NDA 205435
NDA 205436

TEDIZOLID PHOSPHATE
FOR THE TREATMENT OF

ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

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ADVISORY COMMITTEE BRIEFING MATERIALS:
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TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

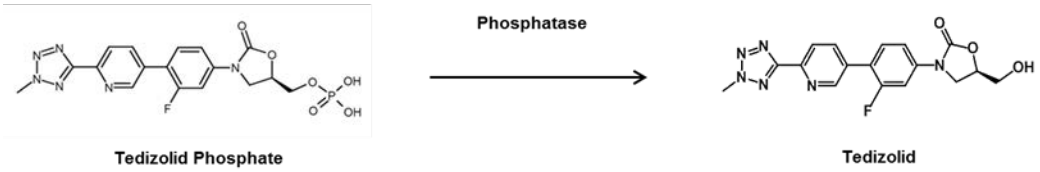
Abbreviation	Definition
°C	Degrees Centigrade
°F	Degrees Fahrenheit
ABSSSI	Acute bacterial skin and skin structure infection
AD	Agar dilution
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from Time 0 to infinity
AUC_{0-24}	Area under the concentration-time curve from Time 0 to 24 hours
BID	Twice a day
BMI	Body mass index
Caco-2	Human colonic carcinoma cells
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CE	Clinically evaluable
CE-EOT	Clinically Evaluable at End of Therapy
CE-PTE	Clinically Evaluable at Post-Therapy Evaluation
cfr	Chloramphenicol/florfenicol resistance gene
Cfr	Methyltransferase protein encoded by *cfr* gene
CFU	Colony-forming unit
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
cm^2	Square centimeter
CoNS	Coagulase-negative staphylococci
CRF	Case report form
cSSSI	Complicated skin and skin structure infections
CV	Coefficient of variation
Cyt-oxidase	Cytochrome c-oxidase
e-CRF	Electronic case report form
ECDC	European Center for Disease Prevention and Control
EMA	European Medicines Agency
EOT	End of therapy
EU	European Union
FA	Free acid
*f*AUC	Area under the free concentration-time curve
FDA	Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
FRS	Faces rating scale
GAIN	Generating Antibiotic Incentives Now (US Congressional Act of 2011)
ICH	International Conference on Harmonisation
IC_{50}	Half maximal inhibitory concentration
INN	International Nonproprietary Names
IP	Intraperitoneal
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent to treat
IV	Intravenous
LDHase	Lactate dehydrogenase
LFU	Late follow-up
LLN	Lower Limit of Normal
LRSA	Linezolid-resistant *Staphylococcus aureus*
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor

Abbreviation	Definition
MBC	Minimum bactericidal concentration
ME	Microbiologically Evaluable
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration against 50% of the isolates
MIC_{90}	Minimum inhibitory concentration against 90% of the isolates
microITT	Microbiological Intent to Treat
mm	Millimeter
MRCoNS	Methicillin-resistant coagulase-negative staphylococci
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MSCoNS	Methicillin-susceptible coagulase-negative staphylococci
N1	Number of patients in a specified category (unless otherwise specified)
n	Number of patients in a specific category (unless otherwise specified)
N	Number of patients in a specified analysis set (unless otherwise specified)
NaBGase	N-acetyl-beta-hexosaminidase
NDA	New Drug Application
No.	Number
PAE	Postantibiotic effect
PA-SME	Postantibiotic sub-MIC effect
PD	pharmacodynamic
PK	pharmacokinetic (adjective) or pharmacokinetics (singular noun)
PTC	Peptidyl transferase center
PTE	Post-therapy evaluation
PVL	Panton-Valentine leukocidin toxin
QD	Once daily
QIDP	Qualified Infectious Disease Product
rRNA	Ribosomal ribonucleic acid
SA	Substantially abnormal
SAR	Structure-activity relationship
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SME	Sub-MIC effect
SPA	Special Protocol Assessment
TEAE	Treatment-emergent adverse event
TR-700	Microbiologically active moiety of TR-701 or TR-701 FA prodrug
TR-701	Disodium phosphate salt prodrug of TR-700
TR-701 FA	Free acid phosphate prodrug of TR-700
TR-701/FA	Disodium phosphate salt prodrug of TR-700 or free acid phosphate prodrug of TR-700
US	United States
USAN	United States Adopted Names (Council)
VRE	Vancomycin-resistant enterococci
VREfa	Vancomycin-resistant *E. faecalis*
VREfm	Vancomycin-resistant *E. faecium*
VSE	Vancomycin-susceptible enterococci
VSEfa	Vancomycin-susceptible *Enterococcus faecalis*
VSEfm	Vancomycin-susceptible *Enterococcus faecium*
WBC	White blood cell

1 EXECUTIVE SUMMARY

Tedizolid phosphate (TR-701 FA) is a novel oxazolidinone prodrug that is rapidly converted in vivo by phosphatases to the microbiologically active antibiotic tedizolid (TR-700) (Figure 1).

Figure 1 Tedizolid Phosphate Conversion to Tedizolid



In this briefing book, tedizolid phosphate is used when reference is made to either the disodium salt (TR-701) or the free acid form (TR-701 FA). Trius Therapeutics (Trius), a wholly owned subsidiary of Cubist Pharmaceuticals, Inc. (Lexington, Massachusetts), submitted 2 New Drug Applications (NDA) for tedizolid phosphate to the FDA on 21 October 2013, one for the tablet formulation of tedizolid phosphate (NDA 205435) and one for the intravenous (IV) formulation (NDA 205436) for treatment of acute bacterial skin and skin structure infections (ABSSSI).

The proposed indication for tedizolid phosphate is treatment of ABSSSI (including cases with concurrent bacteremia) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus, Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus anginosus* Group (including *Streptococcus anginosus, Streptococcus intermedius* and *Streptococcus constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates).

The Anti-Infective Drugs Advisory Committee will evaluate the data derived from two pivotal Phase 3 clinical studies: TR701-112 and TR701-113. Both studies were randomized, double-blind, active-controlled trials comparing tedizolid phosphate to linezolid for the treatment of ABSSSI. Both studies were conducted under Special Protocol Assessments (SPA) with the FDA. This briefing book also reviews the safety findings in TR701-112 and TR701-113 and supportive data from the overall tedizolid phosphate development program.

1.1 Proposed Role for Tedizolid Phosphate in the Treatment of ABSSSI

The majority of ABSSSI are caused by Gram-positive pathogens such as *S. aureus* (including MRSA) and *S. pyogenes*. The indication includes clinical syndromes such as cellulitis, major abscesses, and wound infections. The benefit of systemic antimicrobial therapy is clearly established in cellulitis and wound infections. Clinicians agree that more severe or larger abscesses, abscesses in specific locations, such as the face and neck, abscesses in debilitated patient populations, or abscesses surrounded by a significant area

of redness/cellulitis also require systemic antimicrobial therapy in addition to surgical drainage (Food and Drug Administration [FDA] Guidance ABSSSI 2013). A number of antimicrobial agents are available for the treatment of ABSSSI, but only a limited number of agents can be administered by intravenous (IV) and oral (PO) routes and have been approved for the treatment of ABSSSI due to drug-resistant Gram-positive pathogens.

The incidence of drug-resistant Gram-positive organisms such as MRSA has reached a point at which new therapeutic options are urgently needed. In addition, vancomycin effectiveness is declining (Pépin 2007). Other options for treating these increasingly resistant Gram-positive infections are limited by newly identified resistance and toxicity, as well as the need for parenteral administration (Boucher 2007; Butterfield 2009; Clark 2006; Corey 2009; Lavery 2001; Mangili 2005). In September 2009, the European Medicines Agency (EMA) published a report emphasizing the gap between infections due to drug-resistant bacteria and the development of new antibiotics. A November 2013 summary of data for antibiotic resistance in the European Union highlighted that MRSA remains above 25% in almost one fourth of countries surveyed (ECDC 2013). In the United States (US), Congress approved the Generating Antibiotic Incentives Now (GAIN) Act of 2012 to encourage the development of products to treat, prevent, detect, and diagnose antibiotic-resistant pathogens.

Currently, linezolid is the only approved agent for the treatment of ABSSSI due to MSSA and MRSA that allows an IV-to-PO switch option without necessitating a change in antibiotic. However, hematologic effects (including anemia, leukopenia, thrombocytopenia, or pancytopenia) have been reported in patients receiving linezolid, usually when administered for more than 14 days (Zyvox® U.S. Prescribing Information 2013). The frequency of linezolid-associated hematologic adverse events (thrombocytopenia and anemia) is known to vary depending on certain concurrent clinical factors in patients being treated with the antibiotic. Additional safety concerns with linezolid include the known reversible monoamine oxidase (MAO) inhibition, which required a labeled contraindication to the use of the antibiotic with interacting drugs (MAO inhibitors) and precautions with other drugs (SSRIs, SNRIs and other serotonergic agents) as well as tyramine-rich food products. In addition, sporadic cases of optic or peripheral neuropathy have been reported after prolonged administration of linezolid.

The medical need for an effective and safe oral and IV alternative to linezolid and other available therapies for the treatment of patients with Gram-positive ABSSSI is significant.

This application specifically focuses on tedizolid phosphate given once-daily for 6 days for the treatment of ABSSSI. Results from the clinical development program indicate that tedizolid phosphate is non-inferior to linezolid for the treatment of ABSSSI, and this comparable efficacy is obtained with a shorter and simpler course of therapy (once a day for 6 days versus twice a day for 10-14 days for linezolid).

The high potency of tedizolid allows for a low therapeutic dose and low systemic exposure, leading to a favorable therapeutic index. Overall safety profiles in phase 3 studies were similar for tedizolid phosphate compared to linezolid. Clinical and non-clinical data suggest that administration of tedizolid phosphate has a lower likelihood of

specific safety concerns than linezolid, including hematologic effects, neurotoxicity and MAO inhibition.

If approved, tedizolid phosphate would provide patients and their healthcare providers an effective, convenient and well-tolerated antibiotic that will permit an IV-to-oral switch option for the treatment of ABSSSI.

Future investigations will address the use of long-term administration of tedizolid phosphate, use in pediatric populations and in other indications. A clinical trial to investigate the safety and efficacy of tedizolid for the treatment of for nosocomial pneumonia and a pediatric development program are underway.

1.2 Overview of the Tedizolid Phosphate Clinical Development Program

Tedizolid phosphate is a member of the oxazolidinone class of antibacterial agents, which are protein synthesis inhibitors. Oxazolidinones bind to the peptidyl transferase center (PTC) of the 50S ribosomal subunit and inhibit the initiation phase of translation (Shinabarger 1999).

1.2.1 Microbiology

Profiling and surveillance studies demonstrated that, as expected for an oxazolidinone, the spectrum was largely limited to Gram-positive organisms and overlapped that of linezolid. Tedizolid demonstrated potent activity against staphylococci (*S. aureus*, *Staphylococcus epidermidis*, other coagulase-negative staphylococci), enterococci (*Enterococcus faecium*, *E. faecalis* and other enterococci), and streptococci (*S. pyogenes*, *S. agalactiae*, Group C/F/G streptococci, *S. anginosus* Group streptococci, and *Streptococcus pneumoniae*).

Minimal bactericidal concentration (MBC) experiments conducted with tedizolid indicated a largely bacteriostatic mode of action in vitro, consistent with that of linezolid.

There was a low potential for the spontaneous development of resistance to tedizolid (mutation frequencies less than 10^{-10}) among target pathogens including *S. aureus* (MSSA and MRSA), enterococci (VSE and VRE), and β-hemolytic streptococci.

Tedizolid demonstrates cross-resistance to linezolid-resistant strains that carry a chromosomal mutation. Tedizolid-resistant chromosomal mutants emerged during serial passage in a subset of *S. aureus* and *E. faecium* strains but not until after 20 passages. Unlike linezolid, tedizolid retains activity against isolates that carry the mobile chloramphenicol/florfenicol resistance (*cfr*) gene, which leads to resistance to multiple classes of drugs (Long 2006; Smith 2008).

1.2.2 Tedizolid Pharmacokinetics

Tedizolid phosphate is a prodrug that is rapidly and extensively converted by phosphatases to tedizolid, the microbiologically-active moiety, after oral or IV administration. Only the pharmacokinetic profile of tedizolid is discussed further.

Single dose pharmacokinetic parameters are predictive of multiple doses. Steady-state concentrations are achieved within 3 days and indicate minimal drug accumulation of approximately 30% following multiple once-daily oral or IV administration as predicted by half-life of approximately 12 hours. Tedizolid follows linear pharmacokinetics.

Peak plasma tedizolid concentrations are achieved within approximately 3 hours after oral administration of tedizolid phosphate. Oral bioavailability is high (>80%) indicating no dosage adjustment is required for oral versus IV administration.

Tedizolid rapidly distributes into tissues, with a mean apparent volume of distribution at steady state of ~67 to 80 L. Tedizolid demonstrated moderate protein binding in human plasma of approximately 80%.

Population PK analysis estimates the magnitude of inter-individual variability in clearance (31% CV) and volume of distribution (13.4% CV) to be small and indicates relatively consistent PK will be observed across a wide range of patient intrinsic factors. Further, there was no clinically significant change in the PK profile of tedizolid when administered to adolescent or elderly subjects, subjects with hepatic or renal impairment, or with or without food. A single daily 200 mg dose of IV or oral tedizolid phosphate for 6 days is proposed for all patients.

Tedizolid penetrates into the interstitial space fluid of subcutaneous adipose and skeletal muscle tissues, resulting in exposures in these compartments similar to free drug exposure in plasma. Tedizolid significantly concentrates in pulmonary epithelial lining fluid and alveolar macrophages, ~41-fold and 20-fold respectively, relative to free plasma concentrations.

1.2.3 Tedizolid Phosphate Dose Selection

Tedizolid phosphate's favorable PK profile with low intersubject variability and low accumulation over time allowed selection of the lowest effective and safe dosage evaluated. In a Phase 2 dose-ranging study, doses of 200, 300, and 400 mg tedizolid phosphate once daily for 5 to 7 days were generally safe, well tolerated, and demonstrated similar efficacy. As a result, 200 mg once daily was selected as the lowest effective dose for further development in ABSSSI. No dose adjustment is anticipated for age, sex, race, BMI, and comorbidities, or for the transition from IV-to-oral treatment.

An important landmark of the development program is the establishment of a fixed 6-day duration of therapy thus avoiding unnecessarily prolonged treatment, reducing the potential for safety issues or the selection of resistant bacteria, and improving compliance to therapy. This is a notable improvement over the standard 7- to 14-day courses used for other agents.

1.2.4 Tedizolid Phosphate Clinical Studies

The Sponsor completed 19 tedizolid phosphate clinical studies during the development program, including 2 Phase 3 studies in the targeted indication. The Phase 3 studies for tedizolid phosphate were implemented based on evolving regulatory guidelines at the

time of clinical study design and input from the FDA and the Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom). In addition, both Phase 3 studies were conducted under a SPA with the FDA. Table 1 provides an overview of the Phase 2 and Phase 3 studies conducted with tedizolid phosphate.

