# Safety and Efficacy of Oral and/or Intravenous Tedizolid Phosphate From a Randomized Phase 3 Trial in Adolescents With Acute Bacterial Skin and Skin Structure Infections

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**Background:** Tedizolid phosphate is an oxazolidinone prodrug approved in 2014 for treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs); however, efficacy has not previously been evaluated in children. This study compared the safety and efficacy of tedizolid (administered as tedizolid phosphate) with active antibacterial comparators for the treatment of ABSSSIs in adolescents.

**Methods:** This was a randomized, assessor-blind, global phase 3 study of tedizolid versus active comparators for the treatment of Gram-positive ABSSSIs in adolescents (12 to <18 years of age; NCT02276482). Enrolled participants were stratified by region and randomized 3:1 to receive tedizolid phosphate 200 mg (oral and/or intravenous) once daily for 6 days or active comparator, selected by investigator from an allowed list per local standard of care, for 10 days. The primary endpoint was safety; blinded investigator's assessment of clinical success at the test-of-cure visit (18–25 days after the first dose) was a secondary efficacy endpoint. Statistical comparisons between treatment groups were not performed.

**Results:** Of the 121 participants enrolled, 120 were treated (tedizolid, n = 91; comparator, n = 29). Treatment-emergent adverse events were balanced between treatment groups (tedizolid, 14.3%; comparator, 10.3%). Overall, 3 participants (3.3%) in the tedizolid group and 1 (3.4%) in the comparator group experienced a single drug-related TEAE. Clinical success rates were high in both treatment groups: 96.7% and 93.1% at the test-of-cure visit for the tedizolid and comparator groups, respectively.

**Conclusions:** Tedizolid demonstrated safety and efficacy similar to comparators for the treatment of ABSSSIs in adolescents.

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Acute bacterial skin and skin structure infections (ABSSSIs) are a common cause of hospitalization in children.[1–3] These infections are most frequently caused by Gram-positive bacteria, *Staphylococcus aureus* being the most common.[4] ABSSSIs caused by methicillin-resistant *S. aureus* (MRSA) are associated with significantly higher morbidity and mortality than non-MRSA infections.[5] Current guidelines, such as the Infectious Diseases Society of America's clinical practice guidelines for treatment of skin and soft tissue infections, recommend vancomycin and clindamycin to treat ABSSSIs due to MRSA; however, vancomycin requires monitoring because of nephrotoxicity and ototoxicity, and susceptibility to clindamycin among MRSA isolates varies greatly by region and setting, with reports of resistance rates of up to 40%–71%.[6–12] Few therapy options are approved by the US Food and Drug Administration or European Medicines Agency to treat complicated MRSA ABSSSIs in children, particularly oral options that may have a better safety profile compared with clindamycin (diarrhea) and linezolid (myelosuppression/neurotoxicity).[13,14] Trimethoprim/sulfamethoxazole has been evaluated for treatment of uncomplicated skin infections in adults and children but is not Food and Drug Administration approved for treatment of any *S. aureus* infections, including ABSSSIs.[15,16]

Tedizolid, the active moiety of the tedizolid phosphate prodrug, is an oxazolidinone-class antibacterial agent that binds to the 50S bacterial ribosome subunit, inhibiting protein synthesis, and has broad in vitro activity against Gram-positive bacteria, including MRSA and vancomycin- and linezolid-resistant strains.[17–22] The phase 3 ESTABLISH-1 and -2 trials demonstrated that tedizolid is well tolerated and noninferior to linezolid for the treatment of ABSSSIs in adults, leading to approval of 200-mg tedizolid phosphate for the treatment of ABSSSIs in adults.[22–24] A phase 1 study established that a 200-mg once-daily dose of oral or intravenous (IV) tedizolid phosphate provided appropriate exposure for the treatment of adolescents with ABSSSIs and that dose adjustments are not needed when switching from IV to oral administration.[25]

Herein, we describe a phase 3 registrational trial that assessed the safety and efficacy of tedizolid compared with protocol-specified active comparators in adolescents 12 to <18 years of age with suspected or documented Gram-positive ABSSSIs, a component of a larger investigational plan that is evaluating tedizolid for all pediatric age groups down to birth.

