analysis set included all patients who were randomized and received at least 1 dose of study drug. The clinically evaluable (CE) analysis set included all patients in the ITT set who complied with the protocol without major violations and completed specified assessments for a particular outcome. There were 2 CE sets. Patients in the CE-EOT analysis set completed the 48- to 72-hour and EOT assessments without major protocol violations or receiving treatments that might confound outcomes (nonsteroidal anti-inflammatory drugs or oral steroids up to 72 hours or concomitant antibiotics at any

time). Patients in the CE-PTE analysis set completed the investigator's assessment of outcome at the PTE visit without major protocol violations or receipt of treatments that might confound outcomes.

Efficacy Assessments

The primary efficacy outcome was early clinical response at the 48- to 72-hour assessment in the ITT analysis set. Each patient was categorized as a treatment responder, nonresponder, or indeterminate according to objective criteria. A treatment responder was afebrile (temperature ≤37.6°C at the 48- to 72-hour assessment and confirmed within the next 3-24 hours), had cessation of primary ABSSSI lesion spread (defined as no increase in lesion surface area [length × width]) compared with baseline, did not receive prohibited concomitant antibiotics, and did not die of any cause. A patient classified as indeterminate had data missing that were necessary to determine a treatment response. A treatment nonresponder did not meet the criteria for a responder or an indeterminate (ie, had an increase in lesion surface area or fever).

The secondary outcomes were defined as (1) an objective sustained clinical response (using the same criteria as early response) at the EOT in the ITT analysis set; (2) an objective sustained clinical response at the EOT in the CE-EOT analysis set; (3) the investigator's assessment of clinical success at the PTE in the ITT analysis set; and (4) the investigator's assessment of clinical success at the PTE in the CE-PTE analysis set.

Components of sustained clinical response were the same as early response, but the patient was additionally considered a treatment failure at the EOT if he/she reported pain or if the investigator determined the patient's tenderness was worse than mild. All treatment failures or indeterminates at the 48- to 72-hour assessment were to be carried forward as treatment failures for the secondary outcome at the EOT.

Sensitivity analyses of the primary end points were planned to test the robustness of the data and to correspond with evolving regulatory thinking. These analyses excluded temperature as a variable and outcomes were defined as (1) no increase in lesion area from baseline at the 48- to 72-hour assessment; (2) 20% or greater decrease in lesion area from baseline at the 48- to 72-hour assessment (the primary efficacy outcome proposed by the Foundation for the National Institutes of Health)[17]; and (3) no increase in lesion area, length, or width from baseline at the 48- to 72-hour assessment. A prespecified sensitivity analysis of the secondary outcome of sustained clinical response did not include the presence or absence of pain. Patients who were treatment nonresponders or indeterminates at the 48- to 72-hour assessment were not carried forward as treatment failures to the EOT visit, but were instead assessed for a response at this visit. This is consistent with the draft guidance[13] issued after the initiation of the trial and agreed upon with the FDA.

Safety assessments included adverse events, clinical chemistry and hematology laboratory results, vital signs and electrocardiograms, and physical examinations. Treatment-emergent adverse events (TEAEs) are those that occurred or worsened after the first dose of study drug. Version 13.1 of the Medical Dictionary for Regulatory Activities (MedDRA Maintenance and Support Services Organization) was used to code adverse events.

Microbiology methods are detailed in the eMethods.

Statistical Methods

The sample size was calculated using the method of Farrington and Manning.[18] Assuming a point estimate of 81% in both treatment groups for the primary outcome measure of early clinical response rate at the 48- to 72-hour assessment, a 90% power, 1-sided α level of .025, and a 10% noninferiority margin, a total sample size of 658 patients was required (329 patients in each treatment group). A minimum early treatment response rate of 81% was based on results from the phase 2 dose-ranging study in which 90.6% (95% CI, 80.7%-96.5%) of patients in the 200 mg of tedizolid phosphate group had no increase in lesion size and 100% had no fever at the day 3 assessment.[15] The noninferiority margin of 10% was based on linezolid efficacy,[11] and was agreed upon in a special protocol assessment with the FDA.[15]

Exact 95% confidence intervals for point estimates were determined using the method of Clopper and Pearson.[19] Noninferiority for the primary and secondary efficacy outcomes was determined based on the lower limit of the 2-sided 95% confidence intervals for the difference in treatment response rates. The 95% confidence intervals were computed using the method proposed with stratification (for presence or absence of fever at baseline) by Miettinen and Nurminen.[20] Noninferiority was concluded if the lower limit of the 95% confidence interval was greater than −10%. Indeterminates (ie, patients with missing data) were considered treatment nonresponders for the primary efficacy outcome.