Table 1 Overview of Phase 2 and Phase 3 Tedizolid Phosphate Studies

Study No. and Phase	Dose and Regimen	Purpose	Subjects Enrolled/ Planned
Phase 2 Studies			
TR701-104	Oral 200, 300, or 400 mg tedizolid phosphate once daily; for 5-7 days	Clinical and microbiological response, safety, population PK	192/180
TR701-126	Oral 200 mg tedizolid phosphate once daily for 6 days	Safety and exploratory skin lesion measurement methods	200/200
Phase 3 Studies			
TR701-112	Oral 200 mg tedizolid phosphate once daily for 6 days or 600 mg linezolid twice daily for 10 days	Efficacy, safety, population PK in the treatment of ABSSSI	667/658
TR701-113	IV to oral 200 mg tedizolid phosphate once daily for 6 days or IV to oral 600 mg linezolid twice daily for 10 days	Efficacy, safety, population PK in the treatment of ABSSSI	666/658

1.3 Efficacy Findings in Phase 3 Studies TR701-112 and TR701-113

1.3.1 TR701-112

Study TR701-112 was a non-inferiority, global, multicenter, randomized, double-blind, double-dummy, active-controlled study in adult patients with ABSSSI that evaluated the efficacy and safety of oral tedizolid phosphate 200 mg once daily for 6 days versus oral linezolid 600 mg every 12 hours for 10 days. The protocol was designed under a SPA prior to the issuance of draft FDA guidance on ABSSSI studies in August 2010.

Tedizolid phosphate was statistically non-inferior to linezolid for the primary efficacy outcome of early clinical response of cessation of lesion spread and apyrexia at the 48 to 72 Hour Visit in the ITT Analysis Set. Early clinical response at the 48 to 72 Hour Visit was observed in 79.5% of patients in the tedizolid phosphate group and 79.4% of patients in the linezolid group in the ITT Analysis Set (treatment difference 0.1%; 95% confidence interval [CI]: -6.1%, 6.2%). The lower limit of the 95% CI was greater than -10%, which was the predefined requirement for non-inferiority.

The results from an analysis defining an early clinical response as $\geq$20% reduction in lesion size (same as the primary endpoint from TR701-113) showed that the response rates are similar in the tedizolid phosphate (78.0%) and linezolid (76.1%) groups, (treatment difference 1.9%; 95% confidence interval [CI]: -4.5%, 8.3%), demonstrating non-inferiority.

Clinical response at the End of Therapy (EOT) Visit (defined programmatically from signs and symptoms reported on the eCRF) was observed in a similar percentage of patients in the tedizolid phosphate and linezolid groups in the Intent to Treat (ITT) Analysis Set (69.3% and 71.9%, respectively; treatment difference -2.6%; 95% CI: -9.6%, 4.2%) and in the Clinically Evaluable at EOT (CE-EOT) Analysis Set (80.2% and 81.1%, respectively; treatment difference -0.9%; 95% CI: -7.7%, 5.4%). The lower limit of the 95% CI was greater than -10% for clinical response at the EOT Visit in the ITT and CE-EOT Analysis Sets.

Investigator assessments of clinical success at the Post-therapy Evaluation (PTE) Visit were similar in the tedizolid phosphate and linezolid groups in the ITT Analysis Set (85.5% and 86.0%, respectively; treatment difference -0.5%; 95% CI: -5.8%, 4.9%) and in the CE-PTE Analysis Set (94.6% and 95.4%, respectively; treatment difference -0.8%; 95% CI: -4.6%, 3.0%). The lower limit of the 95% CI was above -10% for this outcome measure for both the ITT and CE-PTE Analysis Sets.

The microbiological response at the PTE Visit by key baseline pathogen from the primary ABSSSI site or blood culture showed that >85% of patients had a favorable response for all Gram-positive aerobes reported at baseline, including the most common pathogens, *S. aureus* and *S. pyogenes*.

1.3.2 TR701-113

Study TR701-113 was also a non-inferiority, global, multicenter, randomized, double-blind, double-dummy, active-controlled trial that evaluated treatment with tedizolid phosphate 200 mg IV with the option of an oral switch to once daily for 6 days versus IV with optional oral linezolid 600 mg every 12 hours for 10 days in patients with ABSSSI.

Regulatory guidance evolved during the development time period between Study TR701-112 and Study TR701-113. The primary endpoint in Study TR701-113 was rendered consistent with the October 2013 FDA guidance, in agreement with the FDA.

The primary outcome was early clinical response at 48-72 hours after the first dose of study drug in the ITT Analysis Set where a responder was defined as ≥20% reduction in lesion size in the ITT Analysis Set. The primary efficacy analysis showed that the early clinical response at the 48 to 72 Hour Visit was observed in 85.2% of patients in the tedizolid phosphate group and 82.6% of patients in the linezolid group in the ITT Analysis Set (treatment difference 2.6%; 95% CI: -3.0%, 8.2%). The lower limit of the 95% CI was greater than -10%, which was the predefined requirement for non-inferiority. Based on this result, tedizolid phosphate was non-inferior to linezolid for the primary efficacy outcome of early clinical response.

Clinical response at the EOT Visit (defined programmatically from sign and symptom data on the eCRF) was observed in a similar percentage of patients in the tedizolid phosphate and linezolid groups in the ITT Analysis Set (87.0% and 88.0%, respectively; treatment difference -1.0%; 95% CI: -6.1%, 4.1%) and in the CE-EOT Analysis Set

(89.5% and 93.6%, respectively; treatment difference -4.1%; 95% CI: -8.8%, 0.3%). The lower limit of the 95% CI was greater than -10% for clinical response at the EOT Visit in the ITT and CE-EOT Analysis Sets.

Investigator assessments of clinical success at the PTE visit were similar in the tedizolid phosphate and linezolid groups for Investigator assessments of clinical response at the PTE Visit in the ITT Analysis Set (88.0% and 87.7%, respectively; treatment difference 0.3%; 95% CI: -4.8%, 5.3%). The lower limit of the 95% CI was above -10% for this outcome measure.

The microbiological response at the PTE Visit by key baseline pathogen showed that >87% of patients had a favorable response for all Gram-positive aerobes reported at baseline, including the most common pathogens, *S. aureus* and *S. pyogenes*.

1.3.3 Concordance between Early and Late Endpoints

A concordance analysis of the early response at 48-72 hours (defined as ≥20% reduction in lesion size) and clinical success at the PTE visit (Day 18-25) was conducted for data pooled across both treatment groups and studies. Concordance between early clinical response and investigator's assessment at the PTE Visit was 80.5%. An early positive clinical response was found to be a good indicator of success at the later time point.

1.4 Overall Safety Experience with Tedizolid Phosphate

The complete tedizolid phosphate safety database comprises data from 1050 patients enrolled in Phase 2/3 clinical trials and 438 subjects (437 unique subjects) enrolled in Phase 1 clinical trials, including both PO and IV administration routes. Healthy volunteers and patients received tedizolid phosphate as single PO administrations of 50 to 1200 mg, multiple PO administrations of 200 to 400 mg per day for up to 21 days, single IV infusions ranging from 50 to 400 mg, and multiple IV infusions of 200 or 300 mg per day for up to 7 days. Table 1 shows the number patients treated with tedizolid phosphate in the indicated clinical phase of development and the duration of treatment.

Comparative safety data from the controlled Phase 3 studies with tedizolid phosphate and the active comparator linezolid showed a comparable adverse event profile. Table 2 shows a comparison of adverse events from the tedizolid phosphate Phase 3 studies. The occurrence of treatment emergent adverse events (TEAE)s, severe TEAEs, serious TEAEs, TEAE leading to drug discontinuation and TEAE with the outcome of death were similar between the tedizolid phosphate 200 mg per day treated patients compared to the linezolid 1200 mg per day treated patients in the Phase 3 studies in the development program.

Table 2. Comparison of Adverse Events from Tedizolid Phosphate Phase 3 Studies

Category	Tedizolid Phosphate (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Treatment-Emergent Adverse Events	283 (42.7)	286 (43.2)
Severe Treatment-Emergent Adverse Events	13 (2.0)	13 (2.0)
Serious Treatment-Emergent Adverse Events	12 (1.8)	13 (2.0)
TEAE Leading to Study Drug Discontinuation	3 (0.5)	6 (0.9)
TEAE with Outcome of Death	2 (0.3)	1 (0.2)

Note: Missing severity is categorized as severe. Note that the Phase 3 protocol design precluded withdrawal from the study due to a TEAE since patients were to complete all study assessments even if study drug was discontinued.
Abbreviations: N=Number of subjects in the Safety Analysis Set; n=Number of subjects in the specified category; TEAE=treatment-emergent adverse event.

In the Phase 3 studies, the overall incidence of TEAEs was similar between the tedizolid phosphate-treated group and the linezolid-treated group (42.7% versus 43.2%, respectively) with the exception of Gastrointestinal Disorders (GI TEAEs) by system organ class (SOC) observed. For this TEAE class, the incidence of GI TEAEs with tedizolid phosphate treatment versus linezolid was lower (16.0% versus 23.0%, respectively).

Adverse events with a ≥2% incidence in the tedizolid phosphate group were nausea, headache, abscess, diarrhea, vomiting, and cellulitis; and in the linezolid group were nausea, headache, vomiting, diarrhea, abscess, cellulitis, and dizziness.

1.4.1 Special Safety Topics

Hematologic parameters of hemoglobin and platelet counts remained generally stable during the course of treatment in the tedizolid phosphate clinical studies. When elevated at baseline, leukocyte counts tended to decrease during the course of treatment of the infections as an expected clinical response to a favorable course of the infection. Overall, patients treated with tedizolid phosphate demonstrated a lower incidence of decreased platelet counts compared to those treated with linezolid in the development program.

No clinical metabolic drug-drug interaction studies were conducted, as in vitro studies indicated no potential for oxidative metabolism drug-drug interactions. Tedizolid is a reversible, nonspecific inhibitor of MAO in vitro. Unlike linezolid, no in vivo effects were predicted for tedizolid since therapeutic peak plasma concentrations were well below its IC_{50} for monoamine oxidase A (MAO_A) inhibition. In 2 clinical studies and 2 nonclinical rodent models (at multiples of up to ~30-fold of the anticipated therapeutic exposure of tedizolid phosphate), where linezolid demonstrated an interaction with MAO,

tedizolid phosphate showed no such effect suggestive of MAO inhibition. Overall, results of tedizolid phosphate nonclinical and clinical studies suggest the probability of adverse consequences due to MAO inhibition is unlikely with clinical use of tedizolid phosphate.

From the published clinical and postmarketing experience, optic and peripheral neuropathy AEs are associated with prolonged treatment with linezolid. These risks were investigated in tedizolid phosphate clinical studies. Routine neurologic examinations were performed in all studies, targeted examinations in selected studies, and extensive specialized ophthalmic and neurologic examinations were performed in Phase 1 studies TR701-101 and TR701-110. A systematic review of neurologic TEAEs was performed using a standardized MedDRA query (SMQ) for peripheral neuropathy on the integrated safety database. Results from analysis of Phase 3 studies showed that 10 (1.5%) patients in the tedizolid phosphate group and 6 (0.9%) in the linezolid group experienced at least 1 TEAE in peripheral neuropathy SMQ. Similarly, an integrated analysis for potential events suggesting optic nerve disorders was performed using an SMQ. There were 2 TEAEs reported in the tedizolid phosphate group and 1 TEAE in the linezolid group in this SMQ. Most identified events were mild, generally transient, with a spontaneous resolution; none were considered to be evidence of optic or peripheral neurotoxicity on expert medical review.

1.4.2 Mortality

Three deaths were reported in the development program. All 3 fatalities occurred in the setting of significant patient comorbidities and other confounding factors. Two deaths occurred in patients after completing treatment with tedizolid phosphate, and one death after completing linezolid treatment. Table 3 summarizes the cases in more detail.

Table 3. Adverse Events Leading to Death

Patient ID	Age	Sex	Country	Treatment	Preferred Term	AE Onset Date (Relative Study Day)	Date of Death
TR701-112-342-605	86	M	Peru	Tedizolid Phosphate 200 mg	Septic shock	(b) (6) (55)	(b) (6)
TR701-113-444-230	33	F	South Africa	Linezolid 1200 mg	Meningitis tuberculous	(b) (6) (14)	(b) (6)
TR701-113-451-258	84	M	South Africa	Tedizolid Phosphate 200 mg	Myocardial infarction	(b) (6) (11)	(b) (6)

1.4.3 Other Special Safety Studies

A thorough QT study showed no clinically meaningful increases in QT interval at the 200 mg or 1200 mg (supratherapeutic exposure) doses of tedizolid phosphate. No clinical

signal for QT prolongation or other clinically important ECG changes were observed during comprehensive electrocardiogram monitoring during the Phase 3 studies.

1.5 Benefit/Risk Conclusion

Tedizolid phosphate administered once daily for 6 days was non-inferior to linezolid administered twice daily for 10 days for the treatment of ABSSSI, as shown by the primary efficacy outcome of early clinical response at 48 - 72 hours after the first dose of study drug. These findings were supported by several secondary efficacy outcome analyses of responses at later time points.

Availability of both IV and oral formulations of antibacterial agents allows for an IV-to-PO switch when clinically indicated. No dosage adjustment is required for tedizolid phosphate between IV and PO administration. Comparable efficacy obtained with a shorter and simpler course of therapy for tedizolid phosphate (once a day for 6 days, versus 10 – 14 days of twice daily dose regimen for linezolid) is a significant advantage to patients.

The overall safety profile of tedizolid phosphate is similar to that of linezolid with potential clinical advantages in terms of reduced MAO interactions, hematologic toxicity and neurotoxicity. No dosage adjustment is required for tedizolid phosphate when treating patients with renal impairment, including those on hemodialysis, or for patients with severe hepatic impairment.

The availability of tedizolid phosphate will provide patients and their healthcare providers with a generally well-tolerated and effective antibiotic with an IV-to-oral switch option and a 6-day course of once daily therapy for the treatment of ABSSSI.

2 PROPOSED ROLE FOR TEDIZOLID PHOSPHATE IN THE TREATMENT OF ABSSSI

2.1 Summary

- Infections with resistant Gram-positive organisms in ABSSSI are increasing in number in both the hospital and community settings in the US
- Resistance to existing antibiotics for the treatment of ABSSSI is emerging as a serious clinical problem; tedizolid has a different molecular target than many other available agents for these pathogens and thus retains antimicrobial activity against organisms such as MRSA and VRE
- The availability of a new, well-tolerated and effective antibiotic option that allows for transition from once daily IV-to-PO therapy at the same dose for the treatment of ABSSSI across different patient types (eg, elderly, renal- and hepatic-impaired patients) is an important clinical advantage
- The lack of in vivo nonclinical and clinical evidence for tedizolid-mediated MAO inhibition suggests that tedizolid phosphate can be co-administered with MAO inhibitors, serotonergic agents, as well as food products with hugh tyramine content

2.2 ABSSSI

A number of antimicrobial agents are available for the treatment of ABSSSI, an indication that includes clinical syndromes such as cellulitis, major abscesses, and wound infections. The majority of ABSSSI infections are caused by Gram-positive pathogens such as *S. aureus* (including MRSA) and *S. pyogenes*. The benefit of systemic antimicrobial therapy is clearly established in cellulitis and wound infections and clinicians agree that more severe or larger abscesses in specific locations, in debilitated populations, or when surrounded by a significant area of redness/cellulitis also require systemic antimicrobial therapy in addition to surgical drainage (FDA Guidance ABSSSI 2013).

Although MRSA infections were previously restricted primarily to hospitals and other health care facilities, a new MRSA clone (USA300) has spread throughout the US, replacing MSSA as the dominant cutaneous pathogen in the community setting. The proportion of hospital-onset MRSA infections reached 64.4% in the US intensive care units in 2003 (Klevens 2006). Although most commonly associated with ABSSSI, community-acquired MRSA (CA-MRSA) also can produce serious or life-threatening infections such as pneumonia, neonatal sepsis, osteomyelitis, and bacteremia (Adem 2005; Boucher 2008; Miller 2005). Of particular concern is the diagnosis of rapidly developing cutaneous infections resulting from CA-MRSA in patients with no established healthcare risk factor. This organism appears to be spreading by casual contact or through contaminated fomites (Boucher 2007; Stryjewski 2008). Although with a lesser prevalence, new community-based clones of MRSA also have surfaced in many parts of the world outside of the US (Byrd 2009; Reyes 2009; Tinelli 2009; Tong 2008). Increasing resistance (Diep 2008) of these newly identified CA-MRSA clones also is of concern. Recent reports indicate that CA-MRSA (USA300) has spread into the hospital setting and may be the dominant cutaneous pathogen in hospitals in this decade (Klein 2009; Klevens 2007; Popovich 2009). Availability of both IV and PO formulations of antibacterial agents allows for an IV-to-PO switch in route of administration that facilitates transition from inpatient to outpatient treatment that commonly occurs in medical practice for the treatment of severe forms of ABSSSI.