## MATERIALS AND METHODS

### Study Design and Participants

This randomized, assessor-blind, phase 3 trial (ClinicalTrials.gov identifier: NCT02276482; protocol MK-1986-012) was

conducted at 65 centers and enrolled patients from 9 countries: Bulgaria, Georgia, Latvia, Lithuania, Poland, South Africa, Spain, Ukraine, and the United States. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the institutional review boards at each participating center and regulatory agencies in each participating country. Consent was obtained from parents/legally acceptable representatives for all participants. Assent was also required where appropriate given a participant's age and comprehension.

Eligible participants were 12 to <18 years of age, diagnosed with ABSSSI with documented or suspected Gram-positive pathogen etiology, and met ≥1 of the following clinical syndrome definitions, designed to capture extensive clinical disease (cellulitis or abscess).

(1) **Cellulitis/erysipelas:** It is characterized by a spreading area of erythema, edema, and/or induration (EEI) extending ≥4 cm in 1 dimension, with ≥2 signs of infection (erythema, induration, swelling/edema, localized warmth, and pain/tenderness), and ≥1 sign of invasive infection [lymph node tenderness and volume increase or palpability proximal to the primary ABSSSI, lymphangitis, fever (≥38°C oral or ≥38.4°C tympanic/rectal), white blood cell count ≥10,000 or <4000 cells/mm$^3$, >10% immature neutrophils, and participant-reported pain ≥6 (Wong-Baker pain scale)].

(2) **Major cutaneous abscess:** It is an infection characterized by a collection of pus apparent upon physical examination that is intradermal or deeper with EEI extending ≥4 cm in 1 dimension, with ≥2 signs of infection (erythema, induration, swelling/edema, localized warmth, pain/tenderness, fluctuance, incision and drainage required, seropurulent drainage, and intradermal or subcutaneous fluid collection) and ≥1 sign of invasive infection (as described above).

(3) **Wound infection:** It is an infection characterized by purulent drainage from a wound with surrounding EEI extending ≥4 cm in 1 dimension, with ≥1 sign of invasive infection (as described above).

Participants were excluded if they had uncomplicated minor skin infections (eg, impetigo), cellulitis/erysipelas, or major cutaneous abscess caused by suspected or documented Gram-negative pathogens (nonsusceptible to tedizolid), bacteremia/severe sepsis/septic shock, recent history of opportunistic infections/tuberculosis/neutropenia/HIV, severe renal/hepatic impairment, device-related infections, or had received ≥24 hours of effective antibacterial therapy (except prior treatment failures, defined as ≥48 hours of treatment without improvement). Infections likely to have primary Gram-negative involvement, including perianal or perioral infections, or infections associated with animal or human bites, were also excluded.

## Randomization and Masking

Enrolled participants were stratified by region and randomized 3:1 to receive tedizolid phosphate or investigator-selected active antibacterial comparator using interactive response technology. The use of local standard-of-care parenteral and oral antibacterials as comparators was designed to facilitate enrollment, given the global diversity of pathogens/susceptibilities and standards of care. Each study site designated ≥1 blinded evaluator to assess efficacy and the relationship of adverse events (AEs) to the study drug. The blinded evaluator did not have access to unblinding information or systems (eg, interactive response technology for randomization).

## Study Treatments

Randomized participants received oral and/or IV tedizolid phosphate 200 mg once daily for 6 days or investigator-selected active comparator per local standard of care (IV vancomycin, linezolid, clindamycin, flucloxacillin, or cefazolin, and/or oral linezolid, clindamycin, flucloxacillin, or cephalexin) for 10 days (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/INF/E238). Participants were permitted to receive IV therapy for the entire treatment duration or switch to oral therapy after 24-hour IV therapy, provided that specific criteria were met for response to therapy (Table S1, Supplemental Digital Content 2, http://links.lww.com/INF/E239). Participants with known/suspected multipathogen wound infections involving known/suspected Gram-positive pathogens, but also potentially involving Gram-negative pathogens, were permitted to receive adjunctive therapy with aztreonam and/or metronidazole as these antibacterials have poor aerobic Gram-positive activity (permitted therapies listed in Table S1, Supplemental Digital Content 2, http://links.lww.com/INF/E239).