To control for inflation of the overall type I error rate, the hierarchical testing procedure of Westfall and Krishen[21] was used with the order of the testing procedure as indicated above for secondary outcomes. Safety data were summarized by treatment group using the numbers and percentages of patients. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS

Patient Disposition and Analysis Sets

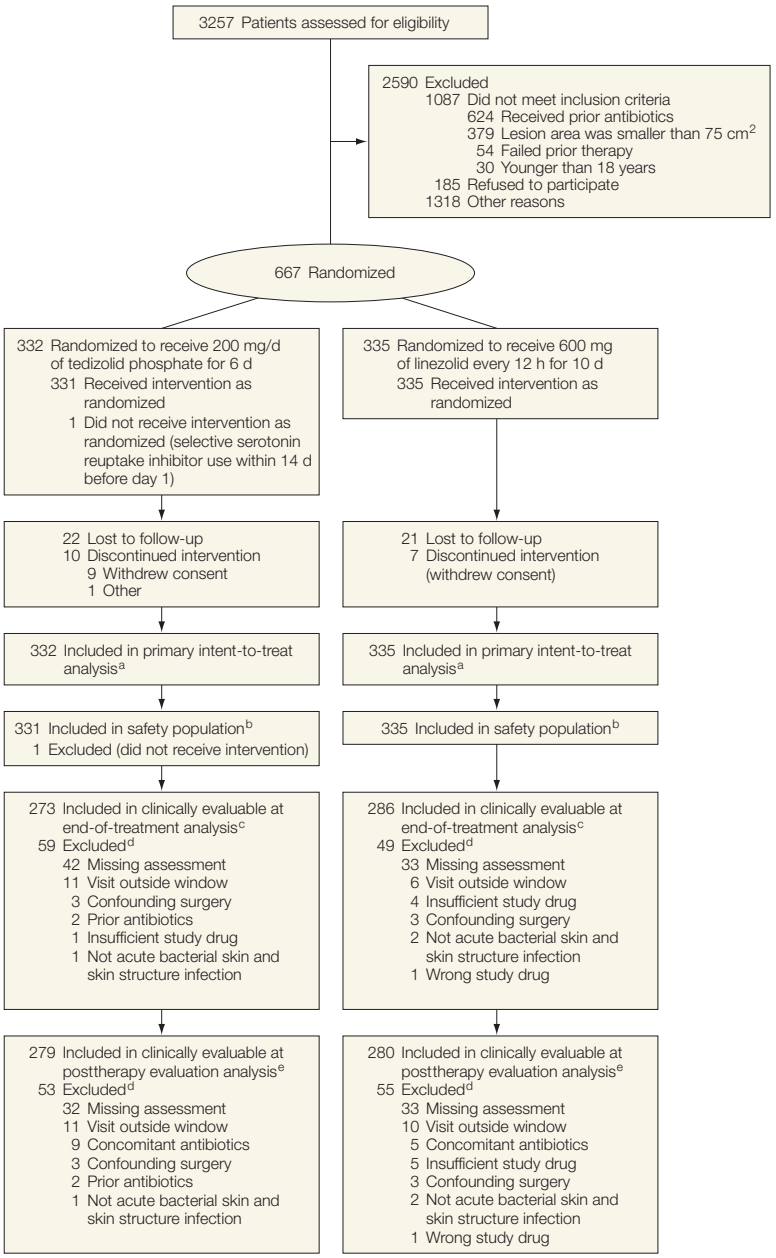
A total of 667 patients were randomized to receive tedizolid phosphate or linezolid and comprised the ITT analysis set (FIGURE). Approximately 90% of patients who were randomized also completed the trial. The safety analysis set consisted of 666 patients who received the study drug. The CE-EOT and CE-PTE analysis sets each consisted of 559 patients (83.8%). The percentage of patients in each analysis set (based on the ITT population) was the same between the 2 treatment groups.

Patient Demographics and Characteristics

Patients in the 2 treatment groups had similar demographics, baseline characteristics, and infection characteristics (TABLE 1). The patient population was predominately male and the median age was 43.0 years (range, 18-100 years). Infection types occurred with similar frequency in the tedizolid phosphate and linezolid groups with cellulitis/erysipelas (40.7% vs 41.5%, respectively), major cutaneous abscess (30.1% vs 29.3%), and infected wound (29.2% vs 29.3%). The median infection area was 188 cm^2 for the tedizolid phosphate group and 190 cm^2 for the linezolid group. Some patients were enrolled prior to a protocol amendment that clarified the minimum area criterion so that each group had approximately 4% of patients with lesions that were smaller than 75 cm^2. Regional and systemic signs of infection were similar in both treatment groups; approximately 87% of patients had lymphadenopathy adjacent to the lesion, 41% had white blood cell counts of 10 000/μL or higher or lower than 4000/μL, 3% had greater than 10% of immature neutrophils, and 18% had temperatures of 38°C or higher.

At least 1 pathogen was isolated from the primary infection site in approximately 63% of patients and most pathogens isolated were gram-positive aerobes (98.6%). Pathogens were isolated from blood from 8 patients (4 in each treatment group) and included MRSA (5 isolates), *Streptococcus* spp *S constellatus* (1 isolate), *S agalactiae* (1 isolate), *S viridans* (1 isolate), and *Gemella morbillorum* (1 isolate). The most common pathogen isolated from the primary ABSSSI site was *S aureus* (82.8%) with MRSA identified in 42.1% of infections in the tedizolid phosphate group and 43.1% of infections in the linezolid group. Minimum inhibitory concentrations (MICs) for tedizolid and linezolid were similar among *S aureus* isolates from the 2 treatment groups. Tedizolid MICs ranged from 0.125 to 0.5 μg/mL; and 95% of MRSA and 72% of MSSA isolates had MICs of 0.25 μg/mL or less. The MICs for linezolid against MRSA ranged from 1 to 4 μg/mL, with 99% of MRSA isolates and 86% of MSSA isolates having MICs of 2 μg/mL or less. A summary of all isolates and MICs for tedizolid and linezolid appear by treatment group in eTables 2-4.