2.3 Antibiotic Resistance

The incidence of drug-resistant Gram-positive organisms such as MRSA is increasing while vancomycin effectiveness is declining (Pépin 2007). Other options for treating these infections are limited by newly-identified resistance, drug-specific toxicities, and the need for parenteral administration (Boucher 2007; Butterfield 2009; Clark 2006; Corey 2009; Lavery 2001; Mangili 2005). In September 2009, the EMA published a report highlighting the gap between infections due to drug-resistant bacteria and the development of new antibiotics. Further, a recent (ECDC 2013) summary of data on antibiotic resistance in the EU highlighted that MRSA remains above 25% in almost one fourth of countries surveyed. In the US, Congress approved the GAIN Act of 2012 to encourage the development of products to treat, prevent, detect, and diagnose antibiotic-resistant pathogens. A Qualified Infectious Disease Product (QIDP) designation was established as part of legislation to expedite this development. FDA granted tedizolid

phosphate (PO and IV formulations) QIDP designation for ABSSSI on 03 January 2013. Clearly, in addition to antibiotic stewardship programs, new antibacterial drugs, especially those available as an oral formulation, are needed urgently to treat infections due to drug-resistant Gram-positive bacteria in both hospital and community settings.

Linezolid resistant strains, although low in frequency, are already found globally. The US-based LEADER surveillance program has shown that linezolid resistance rates ranged from 0.14 to 0.45% across all species, between 2004 and 2012 (Mendes 2014). However outbreaks of linezolid-resistant strains have been documented in the US and internationally (Bonilla 2010; Sánchez Garcia 2010; Cai 2012). Currently, the majority of the strains are resistant due to chromosomal mutations in the genes encoding 23S rRNA or the ribosomal proteins L3 and L4. However, a novel resistance mechanism first emerged clinically in 2005. This Cfr mechanism leads to resistance to multiple classes of ribosome-targeting antibiotics, including linezolid, clindamycin, streptogramins, phenicols, 16-member-ring macrolides, and pleuromutilins (Long 2006; Smith and Mankin 2008). This mechanism of resistance is particularly troubling due to its association with transposons and plasmids, raising the possibility of rapid spread. This spread can potentially be driven by use of many different drugs, including clindamycin and linezolid (Shaw 2011; Shen 2013). Of note, environmental, veterinary, and clinical isolates of *Staphylococcus*, *Streptococcus*, and *Enterococcus* species with the *cfr* gene have been identified with increasing frequency from multiple sites in North America, South America, Europe, and Asia. Several outbreaks of linezolid-resistant, *cfr*-positive strains have been reported (Bonilla 2010; Sánchez Garcia 2010; Cai 2012). Due to differences in structure, the antimicrobial activity of tedizolid is not impacted by the Cfr resistance mechanism.

3 MICROBIOLOGICAL CHARACTERISTICS OF TEDIZOLID

3.1 Summary

- Tedizolid phosphate is a novel oxazolidinone prodrug that is rapidly converted in vivo by phosphatases to the microbiologically active antibiotic tedizolid
- Tedizolid is a protein synthesis inhibitor that interacts with the 50S subunit of the bacterial ribosome
- Tedizolid has activity against Gram-positive bacteria including MRSA and *S. pyogenes*. Although a bactericidal mode of action in vitro was observed with some isolates of staphylococci and *S. pneumoniae* by MBC analysis, tedizolid is bacteriostatic in vitro against the majority of *S. aureus* isolates, enterococci, and other streptococci as shown by minimum bactericidal concentration (MBC) and time kill analysis
- Tedizolid has a low frequency of spontaneous resistance development
- Tedizolid demonstrates cross-resistance to linezolid-resistant strains with chromosomal mutations. Tedizolid retains activity when linezolid resistance is caused by the *cfr* gene

3.2 Overview of Tedizolid Antibacterial Activity

Tedizolid is an antimicrobial agent with potent activity against Gram-positive pathogens, and is consistently more potent in vitro than linezolid, including activity against resistant strains, such as MRSA and vancomycin-resistant enterococci (VRE). The activity of tedizolid against target pathogens was consistent across several profiling studies conducted during development and in a large surveillance study conducted in the US and EU.

Collectively the data from clinical studies support the inclusion of the following organisms in the indications for tedizolid phosphate:

- *S. aureus* (including MRSA and MSSA strains)
- *S. haemolyticus*
- *S. lugdunensis*
- *S. anginosus* Group (including *S. anginosus, S. intermedius,* and *S. constellatus*)
- *S. pyogenes*
- *S. agalactiae*
- *E. faecalis* (vancomycin-susceptible isolates)

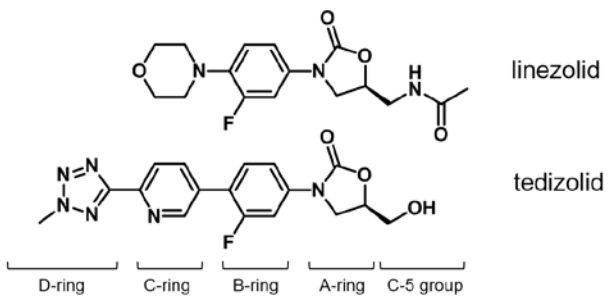
In addition, preclinical data support inclusion of the following organisms for which tedizolid has demonstrated in vitro activity but for which clinical significance is unknown:

- *E. faecalis* (vancomycin-resistant strains)
- *E. faecium* (including vancomycin-resistant strains)
- *S. epidermidis* (including methicillin-resistant strains)

3.3 Mechanism of Action

Tedizolid and linezolid (Figure 2) are members of the oxazolidinone class of antibacterial agents. The enhanced potency of tedizolid relative to linezolid is due to additional ribosomal interactions provided by the pyridine (C-ring) and tetrazole (D-ring) moieties. The hydroxymethyl group attached to the oxazolidinone A-ring of tedizolid has a smaller footprint than the acetamide-containing group of linezolid, and therefore binding of tedizolid to the ribosome is not impacted by Cfr methylation (Locke 2010a).

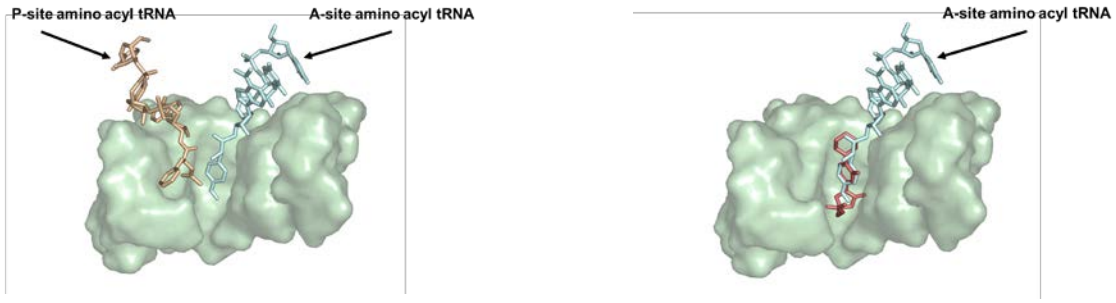
Figure 2. Tedizolid and Linezolid Chemical Structures



The oxazolidinones are protein synthesis inhibitors that act by binding to the peptidyl transferase center (PTC) of the 50S ribosomal subunit and inhibit the initiation phase of translation (Shinabarger 1999). A portion of the PTC with both the acceptor site tRNA (A-site) and peptidyl site tRNA (P-site) is shown in Figure 3A. Figure 3B shows that linezolid (in pink) substantially overlaps with the A-site tRNA, thus preventing binding of the tRNA (Leach 2007). Docking and modeling studies of tedizolid demonstrate a similar mode of binding (see Figure 3).

Figure 3. Linezolid Binds to the Peptidyl Transferase Region of the Ribosome

A B



3.4 Antibacterial Spectrum of Activity

Bacterial susceptibility to tedizolid was assessed using standard susceptibility testing methods (MIC and disk diffusion zone diameter assays) subject to established Clinical and Laboratory Standards Institute (CLSI) quality control ranges for reference strains. Profiling and surveillance studies demonstrated that, as expected for an oxazolidinone antibiotic, the spectrum was largely limited to Gram-positive organisms and overlapped that of linezolid. Tedizolid demonstrated potent antimicrobial activity against staphylococci (*S. aureus*, *S. epidermidis*, and other coagulase-negative staphylococci), enterococci (*E. faecium*, *E. faecalis* and other enterococci), and streptococci (*S. pyogenes*, *S. agalactiae*, Group C/F/G streptococci, *S. anginosus* Group streptococci, and *S. pneumoniae*). A summary of the weighted average MIC values from multiple preclinical studies for tedizolid and linezolid for selected pathogens is shown in Table 4.

Table 4. Summary of Weighted Average MIC Values for Tedizolid and Linezolid for Selected Pathogens

Organism	Total No. Studies	n	Tedizolid Weighted Average		Linezolid Weighted Average		Ratio MIC_{90} Linezolid / Tedizolid
			MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	
MSSA	6	1389	0.28	0.46	1.90	2.19	4.76
MRSA	10	1588	0.33	0.52	2.00	2.72	5.23
MSCoNS	4	165	0.29	0.44	1.18	2.35	5.34
MRCoNS	4	319	0.27	0.37	1.08	2.36	6.38
VS *E. faecalis*	5	329	0.35	0.61	1.77	2.00	3.27
VR *E. faecalis*	3	106	0.47	0.50	1.89	1.89	3.78
VS *E. faecium*	5	202	0.41	0.60	2.00	2.55	4.25
VR *E. faecium*	4	161	0.39	0.45	1.82	2.47	5.49
S. pyogenes	3	268	0.17	0.35	0.72	1.44	4.11
S. agalactiae	3	127	0.25	0.38	1.53	1.53	4.03
PSSP	2	91	0.25	0.25	1.00	1.58	6.32
PISP	2	63	0.25	0.35	1.00	1.41	4.03
PRSP	2	89	0.25	0.25	1.00	1.61	6.44

Abbreviations: MIC_{50}=minimum inhibitory concentration against 50% of the isolates; MIC_{90}=minimum inhibitory concentration against 90% of the isolates; MRCoNS=methicillin-resistant coagulase-negative staphylococci; MRSA=methicillin-resistant *S. aureus*; MSCoNS=methicillin-susceptible coagulase-negative staphylococci; MSSA=methicillin-susceptible *S. aureus;* VS =vancomycin-susceptible; VR=vancomycin-resistant; PSSP=penicillin-sensitive *S. pneumoniae*; PISP=penicillin-intermediate *S. pneumoniae*; PRSP=penicillin-resistant *S. pneumoniae*; n=number of pathogens tested.

Multicenter surveillance studies conducted in the US and Europe in 2011 to 2012 demonstrated that antibiotic activity was similar in bacterial strains from different geographic regions or with differing resistance phenotypes. Most importantly, tedizolid maintained the same level of activity against MRSA and VRE as it did against MSSA and VSE, and similarly maintained activity against other important resistance phenotypes associated with the target pathogens. The MIC of tedizolid was determined for a collection of MRSA strains from 14 different epidemiologically characterized groups that included USA300, USA400, USA500, USA800, and EMRSA15. Tedizolid was highly potent against all MRSA strain types, including those resistant to other classes of drugs (Thomson 2013).

The data in Table 5 show that tedizolid has similar activity against isolates from the 2011/2012 US and EU surveillance studies and the Phase 2 and 3 clinical studies. During tedizolid phosphate clinical trials, no pathogens were observed with MIC values greater than 0.5 µg/ml for all species, including MRSA. No *E. faecium* or methicillin-resistant coagulase-negative staphylococci (MRCoNS) strains were observed in clinical trials.

Table 5. Susceptibility of Surveillance (2011/2012, US and Ex-US) and Phase 2/3 Clinical Study Isolates

Organism	U.S. Surveillance MIC_{90} (µg/mL)	Ex-U.S. Surveillance MIC_{90} (µg/mL)	All Clinical Studies MIC_{90} (µg/mL)
MSSA	0.25	0.5	0.5
MRSA	0.5	0.5	0.25
MSCoNS	0.25	--	--
MRCoNS	0.25	--	--
VS *E. faecalis*	0.5	0.5	--
VS *E. faecium*	0.5	0.5	--
S. pyogenes	0.25	0.25	0.25
S. agalactiae	0.25	0.25	--
S. anginosus Group	--	--	0.25

Note: Dashes indicate no value.
Abbreviations: MIC_{90}=minimum inhibitory concentration against 90% of the isolates; MRCoNS=methicillin-resistant coagulase-negative staphylococci; MRSA=methicillin-resistant *S. aureus*; MSCoNS=methicillin-susceptible coagulase-negative staphylococci; MSSA=methicillin-susceptible *S. aureus;* VS=vancomycin-susceptible; US=United States

Anaerobic Bacteria

While not being considered for product labeling, tedizolid also demonstrates potent activity against Gram-positive anaerobic bacteria. Tedizolid was active against *Peptostreptococcus* spp. including *Peptostreptococcus anaerobius* (MIC_{90} = of 0.5 µg/mL), *Peptostreptococcus micros* (MIC_{90} = 0.5 µg/mL), and *Peptostreptococcus* spp. (MIC_{90} = 0.25 µg/mL). Tedizolid was shown to be active against multiple *Clostridium* spp. including *Clostridium difficile* (MIC_{90} value of 1 µg/mL), *Clostridium perfringens* (MIC_{90} values from 0.25 to 2 µg/mL), and *Clostridium* spp. (non-*perfringens*; MIC_{90} of 0.25 µg/mL).

For Gram-negative anaerobic bacteria, tedizolid MIC values were generally higher than those observed for Gram-positive anaerobes.

MBC Analyses

Bactericidal activity is commonly evaluated by measuring the in vitro MBC or performance in a time-kill kinetic analysis. The MBC is the concentration at which a 99.9% or greater (≥3-log) decrease in viable bacteria is observed relative to the concentration of the starting inoculum. An agent is generally considered bactericidal if the observed MBC values are ≤4-fold higher than the observed MIC values. As an oxazolidinone, it was anticipated that tedizolid would exhibit largely bacteriostatic activity similar to that described for the in-class comparator linezolid. Assessment of bactericidal activity was limited to Gram-positive pathogens (staphylococci, enterococci, and streptococci) for which tedizolid has demonstrated potent in vitro activity.

Although tedizolid is a largely bacteriostatic agent, MBC:MIC ratios were indicative of bactericidal activity for the majority of *S. pneumoniae* isolates (25/33), for a subset of *S.aureus* isolates (27/82), and for 1 *E. faecium* isolate (1/34) (Table 6). Tedizolid MBC activity was consistent with that of a bacteriostatic agent (MBC:MIC ratios >4) for *S. pyogenes*, *S. agalactiae,* and the majority of *S. aureus* (55/82) and enterococci (67/68). Similar results were observed with linezolid across the evaluated species and phenotypes.