## Outcome Measures

The primary objective was to compare the safety of tedizolid with active comparators in the safety population (participants who received any amount of study treatment) using rates of treatment-emergent AEs (TEAEs) and abnormal clinical laboratory values as the primary endpoints. There were 3 secondary endpoints.

The first secondary endpoint was clinical success at the test-of-cure (TOC) visit (18–25 days after the first dose) in the intention-to-treat (ITT) and clinically evaluable at TOC (CE-TOC) populations. The ITT population comprised all randomized participants, and the CE-TOC population included participants who received a full dose of study treatment and completed therapy through the TOC visit. Clinical response was defined as: (1) clinical success (resolution or near resolution of disease-specific signs/symptoms and regional/systemic signs of infection, and no new signs/symptoms/complications attributable to the infection); (2) clinical failure (need for additional antibacterial therapy for treatment of the primary infection, major surgical intervention required after study drug failure, osteomyelitis development, persistent Gram-positive bacteremia, TEAE leading to study drug discontinuation, or death within 28 days of first infusion); or (3) indeterminate (lack of study data availability for determination of efficacy).

The second secondary endpoint was protocol-defined programmatic early clinical response (as assessed in adult studies of tedizolid) in the ITT population as a ≥20% lesion size reduction at the 48- to 72-hour visit compared with baseline.

The third secondary endpoint was clinical success at the end-of-treatment (EOT) visit (day 11) in the ITT and clinically evaluable at EOT (CE-EOT) populations (participants who received a full dose of study treatment and completed the EOT visit).

A key exploratory endpoint was the microbiologic response rate at the TOC visit in the microbiologic ITT (MITT; participants with documented Gram-positive pathogens) and microbiologically evaluable populations (participants in the MITT and CE-TOC populations). These microbiologic responses were categorized as eradication, presumed eradication, persistence, presumed persistence, recurrence, indeterminate, superinfection, or new infection based on central laboratory data and investigator assessment of clinical response (see Table S2, Supplemental Digital Content 3, http://links.lww.com/INF/E240).

## Statistical Analysis

This study was designed with regulatory agency guidance to assess the safety of tedizolid and was not powered for inferential statistics. We established a target of treating 86 adolescents with tedizolid phosphate to provide an 82% probability of detecting ≥1 AE with a true event rate of 2%.[26] Descriptive statistics were provided for safety and efficacy assessments, including the numbers and percentages for categorical variables, and the numbers, means, SDs, medians, and ranges for continuous variables. No hypothesis testing for the efficacy endpoints was planned or conducted for the treatment groups with the assumption that efficacy could be

extrapolated from adults for the same pathogens/sites of infection/tedizolid exposure. The following descriptive statistical analyses were conducted: (1) an exact 2-sided 95% CI was determined for the clinical success rate (per blinded investigator's assessment) in each treatment group at the TOC visit using the Clopper-Pearson method; and (2) the difference in clinical success rates between treatment groups and a 2-sided 95% CI for the difference were determined using the unstratified Miettinen and Nurminen method.[27,28]

## RESULTS

### Participants

From September 2015 to September 2018, 121 participants were randomized at 20 of 65 study sites in 9 countries. Of these, 120 participants from 19 sites received study treatment (tedizolid, n = 91; comparator, n = 29; Fig. S2, Supplemental Digital Content 4, http://links.lww.com/INF/E241). One participant from 1 site was randomized but did not receive study treatment due to incomplete consent and was not included in any study populations.

Demographics and baseline characteristics were similar between the tedizolid and comparator groups (Table 1). The distribution of infection types was generally similar across both groups, although wound infection was more frequent in the comparator group; wound infections in both treatment groups were all monomicrobial or polymicrobial Gram-positive infections (Table 2).