Figure. Disposition and Analysis Sets of Patients in the ESTABLISH-1 Trial



ESTABLISH-1 indicates Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy. [a]Included all randomized patients. [b]Included all patients who received at least 1 dose of study drug. [c]Included patients who received minimal study therapy, completed 48- to 72-hour and end-of-treatment assessments, received no concomitant systemic antibiotic therapy through end of treatment, and had no confounding events or factors. [d]A patient could have more than 1 reason for exclusion from an analysis set. [e]Included patients who received the minimal study therapy, completed end-of-treatment and posttherapy evaluation assessments, received no concomitant systemic antibiotic therapy through posttherapy evaluation, and had no confounding events or factors.

Clinical Outcomes

In the primary efficacy ITT analysis, the response rates at the 48- to 72-hour assessment were 79.5% (95% CI, 74.8% to 83.7%) of 332 patients in the tedizolid phosphate group and 79.4% (95% CI, 74.7% to 83.6%) of 335 patients in the linezolid group (a treatment difference of 0.1% [95% CI, −6.1% to 6.2%]). The lower limit of the 95% confidence interval was above −10%, which was the predefined requirement for noninferiority. The primary reason for clinical outcomes of treatment nonresponder or indeterminate was missing temperature data or outside the prespecified time window in the tedizolid phosphate (11.1%) and linezolid (9.6%) groups. A total of 8.1% and 10.4% of patients in the tedizolid phosphate and linezolid groups, respectively, were true treatment nonresponders (ie, had spread of the primary ABSSSI lesions and/or had temperatures >37.6°C at the 48- to 72-hour assessment) (TABLE 2).

For each of the sensitivity analyses of the primary efficacy outcome, the differences between treatments and 95% confidence intervals were similar to those of the primary analysis (TABLE 3). Excluding the fever/temperature component or varying the lesion response definitions (≥20% decreases in lesion areas from baseline or no increase from baseline in lesion area, length, or width) had no effect on treatment response rates. Of particular interest are the similar treatment response rates in the tedizolid phosphate group (78.0%; 95% CI, 73.2%-82.4%) and in the linezolid group (76.1%; 95% CI, 71.1%-80.6%) in the sensitivity analysis that was based on the Foundation for the National Institutes of Health recommended outcome (≥20% decrease in lesion area).[17]

Sustained clinical treatment response rates at the EOT (day 11) were similar in the tedizolid phosphate and linezolid groups in the ITT analysis set (69.3% vs 71.9%, respectively) and in the CE-EOT analysis set (80.2% vs 81.1%) (Table 2). Investigator-assessed clinical treatment response at the PTE visit was also similar in the tedizolid phosphate and linezolid groups in the ITT analysis set (85.5% vs 86.0%, respectively) and in the CE-PTE analysis set (94.6% vs 95.4%). For all of these secondary analyses, the lower limit of the 95% confidence interval for the difference was above −10%; and thus, based on the hierarchical testing procedure, noninferiority can be concluded for each of these secondary outcome measures.

Because the primary reasons for failure of sustained clinical treatment response at the EOT were nonresponse at the 48- to 72-hour assessment (ie, lesion area increased and/or temperature was >37.6°C) and/or the patient reported pain, a sensitivity analysis of sustained clinical response was conducted that did not include the presence or absence of pain, and in which patients who were treatment nonresponders or indeterminates at the 48- to 72-hour assessment were not carried forward as treatment failures to the EOT visit. The sensitivity analysis was consistent with the FDA guidance,[13] which was issued after the special protocol assessment granted to the sponsor, and showed similar results for the outcome of sustained clinical response as those for the secondary outcome measure (Table 3).

Outcomes for subgroups stratified by type of infection were similar, although treatment response rates at the early and EOT time points were lower for cellulitis/erysipelas than for all infections combined (Table 2). In these smaller samples, the lower limit of the 95% confidence interval for the difference between tedizolid and linezolid was not consistently above −10%.

Susceptibilities to tedizolid and linezolid were similar for bacterial strains isolated from patients in the 2 treatment groups (eTables 3-4). Clinical

Table 1. Demographic and Baseline Patient and Disease Characteristics for Intent-to-Treat Analysis