Table 6. Summary of MBC Data (µg/mL) for Tedizolid and Linezolid

Organism (number of strains)	Drug	MBC range	MBC_{50}	MBC_{90}	MBC:MIC ratio ≤4 (%)
S. aureus (82)	TZD	0.5 - >32	4	16	27 (32.9)
	LZD	2 - >8	>8	>8	41 (51.9)
Coagulase-negative staphylococci[a] (32)	TZD	2 - >32	16	32	0 (0.0)
	LZD	2 - >8	>8	>8	3 (10.0)
E. faecalis (34)	TZD	>8 - >32	>16	>16	0 (0.0)
	LZD	>8 - >8	>8	>8	0 (0.0)
E. faecium (34)	TZD	1 - >16	>16	>16	1 (2.9)
	LZD	4 - >8	>8	>8	1 (3.0)
S. pneumoniae (33)	TZD	0.5 - 16	1	2	25 (75.8)
	LZD	2 - >8	4	8	24 (72.7)
Beta-hemolytic streptococci[b] (22)	TZD	>4 - >16	>8	>16	0 (0.0)
	LZD	>8 - >8	>8	>8	0 (0.0)

Abbreviations: LZD=linezolid; MBC=minimum bactericidal concentration; MIC=minimum inhibitory concentration; TZD=tedizolid.
[a]Consisted of 3 unspeciated coagulase-negative staphylococci, 15 *S. epidermidis*, 4 *S. haemolyticus*, 5 *Staphylococcus hominis*, 1 *Staphylococcus lugdenensis*, and 4 *Staphylococcus saprophyticus*
[b]Consisted of 11 *S. agalactiae* and *11 S. pyogenes*

In summary, tedizolid was comparable to linezolid as measure in the MBC assay, with both exhibiting a largely bacteriostatic mode of action against the evaluated Gram-positive pathogens. However, results indicative of a bactericidal mode of action were observed with some isolates of staphylococci and *S. pneumoniae* by MBC analysis.

3.5 Panton-Valentine Leukocidin Toxin

The expression of Panton-Valentine Leukocidin toxin (PVL) has been linked to CA-MRSA, the most prevalent pathogen of ABSSSIs. The impact of this virulence factor on the activity of tedizolid and linezolid against *S. aureus* was evaluated by broth microdilution assay. The MIC values for tedizolid and linezolid were determined for 50 clinical isolates that varied in the presence or absence of genes responsible for the production of PVL. There was no apparent difference in activity of either tedizolid or linezolid based on PVL status assessed by MIC_{50} or MIC_{90} values. PVL status did correlate with methicillin-resistance; 96% of PVL-positive strains were methicillin-resistant compared with 16% of PVL-negative strains.

3.6 Post-antibiotic Effect

Post-antibiotic effect (PAE) is the ability of an antimicrobial agent to suppress bacterial growth after exposure to suprainhibitory concentrations of the agent and removal of the antibiotic. For some drugs, such as aminoglycosides, long PAE values are thought to contribute to clinical efficacy (Sharma 2002). For drugs with shorter PAE values (eg, 1 hr) such as the oxazolidinones linezolid and tedizolid, the contribution to clinical efficacy would be predicted to be less significant.

3.7 Oxazolidinone Resistance Mechanisms and Structure-activity Relationships

3.7.1 Resistance Mechanism Classes

Oxazolidinone resistance is attributed to conformational changes to the PTC binding site in the 50S ribosomal subunit. Resistance mechanisms fall into two main classes:

- **Chromosomal mutations.** Point mutations in the genes encoding 23S rRNA and ribosomal proteins L3 (*rplC*) and L4 (*rplD*) lead to reduced susceptibility to all oxazolidinones. 23S rRNA mutations have the potential to confer higher levels of oxazolidinone resistance as they compose or are adjacent to the actual binding site, unlike L3 and L4, which are more distant and provide structural support to the 23S rRNA. Because multiple copies of 23S rRNA genes are present in the genome, a gene dosage effect is observed whereby MIC values increase with an increasing proportion of mutant alleles. Fitness costs can be associated with increasing number or severity of 23S rRNA, L3, and L4 mutations. To spread clinically, strains with these chromosomal mutations must arise independently and/or disseminate clonally.

- **Cfr (chloramphenicol/florfenicol resistance).** The plasmid-borne *cfr* gene encodes a methyltransferase that adds a methyl group to 23S rRNA base A2503 of the oxazolidinone binding site. This methylation creates a steric clash that results in resistance to 6 structurally unrelated classes of drugs that bind to the PTC, including linezolid, but not tedizolid due to structural differences. The *cfr* gene can be spread horizontally, has a low fitness cost, and has been found in a wide variety of Gram-positive species and some Gram-negative organisms.

Chromosomal mutations and Cfr resistance mechanisms are not mutually exclusive and strains can possess any number or combination thereof. The effect of simultaneously occurring mutations is typically additive.

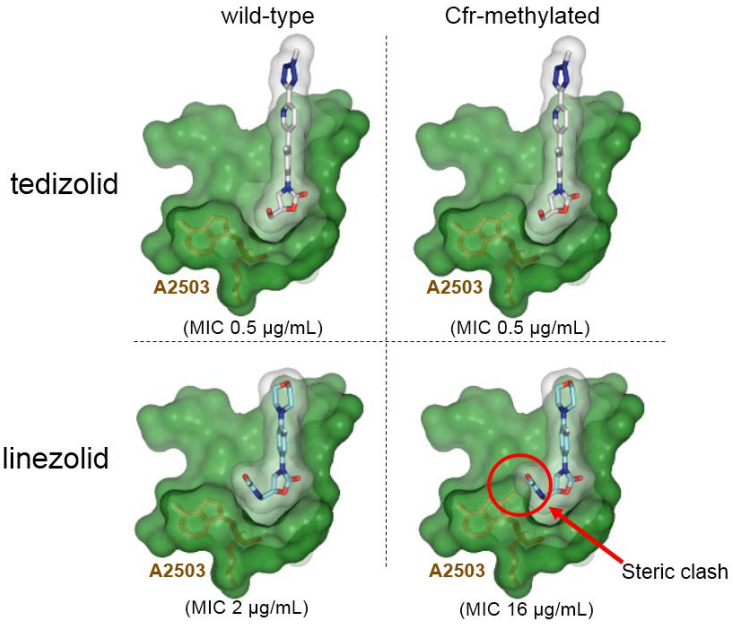
3.7.2 Activity of Tedizolid vs. Linezolid Against Strains with Reduced Susceptibility to Oxazolidinones

The trend of increased antimicrobial potency of tedizolid against wild-type strains is also conserved against strains possessing all classes of linezolid resistance mechanisms. The presence of a methyltetrazole D-ring substituent on tedizolid largely accounts for its increased activity against all strain types likely due to additional interactions with 23S

rRNA bases comprising the PTC binding site. Structure-activity relationship (SAR) studies have demonstrated that the acetamide containing A ring C-5 substituent found on linezolid (and most other clinically-developed oxazolidinones to date) is intrinsically ~2-fold more potent than the hydroxymethyl found on tedizolid (Locke 2010a). This suggests that much of the antimicrobial activity of tedizolid is due to the unique methyltetrazole D-ring and pyrid-3-yl C-ring structural features.

In the case of Cfr-based linezolid resistance, the hydroxy component of the A ring C-5 group of tedizolid is advantageous from a potency perspective because of its smaller size compared to the acetamide of linezolid. The methyl group added by Cfr to 23S rRNA base A2503 results in a steric clash with the acetamide group of linezolid that reduces its antimicrobial potency by 4- to 8-fold (Locke 2010a). However, docking studies demonstrate that tedizolid can be readily accommodated in the methylated binding site, providing a structural rationale for why tedizolid retains antimicrobial activity against *cfr*-positive strains and why it did not select for retention of the *cfr* gene in a serial passage experiment (Locke 2010a, Locke 2012). The structural impact of Cfr methylation of A2503 and MIC values for *S. aureus* ATCC 29213 with and without the *cfr* gene are shown in Figure 4.

Figure 4. Methylation of 23S rRNA Base A2503 by Cfr Creates a Steric Clash with Linezolid but not Tedizolid



MIC values for tedizolid against a variety of laboratory-derived *S. aureus* possessing all major classes of oxazolidinone resistance mechanisms are shown in Table 7 (Locke 2009; Locke 2010a). Consistent with MIC trends against wild-type strains, tedizolid MIC values of 0.25 or 0.5 µg/mL against these three isogenic *S. aureus* parent strains are 4-fold lower than linezolid. 23S rRNA, L3 and L4 ribosomal mutations increased tedizolid MIC values ≥2-fold in all cases except for the single copy G2447T 23S rRNA mutation. Such chromosomal mutations occurring in strain backgrounds with starting

tedizolid MIC values of 0.5 µg/ml would then become tedizolid-resistant based on a proposed breakpoint of 0.5 µg/ml. However for more highly tedizolid-susceptible strain backgrounds (ATCC 33591) with starting MIC values of 0.25 µg/ml, a single chromosomal mutation conferring a 2-fold MIC shift results in a mutant strain that would still be tedizolid-susceptible.

Against *S. aureus* strains possessing the *cfr* gene alone, linezolid MIC values in these backgrounds increased to the typical values of 8 or 16 µg/mL also observed in clinical strains, although some clinical *cfr*-positive isolates with linezolid MIC values of 4 µg/mL have been collected in recent years (Mendes 2014). The corresponding tedizolid MIC values against these *cfr*-only strains remain susceptible at 0.25 or 0.5 µg/mL. If the *cfr* gene is present in a strain background that also has a chromosomal mutation resulting in a tedizolid MIC value of ≥1 µg/mL (see 29213 L3 Gly155Arg) then the resulting strain would be tedizolid-resistant (Table 7).

Table 7. Tedizolid and Linezolid MIC Values for Isogenic Laboratory-derived *S. aureus* with Defined Resistance Mechanisms

Strain Background	Resistance Mechanism(s)[a]	MIC (µg/mL)/Susceptibility[b]	
		Tedizolid	Linezolid
RN4220 (MSSA)	-	0.5/S	2/S
	cfr	0.5/S	8/R
ATCC 29213 (MSSA)	-	0.5/S	2/S
	cfr	0.5/S	16/R
	cfr + L3 (Gly155Arg)	1/R	32/R
	L3 (ΔPhe127-His146)	2/R	8/R
	23S (G2447T x1)	0.5/S	4/S
	23S (T2500A x1)	1/R	4/S
	23S (G2447T x5) + L3 (Gly152Asp)	8/R	128/R
ATCC 33591 (MRSA)	-	0.25/S	1/S
	L3 (Gly155Arg)	0.5/S	2/S
	L4 (Lys68Gln)	0.5/S	2/S
	23S (G2576T x3)	2/R	16/R

[a]23S rRNA mutations (*E. coli* numbering) are given along with the corresponding mutant allele copy number. Ribosomal protein L3 and L4 mutations are given using *S. aureus* numbering.
[b]Tedizolid susceptibility classifications are based on a proposed 0.5 µg/mL breakpoint

3.8 Assessment of Resistance Potential

The overall potential for resistance development for tedizolid was evaluated through analysis of linezolid surveillance data and through laboratory experiments measuring spontaneous mutation frequencies and the emergence of reduced susceptibility through serial passage.

3.8.1 Linezolid Surveillance Trends

The low potential for resistance development for the oxazolidinone class observed in laboratory experiments with linezolid is consistent with clinical observations. Ongoing surveillance studies show that the frequency of resistance to linezolid remains low after over 14 years of clinical use. Between 2004 and 2012 the US-based LEADER (Linezolid

Experience and Accurate Determination of Resistance) surveillance program has tested over 54,000 staphylococci, streptococci, and enterococci isolates and linezolid resistance rates have ranged between 0.14% and 0.45% annually (Jones 2007; Jones 2008; Jones 2009; Farrell 2009; Farrell 2011; Flamm 2012; Mendes 2014).

The majority of linezolid-resistant surveillance isolates possess chromosomal mutations. Studies have demonstrated cross-resistance with this type of mutation, therefore these strains would likely have elevated tedizolid MIC values in excess of the proposed 0.5 µg/mL breakpoint (Locke 2009, Locke 2010b). While initially identified in European veterinary isolates in the late 1990s, the first clinical *cfr*-positive strains were isolated in 2005. Since then *cfr*-positive linezolid-resistant strains have emerged and spread globally, consistent with the mobile nature of the plasmid-borne gene. Outbreaks of *cfr*-positive strains have been observed in the US (Bonilla 2010) and Spain (Morales 2010). *cfr*-positive strains have accounted for upwards of 16% of the linezolid-resistant isolates collected as part of the LEADER surveillance program. Because tedizolid retains activity in the presence of Cfr methylation it has the potential remain active against this subset of the oxazolidinone-resistant isolates.

3.8.2 Spontaneous Mutation Frequency

The frequency of spontaneous mutations that confer reduced susceptibility to tedizolid and linezolid was evaluated in several Gram-positive pathogens. These data showed that there is a low potential for resistance to develop spontaneously to tedizolid among target pathogens including *S. aureus* (MSSA and MRSA), enterococci (VSE and VRE), and beta-hemolytic streptococci (Table 8) (Locke 2009; Jones 2009). Linezolid and tedizolid both have low mutation frequencies in *S. aureus* although tedizolid values were approximately 16-fold lower, when measurable.

Table 8. Summary of Tedizolid Spontaneous Mutation Frequencies for Gram-positive Pathogens

Isolate	Antibiotic Selection	Mutation Frequency
S. aureus ATCC 29213 (MSSA)	2× MIC	1.1×10^{-10}
	4× MIC	$<4.5\times10^{-10}$[a]
S. aureus ATCC 33591 (MRSA)	2× MIC	1.9×10^{-10}
S. aureus USA300-0114 (MRSA)	4× MIC	$<4.5\times10^{-10}$[a]
E. faecalis ATCC 29212 (VanS)	4× MIC	$<5.7\times10^{-11}$
E. faecalis ATCC 700802 (VanR)	4× MIC	$<6.1\times10^{-11}$
S. pyogenes ATCC 49399	4× MIC	$<1.0\ x10^{-10}$
S. agalactiae ATCC 13813	4× MIC	$<3.1\times10^{-10}$

Abbreviations: VanR=vancomycin-resistant; VanS=vancomycin-susceptible
[a]No growth; mutation frequency calculated as <1/inoculum

3.8.3 Serial Passage

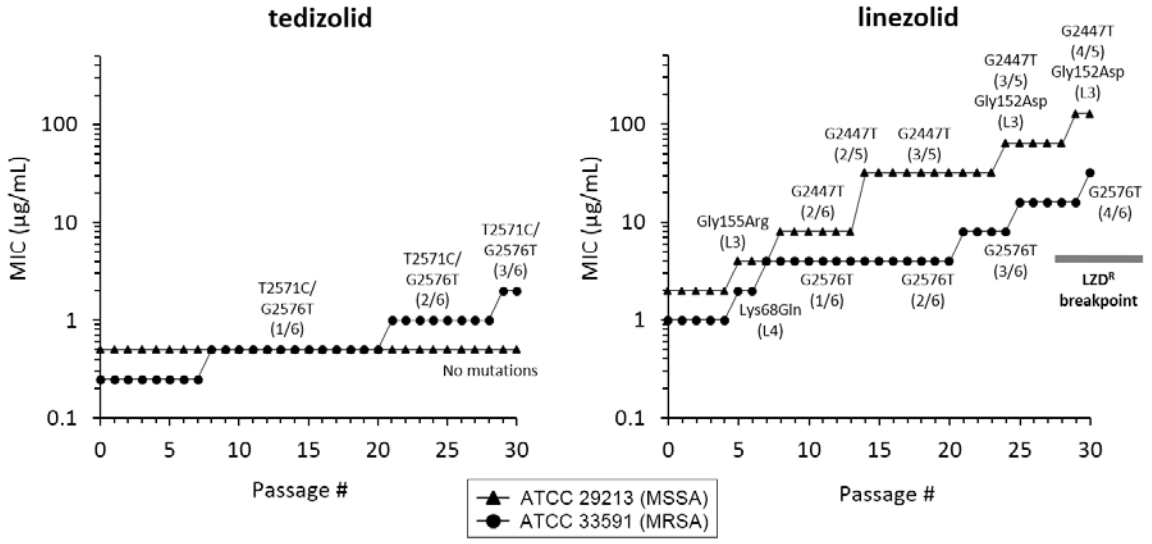
Previous studies have shown that the molecular determinants of spontaneous linezolid resistance are largely limited to mutations in the 23S rRNA of the ribosome. Most bacteria have multiple copies of the rRNA genes, which include the gene for 23S rRNA,

including *S. aureus* (5-6 copies), *S. epidermidis* (5-6 copies), *E. faecalis* (4 copies) and *E. faecium* (5-6 copies). The effect of the number of copies of mutated 23S rRNA alleles relative to wild-type alleles has been systematically examined. It is clear that an increased copy number or proportion of mutated alleles is correlated with increases in the linezolid MIC, especially for the G2576T mutation. This phenomenon has been seen in laboratory isolates as well as in clinical isolates (Besier 2008, Ruggero 2003). Once a strain contains a single copy of the G2576T allele, selection of more highly resistant strains is possible in both the laboratory and the clinic due to gene conversion. In this process, the mutated 23S rRNA allele replaces the wild-type copy by recombination, which occurs at a higher frequency than spontaneous resistance. Through this process, higher levels of oxazolidinone resistance can be achieved.