Within the tedizolid and comparator groups, respectively, 38 (41.8%) and 10 (34.5%) participants had cellulitis/erysipelas, 40 (44.0%) and 11 (37.9%) participants had major cutaneous abscess, and 13 (14.3%) and 8 (27.6%) participants had wound infections. Most participants in both groups had fever (≥38°C oral or ≥38.4°C tympanic/rectal; tedizolid, 56.0%; comparator, 55.2%), with a median (range) lesion surface area of 85.4 (14–978) $cm^2$ and 78.0 (16–210) $cm^2$ in the tedizolid and comparator groups, respectively. Of participants enrolled in the study, 91.7% were hospitalized at day 1.

Similar proportions of participants in both treatment groups received antibacterial therapy before study initiation (tedizolid, n = 26 [28.6%]; comparator, n = 6 [20.7%]). Overall, 67 participants (73.6%) in the tedizolid group and 19 (65.5%) in the comparator group received ≥1 concomitant medication; the most common concomitant medications were antiinflammatory and antirheumatic products (33.3% of all participants) and analgesics (22.5% of all participants). Concomitant adjunctive antibacterial therapy was limited to the administration of metronidazole for the treatment of potential anaerobic Gram-negative pathogens, as permitted by the protocol; only 1 in each treatment group received concomitant metronidazole. The most common initial site-assigned study treatment in the comparator group was cefazolin (11 participants [37.9%]; of these participants, 4 were subsequently treated with oral cephalexin [n = 3] or clindamycin [n = 1] after initial response to parenteral therapy). The next most common was vancomycin (8 participants [27.6%]; 6 participants were subsequently treated with oral therapy: cephalexin [n = 3], flucloxacillin [n = 2], or clindamycin [n = 1]). Five participants (17.2%) received linezolid; of these, 4 participants switched from IV to oral and 1 received only oral. The median (range) duration of treatment was 6.0 (1.0–8.0) days in the tedizolid group and 10.0 (3.0–11.0) days in the comparator group. Within the tedizolid group, investigators decided to discontinue treatment for 2 participants due to Gram-negative infection (n = 1) and serious TEAEs (n = 1), and a single participant withdrew from the study. One participant (3.4%) in the comparator group discontinued the study after 3 days due to an investigator's decision based on the resistance of the isolated pathogen to the permitted oral antibacterial agents. One participant in the tedizolid group received 8 days of treatment as a departure from the study protocol. A total of 88 (96.7%) and 28 (96.6%) participants in the tedizolid and comparator groups, respectively, completed the trial.

**TABLE 1.** Participant Demographics and Baseline Characteristics (Intention-to-Treat Population)

| Characteristic | Tedizolid (n = 91) | Comparator (n = 29) |
|---|---|---|
| Age, yrs, median (range) | 15.0 (12–17) | 15.0 (12–17) |
| Age group, yrs, n (%) | | |
| 12–14 yrs | 43 (47.3) | 14 (48.3) |
| 15 to <18 yrs | 48 (52.7) | 15 (51.7) |
| Male, n (%) | 58 (63.7) | 17 (58.6) |
| Race, n (%) | | |
| Asian | 0 | 1 (3.4) |
| Black or African American | 11 (12.1) | 4 (13.8) |
| White | 80 (87.9) | 24 (82.8) |
| Hispanic or Latino ethnicity, n (%) | 4 (4.4) | 1 (3.4) |
| BMI, $kg/m^2$, median (range) | 20.8 (14–45) | 20.5 (15–33) |
| Geographic region, n (%) | | |
| North America | 8 (8.8) | 2 (6.9) |
| Europe* | 71 (78.0) | 23 (79.3) |
| South Africa | 12 (13.2) | 4 (13.8) |
| Type of infection, n (%) | | |
| Cellulitis/erysipelas | 38 (41.8) | 10 (34.5) |
| Major cutaneous abscess | 40 (44.0) | 11 (37.9) |
| Wound infection | 13 (14.3) | 8 (27.6) |
| Lesion surface area, $cm^2$, median (range) | 85.4 (14–978) | 78.0 (16–210) |
| Hospitalization at day 1, n (%) | 85 (93.4) | 25 (86.2) |
| Lymphadenopathy, n (%) | 8 (8.8) | 2 (6.9) |
| Fever at baseline (≥38°C oral or ≥38.4°C tympanic or rectal), n (%) | 51 (56.0) | 16 (55.2) |
| Elevated immature neutrophils (>10%), n (%) | 13 (14.3) | 5 (17.2) |
| Abnormal WBC count (≥10,000 or <4000 cells/$mm^3$), n (%) | 45 (49.5) | 15 (51.7) |
| Lymph node tenderness, n (%) | 27 (29.7) | 8 (27.6) |
| Pain (≥6; Wong-Baker), n (%) | 68 (74.7) | 21 (72.4) |