	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)
Age, mean (SD), y	43.6 (14.96)	43.1 (15.06)
Male sex, No. (%)	204 (61.4)	198 (59.1)
Region of enrollment, No. (%)		
North America	270 (81.3)	268 (80.0)
Latin America	9 (2.7)	12 (3.6)
Europe	53 (16.0)	55 (16.4)
Current or recent intravenous drug use, No. (%)	117 (35.2)	132 (39.4)
Hepatitis C, No. (%)	(n = 329) 101 (30.7)	(n = 327) 116 (35.5)
Lymphadenopathy, No. (%)	289 (87.0)	289 (86.3)
Temperature ≥38°C (fever), No. (%)	56 (16.9)	63 (18.8)
White blood cell counts ≥10 000/μL or <4000/μL, No. (%)	140 (42.2)	133 (39.7)
Immature neutrophils of >10%, No. (%)	12 (3.6)	8 (2.4)
Pathogen identified at baseline, No. (%)	209 (63.0)	209 (62.4)
Staphylococcus aureus	171 (81.8)	175 (83.7)
MRSA	88 (42.1)	90 (43.1)
MSSA	83 (39.7)	87 (41.6)
Infection area, median (range), cm^2	188.3 (28.5-5572.8)	190.0 (27.0-2952.0)
Type of infection, No. (%)		
Cellulitis/erysipelas	135 (40.7)	139 (41.5)
Gram-positive pathogen isolated	39 (28.9)	44 (31.7)
Major cutaneous abscess	100 (30.1)	98 (29.3)
Gram-positive pathogen isolated	86 (86.0)	83 (84.7)
Wound	97 (29.2)	98 (29.3)
Superficial incisional surgical site	3 (0.9)	3 (0.9)
Posttraumatic wound	94 (28.3)	95 (28.4)
Gram-positive pathogen isolated	84 (86.6)	82 (83.7)

Abbreviations: MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-sensitive *S aureus*.

Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
At the 48- to 72-h assessment (ITT analysis set)			
Treatment responder, No. (%) [95% CI]	264 (79.5) [74.8 to 83.7]	266 (79.4) [74.7 to 83.6]	0.1 (−6.1 to 6.2)
Cellulitis/erysipelas, No./total (%)	101/135 (74.8)	100/139 (71.9)	
Major cutaneous abscess, No./total (%)	80/100 (80.0)	84/98 (85.7)	
Wound infection, No./total (%)	83/97 (85.6)	82/98 (83.7)	
Treatment nonresponder or indeterminate, No. (%)[a]	68 (20.5)	69 (20.6)	
Treatment nonresponder	27 (8.1)	35 (10.4)	
Indeterminate	41 (12.3)	34 (10.1)	
Missing lesion measurements	22 (6.6)	24 (7.2)	
Missing temperature data	37 (11.1)	32 (9.6)	
Sustained at the EOT assessment (ITT analysis set)			
Clinical success, No. (%) [95% CI]	230 (69.3) [64.0 to 74.2]	241 (71.9) [66.8 to 76.7]	−2.6 (−9.6 to 4.2)
Cellulitis/erysipelas, No./total (%)	85/133 (63.9)	84/135 (62.2)	
Major cutaneous abscess, No./total (%)	72/100 (72.0)	78/97 (80.4)	
Wound infection, No./total (%)	73/99 (73.7)	79/103 (76.7)	
Clinical treatment failure or indeterminate, No. (%)	102 (30.7)	94 (28.1)	
Clinical treatment failure	60 (18.1)	61 (18.2)	
Indeterminate	42 (12.7)	33 (9.9)	
Lost to follow-up	14 (4.2)	14 (4.2)	
Gram-negative infection	4 (1.2)	3 (0.9)	
Withdrew consent	6 (1.8)	2 (0.6)	
Indeterminate at the 48- to 72-h assessment	33 (9.9)	26 (7.8)	
Pregnancy	1 (0.3)	1 (0.3)	
Sustained at the EOT assessment (CE-EOT analysis set)	**(n = 273)**	**(n = 286)**	
Clinical success, No. (%) [95% CI]	219 (80.2) [80.0 to 84.8]	232 (81.1) [76.1 to 85.5]	−0.9 (−7.7 to 5.4)
Cellulitis/erysipelas, No./total (%)	77/112 (68.8)	80/117 (68.4)	
Major cutaneous abscess, No./total (%)	69/78 (88.5)	74/78 (94.9)	
Wound infection, No./total (%)	73/83 (88.0)	78/91 (85.7)	
Clinical failure, No. (%)	54 (19.8)	54 (18.9)	
Investigator's assessment at the PTE (ITT analysis set)	**(n = 332)**	**(n = 335)**	
Clinical success, No. (%) [95% CI][b]	284 (85.5) [81.3 to 89.1]	288 (86.0) [81.8 to 89.5]	−0.5 (−5.8 to 4.9)
Cellulitis/erysipelas, No./total (%)	119/135 (88.1)	114/139 (82.0)	
Major cutaneous abscess, No./total (%)	83/100 (83.0)	86/98 (87.8)	
Wound infection, No./total (%)	82/97 (84.5)	88/98 (89.8)	
Clinical failure or indeterminate, No. (%)	48 (14.5)	47 (14.0)	
Clinical failure, No. (%)	15 (4.5)	14 (4.2)	
Indeterminate, No. (%)	33 (9.9)	33 (9.9)	
Extenuating circumstances[c]	6 (1.8)	2 (0.6)	
Gram-negative infection	2 (0.6)	3 (0.9)	
Lost to follow-up	17 (5.1)	20 (6.0)	
No PTE	0	2 (0.6)	
Withdrew consent	8 (2.4)	6 (1.8)	
Investigator's assessment at the PTE (CE-PTE analysis set)	**(n = 279)**	**(n = 280)**	
Clinical success, No. (%) [95% CI][b]	264 (94.6) [91.3 to 97.0]	267 (95.4) [92.2 to 97.5]	−0.8 (−4.6 to 3.0)
Cellulitis/erysipelas, No./total (%)	109/117 (93.2)	100/113 (88.5)	
Major cutaneous abscess, No./total (%)	79/84 (94.0)	83/83 (100)	
Wound infection, No./total (%)	76/78 (97.4)	84/84 (100)	
Clinical failure, No. (%)	15 (5.4)	13 (4.6)	