Tedizolid-nonsusceptible mutants emerged during serial passage in studies with *S. aureus* and *E. faecium*, but not in streptococci. Mutants were successfully generated in two studies where a large starting inoculum was utilized (10^8 CFU/mL), and in a study using gradient plate methodologies (Locke 2009; Figure 5), in which the starting inoculum was significantly larger. For tedizolid, no change in MIC values was seen for one strain and 29 serial passages were necessary to change the MIC value greater than 4-fold. The initial event was a double mutant in one 23S rRNA allele (T2571C/G2576T), which was then propagated to additional alleles. In contrast, linezolid values continued to rise exceeding the breakpoint of 4 μg/mL for both strains of *S. aureus* used in this experiment. For linezolid, shifts in MIC values greater than 4-fold were observed in both strains after 7 or 21 serial passages.

Clinically, linezolid resistance rates have been low, consistent with the low frequency of overall resistance observed in the laboratory for the oxazolidinone class. However, continued exposure, as observed in serial passage experiments, resulted in organisms with high-level resistance to linezolid and multiple copies of the common G2576T or G2447T mutations in 23S rRNA. All laboratory mutants and clinical strains with an increase in MIC to tedizolid also showed an elevated MIC to linezolid while not all mutants and strains with an elevated linezolid MIC demonstrated an increase in the MIC of tedizolid. These data highlight the low potential for resistance development via chromosomal mutations for the oxazolidinone class of antibacterial agents even during prolonged exposure.

Figure 5. Gradient Plate Serial Passage and Mutant Characterization of ATCC 29213 and MRSA ATCC 33591 Strains in the Presence of Tedizolid and Linezolid



Notes: Mutations in 23S rRNA genes (*E. coli* numbering; proportion of mutant alleles indicated) or in ribosomal proteins L3 or L4 (*S. aureus* numbering) are given in the first passage that they were identified.

4 TEDIZOLID PHOSPHATE PHARMACOLOGY AND DOSE SELECTION FOR CLINICAL STUDY

4.1 Summary

- Tedizolid phosphate is rapidly converted in vivo by phosphatases to microbiologically active tedizolid
- Tedizolid's high potency allows for a low therapeutic dose that provides low systemic exposure leading to a high therapeutic index
- Tedizolid's favorable pharmacokinetic profile (linearity, modest accumulation, low inter-subject variability) also contributes to its high therapeutic index
- Clinical and nonclinical evidence suggest that the risks associated with myelosuppression, optic and peripheral neuropathy are very low for the 200 mg once daily 6-day regimen of tedizolid phosphate
- Clinical and nonclinical evidence suggest that the risk for clinically-meaningful MAO inhibition is unlikely at the proposed therapeutic dose
- Dose selection for tedizolid phosphate was supported by nonclinical studies, a Monte Carlo simulation, a Phase 1 and a Phase 2 study that showed the 200 mg dose provided an optimal efficacy/safety ratio for pivotal Phase 3 studies

4.2 Overview of Tedizolid Phosphate

4.2.1 General Toxicology

Multi-dose oral and IV toxicity studies identified bone marrow and gastrointestinal tract as target organs in rats and dogs. The hematopoietic effects were characterized by mild to moderate decreases in circulating red blood cells (RBC), white blood cells (WBC) and platelets and by bone marrow hypocellularity (myeloid, erythroid, and megakaryocytes) that was time- and dose-dependent. The GI effects after oral administration were manifested as decreased food intake and reduced body weight gain, effects on stool, emesis and, at high doses, degeneration and necrosis. The no-adverse effect level (NOAEL) for these changes occurred at overall plasma exposures of up to approximately 7-fold above the human therapeutic exposure level.

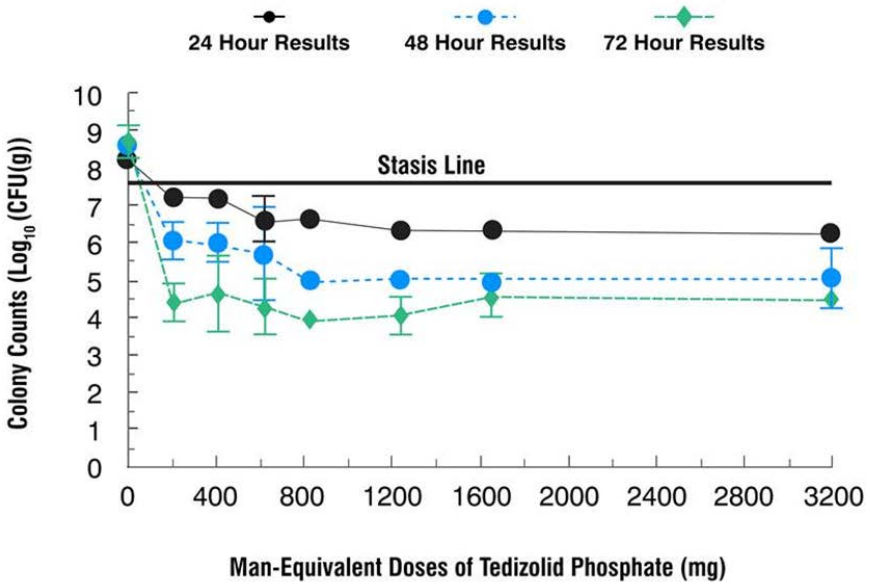
The outcomes of the nonclinical safety program, including safety pharmacology, genotoxicity, reproductive and developmental toxicity, immunotoxicity, phototoxicity, and neuropathology studies, support the safe use of tedizolid phosphate in patients at the intended therapeutic dose.

4.2.2 Nonclinical Pharmacodynamic Studies

A study in neutropenic mice inoculated in thigh muscle with a hospital-acquired MRSA isolate demonstrated that the pharmacodynamic index most closely linked with efficacy was the tedizolid area under the free concentration-time curve (AUC) over 24 hours divided by the MIC (*f*AUC/MIC ratio) (Louie 2011).

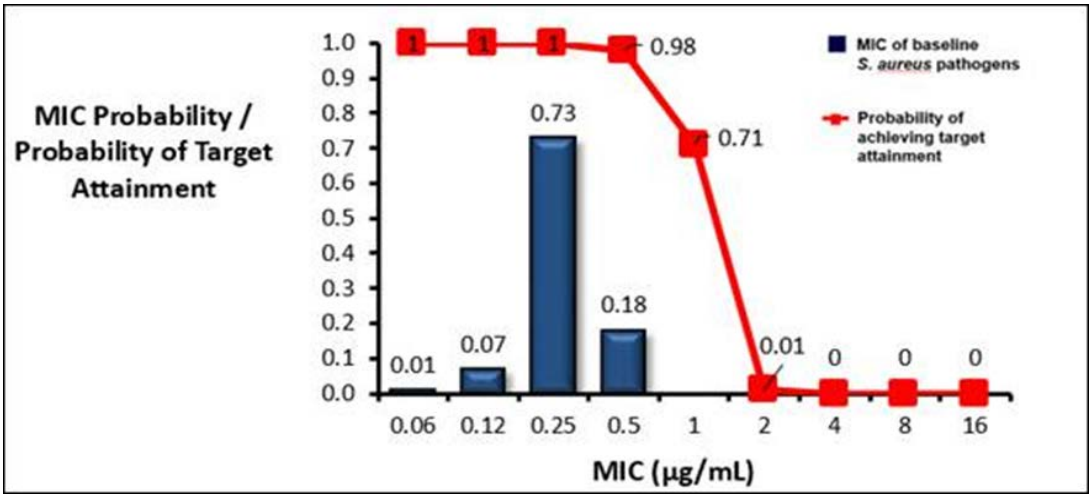
The dose-dependent response to tedizolid phosphate treatment was markedly enhanced (~25-fold on average) in nonneutropenic mice (Figure 6) (Drusano 2011). Effective doses of tedizolid phosphate produced greater efficacy when administered for longer durations (72 hours >48 hours >24 hours). It should also be noted that the maximal effect in the nonneutropenic group, was achieved at lowest dose tested that provided a human equivalent exposure of approximately 200 mg/day. An *f*AUC/MIC ratio of approximately 3 was calculated from the minimum (16-fold) enhancement of effect observed between nonneutropenic versus neutropenic mice (Lodise 2013).

Figure 6. Colony Counts (Colony Forming Units/g) of *S. aureus* in Thigh Tissue of Normal Mice



A Monte Carlo target attainment simulation was performed to estimate the probability of attaining a *f*AUC/MIC ratio of 3. The results of this simulation based upon human pharmacokinetic data are shown in Figure 7. For patients receiving oral 200 mg per day tedizolid phosphate, the probability of achieving the desired ratio is shown (red line) for specific MIC values (distribution based on clinical trial data shown in blue histogram). The simulated probabilities of target attainment at a MIC of ≥2 µg/mL approached 0. There is a high probability (>98%) of attaining the target measure in patients infected with bacterial isolates having MIC values of 0.5 µg/mL or less.

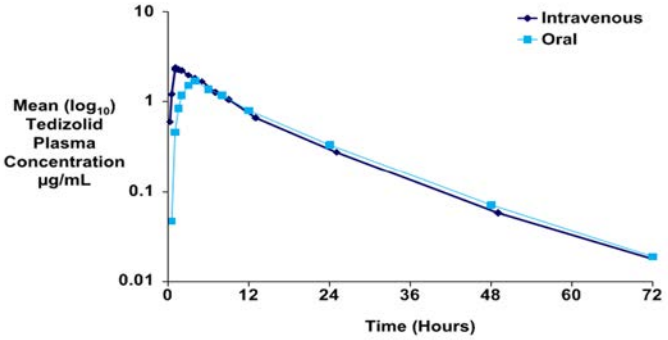
Figure 7. Monte Carlo Simulation of Target Attainment



4.2.3 Clinical Pharmacokinetics of Tedizolid Phosphate

Biopharmaceutical studies have demonstrated that the absolute oral bioavailability of tedizolid phosphate was high (>80%), indicating that the same dose is appropriate for both oral and IV administration (Figure 8).

Figure 8. Tedizolid Oral and IV Pharmacokinetics



Pharmacokinetic studies (PK) of tedizolid demonstrated linear kinetics with time, and that steady-state concentrations achieved within 3 days with modest drug accumulation (~30%). Although only a single daily 200 mg dose strength of IV or oral tedizolid phosphate for 6 days is proposed for all patients, PK exposure, in terms of C_{max} and AUC, increased with IV tedizolid doses from 100 mg to 400 mg or oral tedizolid doses from 200 mg to 1200 mg. The oral clearance (CL/F) and apparent volume of distribution values for tedizolid after tedizolid phosphate administration were independent of dose and duration of exposure.

Less than 1% of the tedizolid phosphate dose was excreted in urine as either tedizolid phosphate or tedizolid. Table 9 shows the mean tedizolid PK parameter values following single- and multiple-dose administration of tedizolid phosphate using oral or IV routes of administration. The tedizolid elimination half-life is ~12 hours for either IV or oral administration.

Table 9. Mean (SD) Tedizolid PK Parameters Following Single and Multiple Doses of 200 mg Tedizolid Phosphate

PK Parameter	Oral		IV	
	Single Dose	Steady State	Single Dose	Steady State
AUC[a] (µg · h/mL)	23.8 (6.8)	25.6 (8.4)	26.6 (5.2)	29.2 (6.2)
C_{max} (µg/mL)	2.0 (0.66)	2.2 (0.64)	2.3 (0.64)	3.0 (0.66)
C_{min} (µg/mL)	not applicable	0.44 (0.19)	not applicable	0.36 (0.09)
t_{max} (h)[b]	2.5 (1 – 8)	3.5 (1 – 6)	1.1 (0.9 – 1.5)	1.2 (0.9 – 1.5)
CL or CL/F (L/h)	6.9 (1.7)	8.4 (2.1)	6.4 (1.2)	5.9 (1.4)

Abbreviations: $AUC_{0-\infty}$=AUC from Hour 0 extrapolated to infinity based on the apparent terminal rate constant; AUC_{0-24}=AUC from Hour 0 to Hour 24.
[a]AUC is $AUC_{0-\infty}$ for single administration and AUC_{0-24} for multiple administrations.
[b]Median (minimum, maximum) presented for t_{max}. Source: TR701-124 for oral single administration, TR701-114 for oral steady-state, and TR701-107 Part B for IV administration.

Tedizolid rapidly distributes into tissues, with mean apparent volume of distribution at steady state of ~67 to 80 L. Tedizolid demonstrated moderate protein binding in human plasma in the range of 70% to 90%.

A clinical microdialysis study has shown that tedizolid penetrated into the interstitial space fluid of subcutaneous adipose and skeletal muscle tissue (regions relevant to the treatment of skin infections), resulting in exposures in these compartments similar to free drug exposure in plasma. In a separate study, tedizolid was shown to concentrate highly in pulmonary epithelial lining fluid and alveolar macrophages, ~41-fold and 20-fold relative to free plasma concentrations, suggesting that tedizolid may have utility for the treatment of lung infections.

Tedizolid is not metabolized to any extent in human liver microsomes; therefore oxidative metabolism is not a significant pathway for elimination. Sulfation is the primary elimination pathway that is unlikely to be influenced significantly by genetic factors. Following oral administration of [^{14}C] tedizolid phosphate, nearly 80% of the dose was excreted as the sulfate conjugate of tedizolid. Tedizolid accounted for <3% of radioactivity recovered in excreta, and no unchanged tedizolid phosphate was detected. Thus, the majority of elimination occurs via the liver, with 81.5% of the radioactive dose recovered in feces and 18.0% in urine. Other than tedizolid, which accounts for approximately 95% of the total radiocarbon AUC in plasma, there are no other significant circulating metabolites in humans. Table 10 shows the percentage of the administered dose of tedizolid phosphate, by metabolite, excreted in healthy subjects.