*Includes Bulgaria (n = 29), Georgia (n = 38), Latvia (n = 9), Lithuania (n = 4), Poland (n = 4), Spain (n = 1), and Ukraine (n = 9).
BMI indicates body mass index; WBC, white blood cell.

### Baseline Pathogens

The baseline microbiologic assessments of the primary infection site were comparable between treatment groups (Table 2). The most commonly isolated Gram-positive pathogen at baseline in the MITT population of each group was *S. aureus* (41 of 48 participants [85.4%] and 14 of 16 participants [87.5%] in the tedizolid and comparator groups, respectively); the *S. aureus* isolates were primarily methicillin-susceptible (35 of 41 [85.4%] in the tedizolid group; 12 of 14 [85.7%] in the comparator group). Overall, 50 of 51 (98.0%) baseline *S. aureus* isolates with available susceptibility data were susceptible to tedizolid (minimum inhibitory concentration that inhibited 90% of isolates [$MIC_{90}$], 0.5 μg/mL); 1 isolate from a participant in the tedizolid group had a MIC of 1 μg/mL (intermediate susceptibility, Clinical and Laboratory Standards Institute criteria).[29] All 10 baseline isolates of *Streptococcus pyogenes* with available susceptibility data from participants in both treatment groups were susceptible to tedizolid ($MIC_{90}$, 0.25 μg/mL).

### Safety

Generally, TEAEs were mild in severity (Table 3). The most common TEAEs in the tedizolid group were phlebitis (3 participants [3.3%]) and blood creatinine phosphokinase increase (2 participants [2.2%]; Table S3, Supplemental Digital Content 5, http://links.lww.com/INF/E242). All phlebitis events were reported in participants who received IV doses and resolved without sequelae;

**TABLE 2.** Summary of Monomicrobial, Polymicrobial, and Mixed Microbial Infections by Type and Baseline Pathogens Isolated From the Primary Infection Site (Microbiologic Intention-to-Treat Population)

| Pathogen | Tedizolid Isolate Total, n (%) (n = 48) | Comparator Isolate Total, n (%) (n = 16) | Tedizolid MIC, µg/mL |
|---|---|---|---|
| Cellulitis/erysipelas | 4 (8.3) | 2 (12.5) | – |
| Monomicrobial Gram-positive infections | 4 (8.3) | 2 (12.5) | – |
| Polymicrobial Gram-positive infections | 0 | 0 | – |
| Mixed Gram-positive and Gram-negative infections | 0 | 0 | – |
| Major cutaneous abscess | 32 (66.7) | 6 (37.5) | – |
| Monomicrobial Gram-positive infections | 29 (60.4) | 6 (37.5) | – |
| Polymicrobial Gram-positive infections | 3 (6.3) | 0 | – |
| Mixed Gram-positive and Gram-negative infections | 0 | 0 | – |
| Wound infection | 12 (25.0) | 8 (50.0) | – |
| Monomicrobial Gram-positive infections | 8 (16.7) | 8 (50.0) | – |
| Polymicrobial Gram-positive infections | 4 (8.3) | 0 | – |
| Mixed Gram-positive and Gram-negative infections | 0 | 0 | – |
| Gram-positive aerobes | 47 (97.9) | 16 (100.0) | ≤0.06 to 1 |
| *Staphylococcus aureus* | 41 (85.4) | 14 (87.5) | ≤0.12 to 1 |
| MRSA | 2 (4.2) | 1 (6.3) | 0.25 to 0.5 |
| MSSA | 35 (72.9) | 12 (75.0) | ≤0.12 to 1 |
| *Staphylococcus haemolyticus* | 2 (4.2) | 0 | ≤0.12 |
| *Staphylococcus lugdunensis* | 1 (2.1) | 0 | ≤0.12 |
| *Streptococcus constellatus* | 1 (2.1) | 0 | – |
| *Streptococcus pyogenes* | 9 (18.8) | 2 (12.5) | ≤0.06 to 0.25 |
| Gram-positive anaerobes | 1 (2.1) | 0 | – |
| *Peptoniphilus asaccharolyticus* | 1 (2.1) | 0 | – |