Abbreviations: CE-EOT, clinically evaluable at end of treatment; CE-PTE, clinically evaluable at posttherapy evaluation; ITT, intent to treat.

[a] Patients considered indeterminate had both lesion and temperature data missing.

[b] Defined as meeting these criteria: (1) resolution or near resolution of most disease-specific signs and symptoms; (2) if present at baseline, absence or near resolution of systemic signs of infection (lymphadenopathy, fever, >10% of immature neutrophils, abnormal white blood cell count); and (3) no new signs, symptoms, or complications attributable to the acute bacterial skin and skin structure infections so no further antibiotic therapy was required for the treatment of the primary lesion.

[c] In the tedizolid phosphate group, 1 patient received no study drug, 1 patient was jailed, 1 patient became pregnant, 1 patient had purulent drainage, 1 patient relocated, and 1 patient was withdrawn by the investigator due to erratic behavior. In the linezolid group, 1 patient was jailed and 1 patient became pregnant.

Table 3. Sensitivity Analyses for the Intent-to-Treat (ITT) and Clinically Evaluable at End of Treatment (CE-EOT) Analysis Sets

	Clinical Success Rate, No. (%) [95% CI]		
	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
Treatment response at the 48- to 72-h assessment (ITT analysis set)			
≥20% Decrease in lesion area, no fever criteria	259 (78.0) [73.2 to 82.4]	255 (76.1) [71.1 to 80.6]	1.9 (−4.5 to 8.3)
No increase in lesion area, no fever criteria	289 (87.0) [83.0 to 90.5]	286 (85.4) [81.1 to 89.0]	1.6 (−3.5 to 7.0)
Sustained treatment response at the EOT[a]			
ITT analysis set	268 (80.7) [76.1 to 84.8]	271 (80.9) [76.3 to 85.0]	−0.2 (−6.2 to 5.8)
CE-EOT analysis set	(n = 273) 239 (87.5) [83.0 to 91.2]	(n = 286) 249 (87.1) [82.6 to 90.7]	0.4 (−5.2 to 6.0)
No pain criteria (ITT analysis set)	289 (87.0) [83.0 to 90.5]	294 (87.8) [83.8 to 91.1]	−0.8 (−5.8 to 4.4)

[a] Indeterminates and treatment failures at the 48- to 72-hour assessment were not carried forward.

response rates according to investigator's assessment at the PTE (TABLE 4) were similar for tedizolid phosphate and linezolid whether patients were infected with MRSA (85.2% and 85.6%, respectively) or MSSA (88.0% and 94.3%). Likewise, both agents were effective for infections involving *PVL*-positive strains of *S aureus*, with 85.6% of patients in the tedizolid phosphate group and 84.3% of patients in the linezolid group responding to treatment. For these treatment responses by pathogen, patients with cellulitis were underrepresented because gram-positive pathogens were isolated from 31% of primary cellulitis lesions vs 85% of primary abscesses or wounds (Table 1). A summary of clinical treatment response rates at the PTE for all pathogens appears in eTable 5.

An exploratory analysis was performed to evaluate concordance and discordance of the early clinical response rate and the rate based on investigators' assessments of clinical treatment response at the PTE, excluding patients with missing data at the 48- to 72-hour assessment (TABLE 5). More than 82% of patients were both early treatment responders and clinical successes at the PTE in the tedizolid phosphate and linezolid groups. Approximately 7% of patients were early treatment nonresponders but clinical successes at the PTE, and 13 patients (2%) responded to treatment at the 48- to 72-hour assessment but were clinical treatment failures at the PTE.

Safety

Treatment-emergent adverse events occurred in 40.8% of patients in the tedizolid phosphate group and 43.3% of patients in the linezolid group (TABLE 6). Treatment-emergent adverse events were most commonly mild or moderate. These adverse events were most commonly reported in the Medical Dictionary for Regulatory Activities for the system organ classes of gastrointestinal disorders (16.3% of tedizolid phosphate group and 25.4% of linezolid group), infections and infestations (15.1% and 11.0%, respectively), and nervous system disorders (10.9% and 9.6%).

Aside from a lower incidence of gastrointestinal disorder TEAEs in the tedizolid phosphate group compared with the linezolid group, there were no notable differences in the types or frequencies of treatment-related TEAEs between the 2 groups, and there was no notable pattern of adverse events within the treatment groups. Commonly reported TEAEs included nausea (8.5% of tedizolid phosphate group and 13.4% of linezolid group), headache (6.3% and 5.1%, respectively), and diarrhea (4.5% and 5.4%).