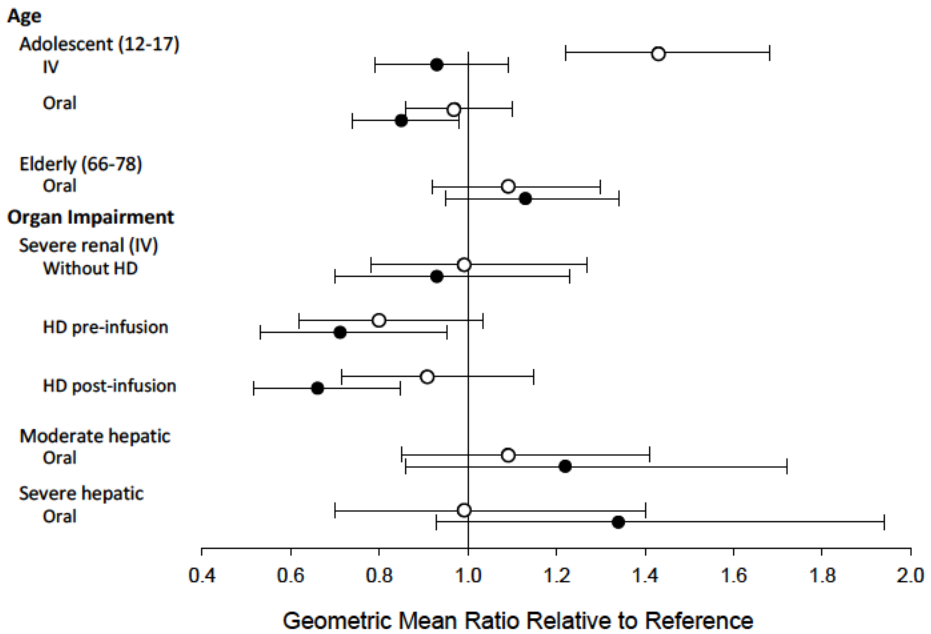
Table 10. Mean Metabolite Percent of Administered Dose of Tedizolid in Excreta (Study TR701-106)

Tedizolid Metabolite	Urine		Feces		Total	
	Mean	SD	Mean	SD	Mean	SD
Desmethyl tedizolid	1.1	0.7	ND	ND	1.1	0.7
Carboxy tedizolid	3.6	0.83	4.2	1.2	7.8	1.1
Tedizolid-sulfate	10.2	2.4	69.2	6.9	79.3	6.4
Tedizolid	1.1	0.4	2.0	0.5	3.0	0.8

Abbreviations: ND=not detected; SD=standard deviation (for N=6 subjects).

PK studies on the effect of intrinsic factors on the PK of IV or orally administered tedizolid phosphate showed that minor changes in exposure were observed in adolescents, elderly, or subjects with advanced renal or moderate or severe hepatic impairment. Hemodialysis had no significant impact on tedizolid PK. PK values were similar between sexes. There were no marked differences in tedizolid PK between Japanese and US subjects. Population PK analysis failed to identify any clinically significant patient covariates that affected tedizolid PK, including sex, race, markers of renal or hepatic function, and comorbidities such as obesity. No dosage adjustments are necessary in any of these special populations. Tedizolid phosphate has not been studied in pregnant or lactating women. Figure 9 shows the geometric mean ratios of tedizolid pharmacokinetic parameters in special population patients.

Figure 9. Geometric Mean Ratio and 90% Confidence Intervals for Tedizolid PK Parameters in Special Patient Population Studies



Abbreviations: AUC=area under the concentration-time curve from time zero to infinity; C_{max}=maximum concentration; Geometric mean ratio=(Geometric mean test)/(Geometric mean reference), where the test group is the special population; IV=intravenous; PK=pharmacokinetics
Note: Area under the concentration-time curve from Hour 0 extrapolated to infinity based on the apparent terminal rate constant (closed circles); maximum observed concentration (open circles).

Studies of extrinsic factors that may influence tedizolid PK showed no effect on the metabolism of selected cytochrome P450 (CYP) enzyme substrates, including time-dependent inhibition of CYP3A. The potential in vitro induction effects of tedizolid (up to 10 μM) on selected CYP isoforms were tested in human hepatocyte cultures using functional or transcriptional endpoints. Together with the metabolic stability data and inhibition data, these results suggest that significant drug-drug interactions based on oxidative metabolism are unlikely. In vitro studies demonstrated that tedizolid and tedizolid phosphate are unlikely to result in meaningful inhibition of P-gp, BCRP, OCT1, OCT2, OAT1, OAT3, OATP 1B1, or OATP 1B3 transporters.

4.2.4 Dose Selection

In Study TR701-104, oral doses of 200, 300, or 400 mg tedizolid phosphate once daily for 5 to 7 days (overall mean duration of treatment 6.4 dosing days [median 7.0 days]) were safe and well tolerated with fewer patients having adverse events (AE), especially gastrointestinal AEs, at the lowest dose of 200 mg (Table 11). There were no deaths or withdrawals of study drug due to AEs and no hematological findings were noted in this study. In addition, the Investigator's assessment of clinical success was consistently high across all dose groups.

Table 11. Study TR701-104: Summary of Treatment Emergent Adverse Events (Modified ITT Population)

	Tedizolid Dose		
	200 mg N = 63 %	**300 mg N = 63 %**	**400 mg N = 62 %**
Clinical Success	88.9	88.9	85.5
Any TEAEs	66.7	69.8	71.0
GI AEs	30.2	38.1	45.2

Abbreviations: MITT=modified intent to treat (all treated patients); TEAE=treatment emergent adverse event

No benefit in efficacy is observed at tedizolid phosphate doses above 200 mg. Thus, the lowest effective dose tested of tedizolid phosphate once daily was chosen as most appropriate for use in the Phase 3 studies for treatment for ABSSSI.

There is no evidence that longer treatment is needed for skin infections and from the principles of good antimicrobial stewardship a 6-day treatment regimen was selected as the optimal treatment duration to study for Phase 3. Relative to durations of 10 to 14 days, a 6-day course of therapy would be expected to have the following advantages: 1) improved safety (since there are less days of treatment), 2) decreased potential for the selection of resistant mutants, and 3) increased compliance. In addition, the results from the Phase 2 Study TR701-104 provided support for a 6-day course of therapy.

5 DESCRIPTION OF THE TEDIZOLID PHOSPHATE CLINICAL DEVELOPMENT PROGRAM

The development program for tedizolid phosphate 200 mg IV or oral once daily administration for the treatment of ABSSSI was designed to establish the safety, efficacy, and PK properties of tedizolid phosphate in comparison with linezolid to support global marketing authorizations. Nineteen tedizolid phosphate clinical studies were completed as described in Table 12.

Table 12. Overview of Tedizolid Phosphate Clinical Development Program

Study No. and Phase	Dose and Regimen	Purpose	Subjects Enrolled/ Planned
Phase 1 Studies			
TR701-101	Part A: single oral placebo or 200, 400, 600, 800, or 1200 mg tedizolid phosphate Part B: oral 200, 300, or 400 mg once-daily tedizolid phosphate, 600 mg twice-daily linezolid, or placebo for 21 days	Safety and PK Safety, tolerability, and PK	40/40 40/50[a]
TR701-102	Single oral 600 mg tedizolid phosphate	Microdialysis in subcutaneous adipose and skeletal muscle tissues	12/12
TR701-103	Single oral 600 mg tedizolid phosphate either after a high-fat meal or in fasting conditions	Food effect	12/12
TR701-105	Multiple oral 200 mg tedizolid phosphate or placebo and tyramine HCl (25 mg then escalated in 50-mg increments until TYR_{30} reached)	Safety, tolerability, and blood pressure response of tedizolid phosphate in combination with tyramine	39/30
TR701-106	Single oral 204 mg [^{14}C]- tedizolid phosphate containing 100 μCi ^{14}C	Safety, tolerability, PK, route of TR-701 excretion, tedizolid phosphate metabolic profile	6/6
TR701-107	A. Single ascending IV dose, placebo or 50 to 400 mg tedizolid phosphate B. Multiple ascending IV dose, placebo or 200 or 300 mg tedizolid phosphate once daily for 7 days C. Open-label bioavailability, 200 mg tedizolid phosphate oral and IV D. Venous tolerability, placebo or 200 mg tedizolid IV once daily for 3 days	Safety, tolerability, PK, absolute bioavailability, venous tolerability	A. 51/52 B. 21/20 C. 8/8 D. 10/10
TR701-108	Single oral tedizolid (as tedizolid phosphate or TR-701 (disodium salt of TR-701) equivalent to 150 mg of TR-700	Relative bioavailability, PK, safety, and tolerability	12/12
TR701-109	Single oral 200 mg tedizolid phosphate	Safety, tolerability, PK in elderly	28/28
TR701-110	Multiple oral 200 mg tedizolid phosphate once daily for 10 days	Safety and ophthalmic and neurologic assessment	72/72
TR701-111	Single oral or IV 200 mg tedizolid phosphate	Safety, tolerability, PK in adolescents	20/20

Table 12. Overview of Tedizolid Phosphate Clinical Development Program (*Continued*)

Study No. and Phase	Dose and Regimen	Purpose	Subjects Enrolled/ Planned
TR701-114	Multiple oral 200 mg tedizolid phosphate or placebo once daily for 5 days and 60 mg PSE on Day 5	Safety and blood pressure response of tedizolid phosphate in combination with PSE	18/18
TR701-115	Single oral 200 mg or 1200 mg tedizolid phosphate, 400 mg moxifloxacin, or placebo	Potential QTcF effects	48/48
TR701-119	Oral 200 mg tedizolid phosphate once daily for 3 days	Safety, PK, and disposition of tedizolid phosphate into pulmonary epithelial lining fluid and alveolar macrophages	20/20
TR701-123	Single IV 200 mg tedizolid phosphate	Safety and PK in advanced renal impairment with or without hemodialysis	24/24
TR701-124	Single oral 200 mg tedizolid phosphate	Safety and PK in moderate or severe hepatic impairment	32/32
Phase 2 Studies			
TR701-104	Oral 200, 300, or 400 mg tedizolid phosphate once daily for 5-7 days	Clinical and microbiological response, safety, pop PK	192/180
TR701-126	Oral 200 mg tedizolid phosphate once daily for 6 days	Safety and exploratory skin lesion measurement methods	200/200
Phase 3 Studies			
TR701-112	Oral 200 mg tedizolid phosphate once daily for 6 days or 600 mg linezolid twice daily for 10 days	Efficacy, safety, pop PK in the treatment of ABSSSI	667/658
TR701-113	IV to oral 200 mg tedizolid once daily for 6 days or IV to oral 600 mg linezolid twice daily for 10 days	Efficacy and safety in the treatment of ABSSSI	666/658
Studies Performed in Japan			
16101	Single 50 or 100 mg tedizolid phosphate IV, I 200 mg tedizolid phosphate IV/oral, or placebo	Safety, tolerability, PK, and absolute bioavailability	36/36
16102	IV or oral 200 mg tedizolid phosphate or placebo once daily for 7 days	Safety, tolerability, PK and intestinal flora evaluation	24/24

Note: TYR_{30}=the dose of tyramine required to raise systolic blood pressure by 30 mmHg:
Abbreviations: PSE=pseudoephedrine; QTcF=QT interval corrected for heart rate using Fridericia's formula
[a]An optional treatment arm of 10 subjects was not conducted.

5.1 FDA Guidance on the Tedizolid Phosphate Clinical Development Program

A summary of key FDA guidance to the Sponsor on the tedizolid phosphate Phase 3 pivotal trials is provided below:

- The trials were each conducted under a Special Protocol Assessment (SPA)
- The SPA for the first Phase 3 study (TR701-112) was issued before the release of the August 2010 draft ABSSSI guidance
- The SPA for the second Phase 3 study (TR701-113) was issued after the release of the August 2010 draft guidance(FDA Guidance ABSSSI 2010) and the study was designed to be consistent with this regulatory guidance
- After the initial SPA agreement for the second Phase 3 study (TR701-113), FDA permitted modification of the primary endpoint to be consistent with the final ABSSSI FDA Guidance in October 2013 with the original protocol-defined primary efficacy endpoint retained as an additional analysis (FDA Guidance ABSSSI 2013)

6 EFFICACY FINDINGS IN TR701-112 AND TR701-113

6.1 Summary

- Non-inferiority of tedizolid phosphate 200 mg once daily for 6 days vs linezolid 600 mg twice daily for 10 days was established for the primary efficacy endpoint of early clinical response at the 48-72 Hour Visit in both Phase 3 trials
- Results from analyses of the secondary endpoints, including clinical response at the EOT Visit and Investigator's assessment of clinical response at the PTE Visit, supported those for the primary endpoints in both TR701-112 and TR701-113

6.2 Study Design

Both Phase 3 studies were randomized, non-inferiority, global, multicenter, double-blind, double-dummy studies to evaluate the efficacy and safety of tedizolid phosphate in comparison to linezolid to treat patients with ABSSSI.

In both studies, patients were randomized 1:1 to receive 200 mg once a day of tedizolid for 6 days or 600 mg twice a day of linezolid. In TR701-112, randomization was stratified by absence/presence of fever at baseline, geographic region and clinical syndrome. In TR701-113, randomization was stratified by geographic region and clinical syndrome.

Patients randomized to the tedizolid arm received placebo therapy for 4 days to ensure the study remained blinded. In TR701-112 patients received all oral medication whereas in TR701-113 patients received at least 1 day of IV therapy with an option to switch to oral therapy. Patients could be switched to oral therapy if two of the following criteria were met:

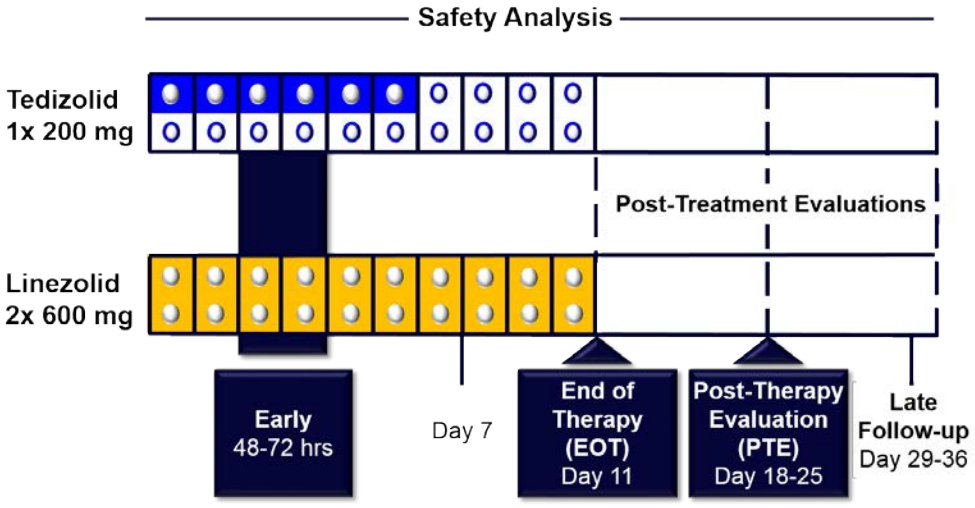
- The primary skin lesion had not increased in area, length, or width from baseline
- Temperature was <37.7°C at last measurement
- No local signs or symptoms of the primary ABSSSI site were worsening since previous visit
- Improvement of at least 1 local sign or symptom of the primary ABSSSI site since previous visit

The study was designed using 10 days of linezolid treatment, consistent with its product labeling. The linezolid clinical studies evaluated 10-14 days of linezolid therapy, thus, efficacy is known only for this length of treatment. If a shorter course of linezolid had been used in studies TR701-112 and TR701-113, the trials would have lacked assay sensitivity. Assay sensitivity is the ability to distinguish an effective treatment from a less effective or ineffective intervention. In a non-inferiority trial, assay sensitivity is required for internal validity and efficacy comparisons, and is a requirement of clinical trials as detailed in ICH E10 and the FDA guidance on non-inferiority trials (ICH E10 2000; FDA Guidance NI Margin 2010).