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

**TABLE 3.** Adverse Events (Safety Population)

| AEs, n (%) | Tedizolid (n = 91) | Comparator (n = 29) |
|---|---|---|
| Any AE | 13 (14.3) | 3 (10.3) |
| Any TEAE | 13 (14.3) | 3 (10.3) |
| Drug-related TEAE | 3 (3.3) | 1 (3.4) |
| TEAE leading to discontinuation of study drug | 1 (1.1) | 0 |
| TEAE leading to death | 0 | 0 |
| Serious TEAE | 1 (1.1) | 0 |
| Drug-related serious TEAE | 0 | 0 |
| TEAEs by system organ class and preferred term | | |
| Blood and lymphatic system disorders | 1 (1.1) | 0 |
| Anemia | 1 (1.1) | 0 |
| Gastrointestinal disorders | 1 (1.1) | 1 (3.4) |
| Nausea | 0 | 1 (3.4) |
| Vomiting | 1 (1.1) | 0 |
| General disorders and administration-site conditions | 1 (1.1) | 0 |
| Asthenia | 1 (1.1) | 0 |
| Infections and infestations | 4 (4.4) | 1 (3.4) |
| Abscess limb | 1 (1.1) | 0 |
| Pneumonia | 1 (1.1) | 0 |
| Respiratory tract infection | 0 | 1 (3.4) |
| Respiratory tract infection viral | 1 (1.1) | 0 |
| Sepsis | 1 (1.1) | 0 |
| Viral pharyngitis | 1 (1.1) | 0 |
| Investigations | 5 (5.5) | 0 |
| Alanine aminotransferase increased | 1 (1.1) | 0 |
| Aspartate aminotransferase increased | 1 (1.1) | 0 |
| Blood creatine phosphokinase increased | 2 (2.2) | 0 |
| Liver function test abnormal | 1 (1.1) | 0 |
| Nervous system disorders | 0 | 1 (3.4) |
| Headache | 0 | 1 (3.4) |
| Vascular disorders | 4 (4.4) | 0 |
| Phlebitis | 3 (3.3) | 0 |
| Venous thrombosis limb | 1 (1.1) | 0 |

AE, adverse event; TEAE, treatment-emergent adverse event.

causality could not be determined because the same infusion site was used for administration of prior/concomitant medications. None of the phlebitis or blood phosphokinase increase events assessed by investigators or the Sponsor were considered study drug related or led to discontinuation. Drug-related TEAEs were reported for 3 participants (3.3%; alanine aminotransferase increase; aspartate aminotransferase increase; and liver function test abnormal) in the tedizolid group and 1 participant (3.4%; nausea) in the comparator group who received linezolid. A single participant in the tedizolid group experienced 3 serious TEAEs (pneumonia, sepsis, and venous thrombosis of the limb), which led to discontinuation of the study drug and withdrawal from the trial. None of these serious TEAEs were considered drug related by the investigator.

A summary of hematologic parameter changes from baseline by visit is provided in Table 4. Overall, the changes from baseline through the TOC visit were comparable between treatment groups; mean baseline leukocyte and neutrophil counts were slightly higher in the tedizolid group than in the comparator group and decreased over the course of study in both groups, reflective of recovering infection. Values in both groups resolved to similar mean values by day 7 and the EOT visit. Between baseline and the EOT visit, comparable numbers of participants in each treatment group experienced changes in categorized values (low/normal/high).