The overall incidence of serious adverse events was low and similar between the tedizolid phosphate group (1.5%; 5 patients) and the linezolid group (1.2%; 4 patients). A single death in the study occurred 49 days after the last dose of tedizolid phosphate. It was the death of an 86-year-old man with a history of chronic obstructive pulmonary disease, congestive heart failure, and dementia and was attributed to sepsis and considered unrelated to study treatment. Only 2 patients (0.6%) in each treatment group discontinued from the study due to an adverse event; 3 of 4 patients discontinued treatment due to 1 or more gastrointestinal disorder–related adverse events (nausea, vomiting, or diarrhea) and the fourth patient discontinued treatment due to severe osteomyelitis.

Twenty-four patients (4.1% of tedizolid phosphate group and 3.5% of linezolid group) had substantially abnormal treatment-emergent alanine aminotransferase elevations (predefined as ≥2 × the upper limit of normal and ≥2 × the baseline value); approximately 34% of all patients had the hepatitis C virus. However, no patient discontinued use of a study drug due to these elevations and no apparent pattern suggesting liver dysfunction or toxicity emerged. Abnormal hematology results included a single case of substantially low hemoglobin concentration (in the linezolid group).

In addition, 2.3% of patients in the tedizolid phosphate group and 4.9% of

Table 4. Investigator Assessment of Clinical Response at the Posttherapy Evaluation (PTE) by Baseline Pathogen in Microbiological Intent-to-Treat Analysis Set[a]

	No. (%) of Patients			
	Tedizolid Phosphate (n = 209)		Linezolid (n = 209)	
Baseline Pathogen	With Isolates	With Clinical Success at the PTE[b]	With Isolates	With Clinical Success at the PTE[b]
Gram-positive aerobes	207 (99)	176 (85.0)	205 (98)	179 (87.3)
Staphylococcus aureus[c]	171 (82)	148 (86.5)	175 (84)	157 (89.7)
MRSA	88 (42)	75 (85.2)	90 (43)	77 (85.6)
MSSA	83 (40)	73 (88.0)	87 (42)	82 (94.3)
PVL-positive strains	97 (46)	83 (85.6)	102 (49)	86 (84.3)
Streptococcus anginosus-milleri group	15 (7)	11 (73.3)	15 (7)	12 (80.0)
Streptococcus constellatus	8 (4)	5 (62.5)	8 (4)	6 (75.0)
Streptococcus pyogenes	8 (4)	7 (87.5)	4 (2)	4 (100)
Streptococcus agalactiae	9 (4)	8 (88.9)	5 (2)	3 (60.0)
Gram-positive anaerobes	3 (1)	2 (66.7)	8 (4)	4 (50.0)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*; *PVL*, Panton-Valentine leukocidin gene.
[a] All gram-positive pathogens with 10 or more representatives in the combined microbiological intent-to-treat population are shown. Patients with the same pathogen isolated from multiple specimens are counted only once for that pathogen.
[b] Clinical success was determined by investigator assessment and was defined as resolution of most disease-specific signs and symptoms, including systemic signs of infection present at baseline, and no new signs, symptoms, or complications attributable to the acute bacterial skin and skin structure infection such that further antibiotic therapy is required to treat the primary lesion. Percentages were calculated as 100 × number of patients with clinical success at the PTE divided by the number of patients with isolates.
[c] Patients with both MRSA and MSSA are counted only once in the overall *S aureus* row, and untyped *S aureus* pathogens are counted only once in the *S aureus* row.

Table 5. Concordance and Discordance of Early Clinical Response and Investigator Assessment of Clinical Response at the Posttherapy Evaluation (PTE)

	Early Clinical Treatment Response, No. (%)[a]			
	Tedizolid Phosphate (n = 291)		Linezolid (n = 301)	
Response at PTE	Responder	Nonresponder	Responder	Nonresponder
Clinical success	243 (83.5)	21 (7.2)	247 (82.1)	24 (8.0)
Clinical failure	7 (2.4)	5 (1.7)	6 (2.0)	7 (2.3)
Indeterminate	14 (4.8)	1 (0.3)	13 (4.3)	4 (1.3)

[a] Excludes missing data at the 48- to 72-hour assessment.

Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set[a]

	No. (%) of Patients[b]	
Preferred Term	Tedizolid Phosphate (n = 331)	Linezolid (n = 335)
≥1 TEAE	135 (40.8)	145 (43.3)
≥1 Serious TEAE	5 (1.5)	4 (1.2)
Death	1 (0.3)	0
Discontinuation due to TEAE	2 (0.6)	2 (0.6)
Most commonly reported TEAE[c]		
Nausea	28 (8.5)	45 (13.4)
Headache	21 (6.3)	17 (5.1)
Diarrhea	15 (4.5)	18 (5.4)
Abscess	14 (4.2)	8 (2.4)
Abscess limb	12 (3.6)	10 (3.0)
Vomiting	9 (2.7)	20 (6.0)
Cellulitis	8 (2.4)	8 (2.4)
Dizziness	8 (2.4)	7 (2.1)
Pruritus	3 (0.9)	8 (2.4)
Dyspepsia	2 (0.6)	7 (2.1)

[a] Patients reporting a particular adverse event more than once are counted only once by preferred term.
[b] Percentages were calculated as 100 × (number of patients/total number).
[c] In either treatment group, 2% or more reported 1 of these adverse events.

patients in the linezolid group had substantially abnormal platelet counts (<75% the lower limit of normal and <75% of a patient's abnormally low baseline count); these abnormalities resolved without medical intervention. Half of the patients (11/22) with substantially low platelet counts also had the hepatitis C virus.