Study visits were conducted as follows: Baseline – within 24 hours before the first dose of study drug, Study Day 1, Study Day 2, 48 to 72 hours after the first dose of study drug, Study Day 7 (+ 2 days), End of therapy (EOT) – on Study Day 11 (+2 days), Post-Therapy Evaluation Visit (PTE) – Study Days 18-25, and at the Late Follow-up Visit – Study Days 29-36.

A schematic of the Phase 3 studies is shown in Figure 10.

Figure 10. Schematic Diagram: Tedizolid Phase 3 Clinical Studies



6.2.1 Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria were the same for both TR701-112 and TR701-113. An amendment of the protocol for Study TR701-113 allowed patients ≥12 years old to enroll, however since the study was nearly complete by the time of this change, only 2 adolescents were enrolled.

The key inclusion criteria:

Infection:

- Cellulitis/erysipelas or
- Major cutaneous abscess (≤30% allowed to be enrolled) or
- Wound infection – at surgical site or post-traumatic wounds

Size of lesion:

- Lesion surface area ≥75 cm2 (head-to-toe length times the widest perpendicular width); for patients with abscess or wound infection, the surrounding erythema was required to extend at least 5 cm in the shortest distance from the peripheral margin of the abscess or wound

Regional and systemic involvement:

- At least 1 regional or systemic sign of infection to include:
    - Lymphadenopathy (defined as lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI)
    - Temperature ≥38°C
    - WBCs ≥10,000 **or** ≤4,000 cells/mm^3
    - Immature neutrophils >10%

The key exclusion criteria:

- Receipt of any systemic or topical antibiotic with Gram-positive activity within 96 hours prior to first dose of study drug
- Uncomplicated skin and skin structure infection such as furuncles, minor abscess, etc.
- Known bacteremia at time of screening
- ABSSSI due to a suspected or documented Gram-negative pathogen
- Diabetic foot infection
- Use of MAO inhibitors or serotonergic compounds
- High tyramine diet

A complete listing of all inclusion and exclusion criteria for both TR701-112 and TR701-113 can be found in Appendix 1.

6.2.2 Study Endpoints

Primary Efficacy Endpoint

For both Study TR701-112 and Study TR701-113, the primary outcome was early clinical response at the 48-72 Hour Visit in the ITT population. However, the definitions were different between the two studies as detailed below in Table 13.

Table 13. Definitions of Early Clinical Response in Study 112 and Study 113

Study TR701-112	Study TR701-113
Patient meeting the following criteria were to be programmatically defined as responders:	
Cessation of spread of the primary ABSSSI lesion based on erythema, compared with baseline (cessation of spread is defined as no increase in lesion surface area [length × width] as compared to baseline)	At the 48 to 72 Hour Visit, ≥20% reduction in area of erythema, edema, and/or induration (length × width) of the primary ABSSSI lesion compared with baseline.
Temperature measurement (assessed by the Investigator) is ≤37.6°C (oral) and the next measurement (taken within 24 hours) is also ≤37.6°C (oral)	Not applicable
Patients meeting any of the following criteria were to be programmatically defined as nonresponders:	
Spread of the primary ABSSSI lesion based on erythema, compared with baseline (spread of the lesion is defined as an increase in lesion surface area [length × width] as compared to baseline)	<20% reduction in the area of the primary ABSSSI lesion compared with baseline
Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections	Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
Any of the two temperature measurements is >37.6°C (oral)	Not applicable
Death (all-cause mortality)	Death (all-cause mortality)

An additional pre-specified analysis in Study TR701-112 defining the primary endpoint as in Study TR701-113 was conducted.

Secondary Outcome Measures

Secondary outcome measures included a programmatically determined clinical response at the EOT Visit in the ITT and Clinically Evaluable at EOT (CE-EOT) Analysis Sets and Investigator's assessment of clinical response at the PTE Visit in the ITT and Clinical Evaluable at PTE (CE-PTE) Analysis Sets. In Study TR701-112, patients assessed as nonresponders at the 48-72 Hour Visit were defined as a clinical failure at the EOT Visit

and thus, the response was defined as a sustained clinical response. For a patient to be defined as a clinical success, all of the criteria in Table 14 had to be met.

Table 14. Criteria for Clinical Success in Study 112 and Study 113

Study TR701-112 (Sustained Clinical Response at the EOT Visit)	Study TR701-113 (Clinical Response at the EOT Visit)
At the EOT Visit	
Patient is afebrile ≤ 37.6°C (oral or oral equivalent; investigator reported) or the fever>37.6°C is attributable to a cause other than the primary skin infection.	Patient is afebrile ≤37.6°C (oral or oral equivalent; investigator reported) or the fever >37.6°C is attributable to a cause other than the primary skin infection.
Decrease from baseline in the size of the primary ABSSSI lesion. Size is defined as lesion surface area, length, and width.	Decrease from baseline in the size of the primary ABSSSI lesion. Size is defined as lesion area, length, and width.
Clinician assessment of tenderness of mild or absent	Clinician assessment of tenderness of mild or absent
Investigator report of patient pain as absent	No Applicable
Not Applicable	No purulent drainage from a wound infection or the purulent drainage is of a lesser intensity than at Screening.
Patient was a responder at the 48-72 Hour Visit	Not Applicable
Through the EOT Visit:	
Did not receive any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections	Did not receive any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
Did not have a treatment-emergent AE leading to discontinuation of study drug and required additional antibiotic therapy to treat the ABSSSI	Did not have a treatment-emergent AE leading to discontinuation of study drug and required additional antibiotic therapy to treat the ABSSSI
No additional antibiotic therapy for treatment of the primary lesion	No additional antibiotic therapy for treatment of the primary lesion
No unplanned major surgical intervention required due to failure of study drug (ie, amputation)	No unplanned major surgical intervention required due to failure of study drug (ie, amputation)
Did not develop osteomyelitis after baseline	Did not develop osteomyelitis after baseline
For wounds and abscess: no incision and drainage of the ABSSSI site was performed more than 24 hours after the first dose of study drug unless it was planned before randomization	For wounds and abscess: no incision and drainage of the ABSSSI site was performed more than 24 hours after the first dose of study drug unless it was planned before randomization
For cellulitis/erysipelas: no incision and drainage of the ABSSSI site after the 48-72 Hour Visit	For cellulitis/erysipelas: no incision and drainage of the ABSSSI site after the 48-72 Hour Visit

Patients were defined as a clinical failure at the EOT Visit if at least one of the above criteria were not met. In both studies, patients were defined as an indeterminate response based on the criteria below:

- Osteomyelitis present at baseline
- Lost to follow up prior to EOT (Day 11)
- For patients with cellulitis/erysipelas or major cutaneous abscess: Gram-negative organism isolated at baseline that required a different antibiotic therapy
- For patients with wound infections: Gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole
- Patient withdraws consent prior to the EOT Visit

In addition, in Study TR701-112, patients with missing data such that a response at the 48-72 Hour Visit could not be determined and who were not defined as a clinical failure based on the criteria detailed above, were defined as an indeterminate response.

An additional pre-specified secondary outcome in Study TR701-112, programmatic clinical response at EOT, was analyzed. This outcome measure is similar to the secondary outcome measure defined in Study TR701-113 and the 2010 draft FDA guidance where the assessment at the 48 - 72 Hour Visit and the Investigator assessment of patient pain were not included in the definition (FDA Guidance ABSSSI 2010).

Investigator's assessment of clinical response at the PTE Visit was defined the same in both studies, as shown in Table 15. A complete list of the definitions of trial responder at EOT and PTE for both studies is provided in Appendix 3.

Table 15. Definitions of Clinical Response at the PTE Visit

Term	Definition
Clinical Success	Meets the following three criteria: • Resolution or near resolution of most disease-specific signs and symptoms • Absence or near resolution of systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count), if present at baseline • No new signs, symptoms, or complications attributable to the ABSSSI so no further antibiotic therapy is required for the treatment of the primary lesion
Clinical Failure	Any of the following: • Requires additional antibiotic therapy for treatment of the primary lesion • Unplanned major surgical intervention required due to failure of study drug (ie, amputation) • Developed osteomyelitis after baseline • Persistent gram-positive pathogen bacteremia • Treatment-emergent AE leading to discontinuation of study drug and patient required additional antibiotic therapy to treat the ABSSSI • Death (all-cause mortality) within 28 days of first dose
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including: • Osteomyelitis present at baseline • Lost to follow up • Extenuating circumstances that preclude the classification of a clinical success or failure • For patients with cellulitis/erysipelas or major cutaneous abscess: gram-negative organism isolated at baseline that required a different antibiotic therapy • For patients with wound infections: gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole • Patient withdraws consent

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; AE=adverse event; WBC=white blood cell.

6.2.3 Statistical Methodology

Sample Size

The estimate of the outcome rate was based on results from the TR701-104 study, which showed that in the 200 mg group, 90.6% (95% confidence interval [CI] 80.7% - 96.5%) of patients had no increase from baseline in lesion size at Day 3. Thus, it is reasonable to assume that the true rate of early clinical response is at least 81% in the tedizolid phosphate and linezolid groups. For the secondary outcome of clinical response at the EOT Visit, the true rates of the clinical success are assumed to be 78% for linezolid and 78% for tedizolid phosphate in the ITT Analysis Set and 88% for both treatment groups in the CE-EOT Analysis Sets. The true rates of the Investigator's assessment of clinical response are assumed to be 76% in both the tedizolid and linezolid groups in the ITT Analysis Set and 86% in both treatment groups in the CE-PTE Analysis Set. Assuming an NI margin of 10%, a 1-sided alpha of 0.025, an 80% evaluability rate for the CE-EOT Analysis Set and a 75% evaluability rate for the CE-PTE Analysis Set, and using the

sample size determination method of Farrington and Manning (Farrington 1990), the sample size and power in each Analysis Set for the primary and secondary outcomes are provided in Table 16.

Table 16. Sample Size and Power for the Primary and Secondary Efficacy Outcomes

	Primary Outcome (48-72 hours after the first infusion of study drug)	Secondary Outcome (Programmatic assessment of clinical response at EOT)		Secondary Outcome (Investigator's assessment of clinical response at PTE)	
Analysis Set	ITT	ITT	CE-EOT	ITT	CE-PTE
N	658	658	524	658	494
Power	90%	87%	93%	85%	88%

Abbreviations: CE=clinically evaluable; EOT=end of therapy; ITT=intent to treat; PTE=post-therapy evaluation

Thus, the sample size for the study is 658 randomized patients (ITT Analysis Set).

Non-Inferiority Margin Justification

A literature review to determine the non-inferiority margin was conducted and it was determined that there were no placebo controlled trials. Two historical studies were identified, by Snodgrass and Anderson, involving treatment versus standard of care to determine the NI margin. The results of a meta-analysis of these two studies demonstrated a treatment difference of 27.1% (95% CI 21.0% - 33.2%) for cessation of spread at 48 hours after the first dose of study drug. Thus, using the lower bound of the confidence interval as a conservative estimate of the treatment effect results in an M1 of 21.0%. To preserve at least 50% (M2) of the treatment effect, the non-inferiority margin can be no larger than 10.5%. Based on these data, a 10% NI margin for the primary outcome measure is robust to establish the non-inferiority of tedizolid phosphate to linezolid in the treatment of ABSSSI. A non-inferiority margin of 10% is also consistent with the recent FDA guidance for the proposed indication (FDA Guidance NI Margin 2010).

Study Analysis Sets

The Analysis Sets were defined as follows for the Phase 3 studies:

1. Intent-to-Treat (ITT) Analysis Set: All randomized patients regardless of whether or not the patient received study drug.
2. Microbiological Intent-to-Treat (microITT) Analysis Set: All patients in the ITT Analysis Set who had at least one Gram-positive bacterial pathogen identified from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site at baseline using a valid sampling technique.
3. Clinically Evaluable at End of Therapy Analysis Set (CE-EOT): All randomized patients receiving minimal study therapy, who completed the EOT assessments, who had no concomitant antibiotic therapy through EOT, and who had no confounding

events or factors. A complete list of reasons for inclusion in or exclusion from the CE-EOT Analysis Set is provided in the Appendix 4.

4. Clinically Evaluable at Post Therapy Evaluation Analysis Set (CE-PTE): All randomized patients receiving minimal study drug therapy, completed EOT and PTE Investigator's assessments, who had no concomitant systemic antibiotic therapy through PTE and no confounding events or factors. A complete list of reasons for inclusion in or exclusion from the CE-PTE Analysis Set is provided in the Appendix 4.
5. Microbiological Evaluable Set (ME): All patients in both microITT and CE-PTE Analysis Sets.
6. Safety Analysis Set: All patients who received any amount of study medication.

Primary Efficacy Analysis

The primary efficacy analysis for both Phase 3 studies was based on the ITT Analysis Set.

The primary efficacy outcome was the percentage of patients with the programmatic determination of early clinical response at the 48 to 72 Hour Visit. Patients with missing data such that a response could not be determined were considered nonresponders. A two-sided 95% CI for the observed difference in primary outcome rates (tedizolid phosphate treatment group minus linezolid treatment group) was calculated using the Miettinen and Nurminen method (Miettinen 1985). For TR701-112, the 95% CI was stratified for the presence/absence of fever at baseline (Cochran-Mantel-Haenszel weights were used for the stratum weights) whereas for TR701-113 an unstratified 95% CI was determined. This CI approach corresponds to the non-inferiority test (a p-value approach) proposed by Farrington and Manning (Farrington 1990). If the lower limit of the 95% CI for the treatment difference in the ITT Analysis Set was greater than -10%, then the null hypothesis was rejected and the non-inferiority of tedizolid phosphate to linezolid was declared.

Secondary Endpoints

The number and percentage of patients in each treatment group with a clinical success, clinical failure, and indeterminate response based on clinical response at the EOT Visit and Investigator's assessment of response at the PTE Visit was determined for the ITT, CE-EOT and CE-PTE Analysis Sets. Since indeterminate responses are included in the denominator, these are essentially considered clinical failures in the ITT Analysis Set. By definition, the CE-EOT and CE-PTE Analysis Sets do not include patients with an indeterminate response.

Two-sided 95% CIs using the method of Miettinen and Nurminen were constructed for the differences between the tedizolid phosphate and linezolid treatment groups in the clinical success rates. For Study 112, the 95% CI was stratified for the presence/absence of fever at baseline (Cochran-Mantel-Haenszel weights were used for the stratum weights) whereas for Study 113 an unstratified 95% CI was determined.

Handling of Missing Data

For the primary outcome measure, if any data field needed to determine the response was missing at 48 to72 hours after the first infusion of study drug, the patient was to be considered nonresponders. If the time of administration of the first dose of study drug was missing, the patient was to be defined as an indeterminate response.

For the secondary outcome measures of clinical response at the EOT and PTE Visits, if any data needed to determine the response was missing at the EOT Visit, or if the Investigator could not determine the response (at the EOT or PTE Visits), the patient was considered an indeterminate response. For analyses of the secondary outcome measures, patients with an indeterminate response were included in the denominator, and thus, were considered as clinical failures.

For microbiological response, if no source specimen was obtained and the patient had an Investigator's assessment of clinical response, the per-pathogen microbiological response was to be based on the Investigator's assessment of clinical response. A per-pathogen microbiological response at the PTE Visit was to be considered missing or indeterminate only if the clinical response at PTE is also missing or indeterminate.