## Efficacy

Blinded investigator-assessed clinical success rates at the TOC visit were similar across the tedizolid and comparator groups (96.7% vs. 93.1% and 100.0% vs. 96.3% for the ITT and CE-TOC populations, respectively; Fig. 1). High and similar rates of clinical success were also achieved at the early assessment timepoints (48- to 72-hour visit), including >90% in both treatment groups (ITT population; Fig. 1), based on protocol-defined clinical assessment, and >95% in both treatment groups (ITT and CE-EOT populations) at the EOT visit, based on blinded investigator assessment (Fig. S3, Supplemental Digital Content 6, http://links.lww.com/INF/E243). Favorable

**TABLE 4.** Hematology Summary and Change From Baseline by Visit

| Parameter and Visit | Tedizolid (n = 91) n | Tedizolid (n = 91) Mean (SD) | Comparator (n = 29) n | Comparator (n = 29) Mean (SD) |
|---|---|---|---|---|
| Absolute neutrophil count, $10^9$/L | | | | |
| Baseline | 82 | 7.3 (3.9) | 24 | 5.8 (2.7) |
| Day 7 | 86 | 4.5 (2.0) | 25 | 4.0 (1.5) |
| Change from baseline to day 7 | 78 | –2.8 (4.0) | 22 | –1.9 (3.3) |
| EOT | 88 | 4.5 (2.0) | 25 | 4.0 (1.5) |
| Change from baseline to EOT | 79 | –2.6 (3.4) | 22 | –1.9 (3.1) |
| Leukocyte count, $10^9$/L | | | | |
| Baseline | 82 | 10.1 (4.0) | 24 | 8.4 (3.2) |
| Day 7 | 86 | 7.7 (2.5) | 25 | 7.4 (1.7) |
| Change from baseline to day 7 | 78 | –2.5 (4.1) | 22 | –1.3 (3.3) |
| EOT | 88 | 7.6 (2.4) | 25 | 7.4 (1.6) |
| Change from baseline to EOT | 79 | –2.3 (3.4) | 22 | –1.2 (3.5) |
| Platelet count, $10^9$/L | | | | |
| Baseline | 80 | 300.9 (90.2) | 24 | 284.1 (85.9) |
| Day 7 | 83 | 329.6 (95.6) | 24 | 326.8 (71.3) |
| Change from baseline to day 7 | 75 | 26.0 (79.1) | 21 | 34.1 (63.8) |
| EOT | 86 | 304.8 (90.4) | 25 | 314.9 (55.3) |
| Change from baseline to EOT | 76 | –3.5 (86.2) | 22 | 24.8 (72.5) |
| Hemoglobin, g/L | | | | |
| Baseline | 82 | 134.8 (15.0) | 24 | 132.5 (16.8) |
| Day 7 | 86 | 137.7 (15.4) | 25 | 137.0 (10.7) |
| Change from baseline to day 7 | 78 | 2.9 (10.2) | 22 | 5.0 (15.1) |
| EOT | 88 | 134.1 (13.6) | 25 | 136.4 (10.6) |
| Change from baseline to EOT | 79 | –1.0 (10.2) | 22 | 4.2 (14.7) |

EOT, end of treatment.

microbiologic response was achieved in nearly all participants in the MITT (tedizolid, 92.9%; comparator, 100.0%) and microbiologically evaluable populations (tedizolid, 98.1%; comparator, 100.0%; Fig. S3, Supplemental Digital Content 6, http://links.lww.com/INF/E243).

## DISCUSSION

Results from this randomized, single-blind, global phase 3 trial suggest the safety and efficacy of tedizolid is comparable to active comparators for the treatment of ABSSSIs in adolescents 12 to <18 years of age. The study population included 120 participants from several geographic regions. Most participants (70%–85%) in both treatment groups were diagnosed with cellulitis/erysipelas or major cutaneous abscess. Consistent with previous reports for ABSSSIs, most infections with documented Gram-positive pathogens were caused by *S. aureus* (≥85% in both treatment groups), and nearly all *S. aureus* isolates (98%) were susceptible to tedizolid.[4] The second most frequent causative pathogen was *S. pyogenes*, and all isolates were susceptible to tedizolid.