COMMENT

Treatment with 200 mg of tedizolid phosphate once daily for 6 days was statistically noninferior in efficacy to 600 mg of linezolid twice daily for 10 days at both early and late time points and was generally well tolerated in this randomized controlled trial of patients with ABSSSIs. The clinical response rate at the PTE (7 to 14 days after completing therapy) was high (85%) for 178 patients infected with MRSA and similar in both the tedizolid phosphate and linezolid treatment groups.

Adverse event rates were similar for the tedizolid phosphate and linezolid treatment groups, with fewer gastrointestinal adverse events among patients treated with tedizolid phosphate. Low platelet counts were less than half as frequent in the tedizolid phosphate group as in the linezolid

group, but the study was not adequately powered to make conclusions about the risk of myelosuppression with tedizolid phosphate.

Postmarketing safety concerns associated with linezolid include myelosuppression, peripheral or optic neuropathy, and monoamine oxidase inhibition, which limits its use in patients receiving monoamine oxidase inhibitors or serotonergic or adrenergic agents.[10] Isolated cases of serotonin syndrome, a rare but potentially fatal condition, have been reported with linezolid therapy. Preliminary results of preclinical and clinical pharmacology studies suggest that the unique mode of action of tedizolid phosphate, improved pharmacokinetics/pharmacodynamics, lower doses, and lack of monoamine oxidase inhibition in vivo may translate to improved safety vs linezolid.[22,23]

Guidelines on the primary efficacy end points in noninferiority studies of ABSSSIs are rapidly evolving and discussions are ongoing. In 2010, the types of skin infections that should be included in clinical trials to support an indication in the United States for treatment were reevaluated and redefined by the FDA as ABSSSIs, excluding any chronic cutaneous infections that affect contiguous tissues and are often polymicrobial in nature (eg, diabetic foot infection, chronic infected skin ulcer).[12,13] The new draft guidance also redefined clinical response criteria and changed the primary noninferiority end point from evaluation at the test-of-cure visit, 7 to 14 days after completion of therapy, to early assessment of clinical response during therapy to correspond with historical studies.[24,25]

The early end point specified by the draft guidance[16] is still controversial and the results from ongoing trials in ABSSSIs will inform the discussions.[17,26-30] In August 2011, the Foundation for the National Institutes of Health Biomarkers Consortium provided recommendations to the FDA for clinical trials in ABSSSIs.[17] Recommendations included a 20% or greater decrease in lesion area (longest length × longest width) for a primary outcome of clinical success at the 48- to 72-hour assessment and no body temperature requirement for treatment response.

Due to the uncertainties regarding well-defined and reliable primary efficacy end points in noninferiority studies of ABSSSIs, clinical response in this trial was analyzed using varied end point definitions and criteria. Treatment with tedizolid phosphate once daily was noninferior to linezolid twice daily for the primary end point. Early clinical treatment response rates based on cessation of lesion spread and 2 temperature measurements of 37.6°C or below (the primary outcome measure) differed by 0.1% between the 200 mg of tedizolid phosphate once daily group and the 600 mg of linezolid twice daily group. Secondary outcome assessments at the EOT and the PTE evaluation time points also established that 6 days of treatment with tedizolid phosphate was noninferior to 10 days of treatment with linezolid.

The main reason for treatment failure at the early 48- to 72-hour assessment in either treatment group was missing temperature data within that period. The validity of fever as a component of the primary efficacy outcome measure in ABSSSIs has been disputed,[12,17,28,29] and the results of our study suggest that it is also a practical challenge for the conduct of trials because only 18% of patients had fever at baseline and 10% of patients were missing temperature measurements for the early treatment response end point. Among patients in the Ceftaroline Versus Vancomycin in Skin and Skin Structure Infections (CANVAS) trials, more had fever at baseline (43%).[31]

Because ceftaroline is administered intravenously, investigators may have tended to enroll more severely ill patients; the population had larger median lesion areas, proportionately more cellulitis, and was on average older than the ESTABLISH-1 population. In a phase 2 trial comparing a novel fluoroquinolone with linezolid and enrolling 161 patients in the United States with ABSSSIs (approximately one-third each for abscess, cellulitis, and wounds), only 7 (4%) had fever at baseline.[32] The authors concluded that "fever is not a compelling surrogate measure of systemic disease resolution for this indication." In our study, patients in the United States and Canada (81% of the ITT population) tended to have smaller lesions and fewer had fever compared with patients enrolled in Europe.

Early clinical treatment response rates in this trial based only on cessation of lesion spread without fever were 7.5% higher in the tedizolid phosphate group and 6.0% higher in the linezolid group compared with the primary analysis (absolute differences). The sensitivity analyses of the primary end points generally reflect the evolution of regulatory science's thinking,[17] and may represent the future direction of the field. For example, early clinical response rates based only on a 20% reduction or greater of lesion spread (as proposed by the Foundation for the National Institutes of Health) were within 3% of the primary analysis response rates for both treatment groups. Tedizolid phosphate was noninferior to linezolid in this analysis and in all other sensitivity and subgroup analyses based on type of infection and presence or absence of fever at baseline, confirming the results of the primary end point.

Early and EOT end points in this study relied on measurement of lesion dimensions. The accuracy and reliability of using a ruler to measure ABSSSI lesion size has not been thoroughly studied, but any variability would not be expected to be different between the 2 treatment groups. A recent observational study of patients with ABSSSIs found good intraobserver and interobserver correlation of ruler measurements (intraclass correlation coefficients >0.90), and variability decreased with increasing lesion size.[33]

Secondary outcome measures in this trial corresponded to traditional analysis sets and end points at a time point several days or weeks after comple-

tion of therapy (eg, at the EOT or PTE visit). Multiplicity was controlled for by using a hierarchical testing procedure. Early effect was sustained until the EOT and was consistent with the investigators' assessments at the PTE. Tedizolid phosphate was not inferior to linezolid in each of these analyses or in all other sensitivity and subgroup analyses of the secondary end points.

There is concern that a late post-therapy clinical response could reflect the natural history of the disease rather than the effect of antibacterial treatment.[12] In this trial, there was good concordance (>80%) between early objective and late investigator-assessed primary end points, suggesting that the early end point is indicative of a sustained and late clinical outcome. Clinical response at early time points (based primarily on change in lesion area) appears to be a valid approach to evaluate the effectiveness of antibacterials for ABSSSIs and may be an early indicator of response and prognosis.

A subset of 13 patients who responded to treatment at the 48- to 72-hour time point were later judged by investigators to be clinical treatment failures at the PTE. At the 48- to 72-hour assessment, none had a fever above 37.6°C and 12 had a decrease in lesion area (range, −6% to −85%); and 9 were treatment failures at the EOT. One withdrew for a TEAE (after 6 days of linezolid therapy), 1 required additional antibiotics (after 7 days of linezolid therapy), and 11 required additional antibiotics after the EOT (5 in the tedizolid phosphate group and 2 in the linezolid group) or PTE assessments (2 in the tedizolid phosphate group and 2 in the linezolid group). Four were intravenous drug users, 5 had type 2 diabetes, and most had multiple comorbidities.

The early primary end point was adopted by the FDA to justify the noninferiority margin in ABSSSI trials.[12] However, contemporary clinicians often wait for more clinical information to become available before concluding the outcome as favorable or unfavorable, leading to unnecessary and prolonged hospitalization or inappropriate use of antibiotics. Historical[24,25] and contemporary[34,35] research confirms that decision strategies based on cessation of lesion spread at early time points provides an indication of outcome that is usable in clinical practice and demonstrates that the new regulatory end point of cessation of spread at 48 through 72 hours is appropriate to clinical medicine.[17,30]

CONCLUSIONS

A short course of tedizolid phosphate was statistically noninferior to a 10-day course of linezolid for both early and sustained clinical responses in patients with ABSSSIs. Results were consistent for primary and sensitivity analyses, using either objective criteria or investigators' assessments, and treatment response rates were concordant for early and late time points.

Author Contributions: Drs Prokocimer and Mehra had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Prokocimer, De Anda, Das.
Acquisition of data: De Anda, Fang, Mehra.
Analysis and interpretation of data: Prokocimer, De Anda, Fang, Das.
Drafting of the manuscript: Prokocimer, De Anda, Fang, Das.
Critical revision of the manuscript for important intellectual content: De Anda, Fang, Mehra.
Statistical analysis: Das.
Administrative, technical, or material support: De Anda, Fang.
Study supervision: Prokocimer, De Anda, Mehra.
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Prokocimer, De-Anda, and Fang each reported holding stock/stock options in Trius Therapeutics; and each was an employee at the time the work and analyses were performed. Dr Das reported receiving the following from Trius Therapeutics: consulting fees, support for travel expenses, fees for participating in review activites, and payment for writing or reviewing the manuscript; and serving as a consultant to Cerexa Inc, Achaogen Inc, Nabriva Therapeutics, Durata Therapeutics, Cubist Pharmaceuticals Inc, Cempra Pharmaceuticals Inc, Polymedix Inc, and Kalidex Inc. Dr Mehra reported not having any conflicts of interest.
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Independent Statistical Analysis: All primary and secondary analyses of efficacy, primary safety results, and conclusions presented in this article have been confirmed by an independent statistical review and analysis performed by Hector Lemus, PhD (Division of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, San Diego, California). Dr Lemus was provided all raw SAS data sets, analysis SAS data sets, the study protocol, the statistical analysis plan, a blank copy of the study case report form, the analysis database specifications, and the original version of the manuscript by the authors and the sponsor of this study. Dr Lemus was in agreement with the statistical methods used in the manuscript and independently verified the primary and secondary efficacy results. The results presented herein are those verified by Dr Lemus, who was compensated by Trius Therapeutics for his statistical review.
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