Overall, tedizolid was well tolerated and had a low rate of TEAEs, most of which were mild in severity. No participants were overdosed. The serious TEAEs experienced by a single participant in the tedizolid group who discontinued treatment were not considered drug related but were consistent with disseminated staphylococcal infection. The incidences of reported AEs and drug-related AEs were lower in the adolescent tedizolid group compared with adults with ABSSSI in the phase 3 adult studies.[23,24] Rates of drug-related serious AEs and discontinuations due to an AE were low in

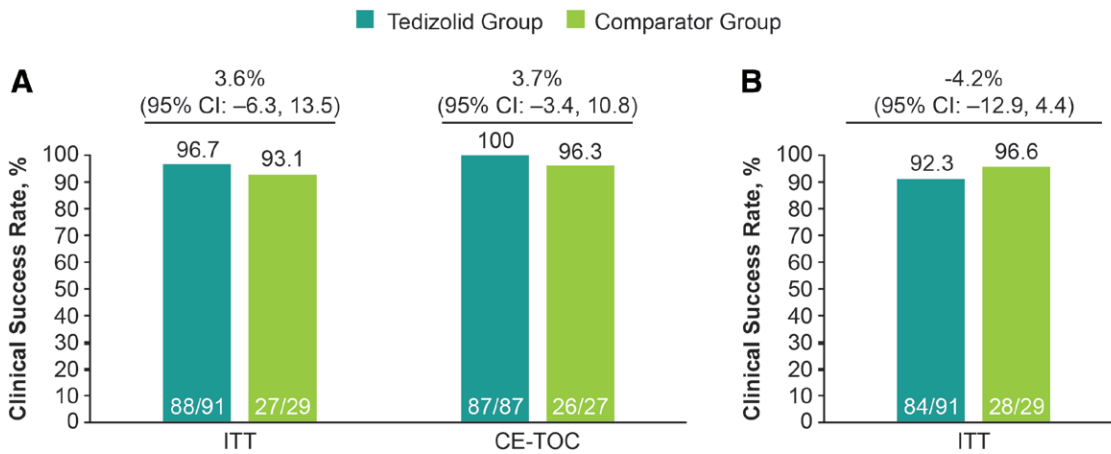


**FIGURE 1.** (A) Investigator-assessed clinical response at the TOC visit in the ITT and CE-TOC populations, and (B) programmatic early clinical response at 48–72 hours in the ITT population. CE indicates clinically evaluable; ITT, intention-to-treat; TOC, test of cure. full color online

the adolescent population and similar to rates observed in adults. The differences in safety results are likely due to the generally better health and lower rates of comorbidities in adolescents compared with adults. No new safety signals were identified in adolescents compared with adults. Hematologic toxicity has been previously reported in adults with linezolid, another oxazolidinone-class antibacterial agent.[30,31] However, in this study, no clinically significant differences were observed between treatment groups in change from baseline through the TOC visit for hematologic parameters, including absolute neutrophil count, leukocyte count, platelet count, and hemoglobin. These results are consistent with previous phase 2 and 3 clinical trials of tedizolid in adults, in which low incidences of reduced platelet counts and reduced absolute neutrophil counts were observed with tedizolid therapy.[24,32,33]

Observed efficacy was high for both tedizolid and comparator groups in this adolescent population. Rates of clinical response and microbiologic eradication within the tedizolid group were >90%, and the treatment groups had comparable efficacy across all endpoints and study populations. The high rates of clinical success with tedizolid are consistent with previous phase 3 studies conducted in adults.[23,24]

A limitation of this study was the small population size. The objective was to determine the safety of tedizolid; therefore, this study was not powered for inferential statistics and no hypothesis testing was planned for the efficacy endpoints, although clinical and microbiologic response rates appeared high and similar between groups. The population size in this phase 3 trial was consistent with the smaller population included in most recent phase 3 trials in children with ABSSSIs and is based on regulatory guidance that supports extrapolation of efficacy from adult clinical trials in the context of a formal evaluation of pharmacokinetics and safety in children.[34–36]

In summary, tedizolid was well tolerated in adolescents and TEAE rates were comparable to those previously observed in adults.[23,24] No new safety concerns were identified in the adolescent population. Efficacy rates for tedizolid were high and similar to those of comparators. Overall, these results suggest that tedizolid is a well-tolerated and effective treatment option for adolescents with ABSSSIs, particularly those with *S. aureus*-susceptible strains.

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