6.3 TR701-112

6.3.1 Patient Disposition

Study drug completion rates were high in both groups; 91.6% of patients in the tedizolid phosphate group and 88.7% of patients in the linezolid group. Study completion rates were also high in both groups, 90.1% of patients in the tedizolid phosphate group and 91.6% of patients in the linezolid group completed the study, respectively). Table 17 shows the specific patient disposition data for the ITT Analysis Set for TR701-112.

Table 17. Study TR701-112: Patient Disposition (ITT Analysis Set)

	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)
Patient randomized but did not receive study drug	1 (0.3)	0
Patients completed study drug	304 (91.6)	297 (88.7)
Patients prematurely discontinued study drug	27 (8.1)	38 (11.3)
Primary reason for study drug discontinuation		
Adverse Event	1 (0.3)	2 (0.6)
Treatment failure	2 (0.6)	7 (2.1)
Patient withdrew consent	7 (2.1)	5 (1.5)
Patient lost to follow-up	12 (3.6)	13 (3.9)
At request of sponsor or Investigator	2 (0.6)	4 (1.2)
Staphylococcus aureus bacteremia	0	0
Patient requires prohibited medication	0	1 (0.3)
Abnormal liver function tests	0	0
Gram-negative infection	2 (0.6)	5 (1.5)
Other	1 (0.3)	1 (0.3)
Patients completed study	299 (90.1)	307 (91.6)
Patients prematurely discontinued from the study	33 (9.9)	28 (8.4)
Primary reason for study discontinuation		
Patient randomized but did not receive study drug	1 (0.3)	0
Patient withdrew consent	9 (2.7)	7 (2.1)
Patient lost to follow-up	22 (6.6)	21 (6.3)
At request of Sponsor or Investigator	0	0
Other	1 (0.3)	0

Abbreviations: FA=free acid; ITT=intent-to-treat; N=number of patients in the Analysis Set; n=number of patients in the specific category.

6.3.2 Oral Dosing Exposure

Of the 332 patients in the tedizolid phosphate group, 331 patients were included in the Safety Analysis Set, and the majority (310 patients [93.7%]) received 5 to 6 doses of tedizolid phosphate. Of the 335 patients in the linezolid group, all 335 patients were included in the Safety Analysis Set, and the majority (281 patients [83.9%]) received 19 to 20 doses of linezolid (Table 18).

Table 18. Study Drug Exposure (Safety Analysis Set)

Number of Active Doses	Tedizolid Phosphate (N=331) n (%)	Linezolid (N=335) n (%)
1-2 doses	12 (3.6)	NA
3-4 doses	9 (2.7)	NA
5-6 doses	310 (93.7)	NA
1-4 doses	NA	12 (3.6)
5-8 doses	NA	17 (5.1)
9-12 doses	NA	6 (1.8)
13-18 doses	NA	19 (5.7)
19-20 doses	NA	281 (83.9)

6.3.3 Demographics and Baseline Characteristics

The majority of patients enrolled in the study were male (tedizolid phosphate 61.4%, linezolid 59.1%) and relatively young (mean age - tedizolid phosphate 43.6 years, linezolid 43.1 years). Demographics and baseline characteristics of patients in Study TR701-112 are summarized for the ITT Analysis Set in Table 19.

The geographical distribution of enrolled patients in TR701-112 shows that 81% of enrolled patients were in North America (538 patients), followed by 16% from Europe (108 patients), and the remaining 3% from Latin America (21 patients).

Table 19. Study TR701-112: Demographic and Baseline Characteristics (ITT Analysis Set)

Characteristic	Statistic	Tedizolid Phosphate (N=332)	Linezolid (N=335)
Sex			
Female	n (%)	128 (38.6)	137 (40.9)
Male	n (%)	204 (61.4)	198 (59.1)
Age (years)	Mean	43.6	43.1
	SD	14.96	15.06
Age group			
<65 years	n (%)	303 (91.3)	309 (92.2)
≥65 to ≤75 years	n (%)	19 (5.7)	19 (5.7)
>75 years	n (%)	10 (3.0)	7 (2.1)
Ethnicity: Hispanic or Latino	n (%)	115 (34.6)	108 (32.2)
Race			
White	n (%)	280 (84.3)	275 (82.1)
Asian	n (%)	2 (0.6)	7 (2.1)
Black or African American	n (%)	39 (11.7)	38 (11.3)
Native Hawaiian or Other Pacific Islander	n (%)	0	2 (0.6)
American Indian or Alaskan Native	n (%)	4 (1.2)	5 (1.5)
Other	n (%)	7 (2.1)	8 (2.4)
Region			
North America	n (%)	270 (81.3)	268 (80.0)
Latin America	n (%)	9 (2.7)	12 (3.6)
Europe	n (%)	53 (16.0)	55 (16.4)
BMI (kg/m^2)	Median	27.5	27.3
	Min, Max	15.99, 39.97	16.76, 39.99

Abbreviations: BMI=body mass index; ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation.
Notes: N=number of patients in the Analysis Set; n=number of patients in the specific category. Percentages are calculated as 100 × (n/N).

The most common ABSSSI relevant medical history (reported in ≥20% of patients in either treatment group) in the ITT Analysis Set were current or recent IV drug use (35.2% tedizolid phosphate, 39.4% linezolid) and Hepatitis C positive at baseline (30.7% for tedizolid phosphate, 35.5% for linezolid) (Table 20). A similar percentage of patients in both groups (7.8% tedizolid phosphate, 12.3% linezolid) had a history of diabetes mellitus.

Table 20. Study TR701-112: ABSSSI Relevant Medical History (ITT Analysis Set)

Characteristic	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)
Hospitalization during treatment	35 (10.5)	34 (10.2)
Antibacterials (within 4-30 days prior to randomization)	12 (3.6)	15 4.5)
Hepatitis C positive at baseline	101 (30.7)	116 (35.5)
HIV positive	5 (1.5)	1 (0.3)
Current or recent IV drug use	117 (35.2)	132 (39.4)
Diabetes	26 (7.8)	26 (7.8)

Notes: N=number of patients in the Analysis Set; n=number of patients in the specific category.
Percentages are calculated as 100 × (n/N).
Abbreviations: ITT=intent-to-treat

Most patients enrolled in Study TR701-112 had cellulitis/erysipelas (40.7% tedizolid phosphate, 41.5% linezolid), followed by major cutaneous abscess (30.1% tedizolid phosphate, 29.3% linezolid) and wound infection (29.2% tedizolid phosphate, 29.3% linezolid). All patients with cutaneous abscess were enrolled at sites in North America as Europe and Latin America were initiated later in the study after the prespecified maximum number of patients (30%) with cutaneous abscess was reached. Most infections occurred on the leg or arm. The type and location of ABSSSIs are summarized for the ITT Analysis Set in Table 21.

Table 21. Study TR701-112: Type and Location of ABSSSI (ITT Analysis Set)

Characteristic	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)
Type of ABSSSI infection		
Cellulitis/erysipelas	135 (40.7)	139 (41.5)
Major cutaneous abscess	100 (30.1)	98 (29.3)
Wound infection	97 (29.2)	98 (29.3)
Superficial incisional surgical site infection	3 (0.9)	3 (0.9)
Post-traumatic wound	94 (28.3)	95 (28.4)
Anatomical site		
Head	15 (4.5)	11 (3.3)
Neck	6 (1.8)	6 (1.8)
Chest	4 (1.2)	10 (3.0)
Abdomen	21 (6.3)	8 (2.4)
Back	7 (2.1)	6 (1.8)
Groin	13 (3.9)	9 (2.7)
Buttock	36 (10.8)	33 (9.9)
Shoulder	3 (0.9)	4 (1.2)
Axillary	6 (1.8)	6 (1.8)
Hand	16 (4.8)	11 (3.3)
Arm	77 (23.2)	92 (27.5)
Leg	132 (39.8)	137 (40.9)
Foot	19 (5.7)	24 (7.2)

Note: N=number of patients in the Analysis Set; n=number of patients in the specific category. Percentages are calculated as 100 × (n/N). A patient may have multiple anatomical sites as long as they are contiguous. If the primary infection is present on both anatomical sides (eg, left and right), the site is counted only once. Data drawn from e-CRFs. Type of ABSSSI infection is from the CRF rather than the infection used for randomization, if different.
Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; e-CRF=electronic case report form; ITT=intent-to-treat

The population studied had severe infections. Severity of infection was defined by the following:

1. The size of the cutaneous lesion (≥75 cm^2).
2. The presence/absence of adjacent lymphadenopathy (increased in volume and sensitivity.
3. Systemic signs of infection: fever and hyperleukocytosis/bands.

The key marker of severity of the skin infections treated was the large lesion area. Overall across all infection types, the median surface area of erythema at baseline was 188.3 cm^2 in the tedizolid phosphate group and 190.0 cm^2 in the linezolid group for the

ITT Analysis Set. Prior to Protocol Amendment 3, abscess and wound size measurement required that erythema extend at least 5 cm from the peripheral margin of the abscess at its greatest distance for a patient to be enrolled. During initial data reviews, it was discovered that 10 tedizolid phosphate-treated and 12 linezolid-treated were enrolled with an abscess or wound surface area of <75 cm^2 and the protocol was subsequently amended (Protocol Amendment 3) to require the erythema extend at least 5 cm from the peripheral margin at its shortest distance.

Adjacent lymphadenopathy, a marker of dissemination of the infection beyond the primary lesion was the sign most frequently seen (87.0% tedizolid phosphate and 86.3% linezolid), followed by WBC count ≥10,000 cells/mm3 or <4000 cells/mm^3 (42.2% tedizolid phosphate and 39.7% linezolid). Fever (≥38°C) was also noted in 16.9% and 18.8% of patients in the tedizolid phosphate and linezolid groups, respectively. A summary of the severity of infection at baseline for Study 112 is shown in Table 22.

Table 22. Study TR701-112: Baseline Regional and Systemic Signs of Infection (ITT Analysis Set)

Regional/Systemic Sign of Infection	Tedizolid Phosphate (N=332)	Linezolid (N=335)
Lesion Area, (cm^2), median (range)	188.3 (28.5, 5572.8)	190.0 (27.0, 2952.0)
Lymphadenopathy, n (%)	289 (87.0)	289 (86.3)
Lymph node tenderness	283 (85.2)	286 (85.4)
Lymph node increase in volume or palpable	287 (86.4)	281 (83.9)
WBC ≥10,000 cells/mm^3 or <4000 cells/mm^3, n (%)	140 (42.2)	133 (39.7)
Immature neutrophils >10%, n (%)	12 (4.1)	8 (2.6)
Temperature ≥38°C (fever), n (%)	56 (16.9)	63 (18.8)

Note: lesion surface area is length × width. Baseline is the last assessment made before first dose of study drug.
Abbreviations: ITT=intent-to-treat; max=maximum; min=minimum; N=number of patients in the Analysis Set; n=number of patients in the specific category; WBC=white blood cell

A Gram-positive pathogen was isolated from the primary infection site at baseline in approximately 63% of patients in both groups (and included in the microITT Analysis Set) and most pathogens isolated were Gram-positive aerobes (99.0% tedizolid phosphate and 98.1% linezolid). The most common pathogen isolated was *S. aureus* (81.8% tedizolid phosphate and 83.7% linezolid) with MRSA accounting for 42.1% and 43.1% of infections in the in the tedizolid phosphate and linezolid groups, respectively and MSSA accounting for 39.7% and 41.6% of infections in the tedizolid phosphate and linezolid groups, respectively (Table 23). Other Gram-positive aerobes and anaerobes were each reported in <10% of patients in either treatment group.

Table 23. Pathogenic Organisms from Baseline Primary ABSSSI Site or Blood Culture by Genus and Species (microITT Analysis Set)

Pathogenic Organism	TR-701 FA (N=209) n (%)	Linezolid (N=209) n (%)
Gram-positive organisms (aerobes)	**207 (99.0)**	**205 (98.1)**
S. aureus	171 (81.8)	175 (83.7)
MRSA	88 (42.1)	90 (43.1)
MSSA	83 (39.7)	87 (41.6)
PVL *S. aureus*	97 (46.4)	102 (48.8)
S. pyogenes	8 (3.8)	4 (1.9)
S. anginosus-milleri group	15 (7.2)	15 (7.2)
S. anginosus	4 (1.9)	3 (1.4)
S. intermedius	3 (1.4)	4 (1.9)
S. constellatus	8 (3.8)	8 (3.8)
E. faecalis	5 (2.4)	0
E. faecium	1 (0.5)	2 (1.0)
S. agalactiae	9 (4.3)	5 (2.4)
Gram-positive organisms (anaerobes)	**3 (1.4)**	**8 (3.8)**
Gram-negative organisms (aerobes)	**6 (2.9)**	**6 (2.9)**
Gram-negative organisms (anaerobes)	**0**	**1 (0.5)**

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; FA=free acid; microITT=microbiological intent-to-treat; MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-sensitive *S. aureus*; N=number of patients in the Analysis Set; n=number of patients in the specific category; PVL=Panton-Valentine Leukocidin, PVL *S. aureus* refers to PVL positive status in *S. aureus*.
Note: Patients with the same pathogen isolated from multiple specimens are counted only once for that pathogen. Patients with the same pathogen identified from both the blood and primary ABSSSI cultures are counted only once. Patients with both MRSA and MSSA are counted only once in overall *S. aureus* row, and untyped *S. aureus* pathogens are only counted in the overall *S. aureus* row.

6.3.4 Primary Endpoint: Early Clinical Response

In the primary efficacy analysis, early clinical response (cessation of lesion spread and apyrexia) at the 48 to 72 Hour Visit was observed in 79.5% of patients in the tedizolid phosphate group and 79.4% of patients in the linezolid group in the ITT Analysis Set (treatment difference 0.1%; 95% confidence interval [CI]: -6.1%, 6.2%. The lower limit of the 95% CI was greater than -10%, which was the predefined requirement for non-inferiority (Prokocimer 2013). Based on these results, tedizolid phosphate was non-inferior to linezolid for the primary efficacy analysis of early clinical response. Primary endpoint data for TR701-112 is shown in Table 24.

Table 24. Study TR701-112: Primary Efficacy Analysis - Early Clinical Response at the 48 - 72 Hour Visit (ITT Analysis Set)

Response	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)	Difference (%)	95% CI for Difference
Responder	264 (79.5)	266 (79.4)	0.1	(-6.1, 6.2)
Nonresponder or missing data	68 (20.5)	69 (20.6)		
Nonresponder	27 (8.1)	35 (10.4)		
Missing Data	41 (12.3)	34 (10.1)		

Abbreviations: CI=confidence interval; ITT=intent-to-treat
Notes: N=number of patients in the Analysis Set; n=number of patients in the specific category. Percentages are calculated as 100 × (n/N).
Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group. 95% CI is adjusted for stratification factor of presence/absence of fever at baseline using the method of Miettinen and Nurminen.

A total of 20.5% of patients in the tedizolid phosphate group and 20.6% of patients in the linezolid group were nonresponders or had missing data in the ITT Analysis Set. The primary reasons for early clinical outcomes of nonresponder or missing data were missing temperature data including temperature measurements collected outside the prespecified time period (11.1% of tedizolid phosphate patients and 9.6% of linezolid patients) and missing lesion measurement (6.6% of tedizolid phosphate patients and 7.2% of linezolid patients). The reasons for categorization as nonresponder or missing data in each treatment group are shown in Table 25.

Table 25. Study TR701-112: Reasons for Early Clinical Nonresponse at the 48 - 72 Hour Visit (ITT Analysis)

Reasons for Nonresponse or Missing Data	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)
Spread of primary ABSSSI lesion only	17 (5.1)	18 (5.4)
Temperature >37.6°C only	7 (2.1)	10 (3.0)
Spread of primary ABSSSI lesion and temperature >37.6°C	0	3 (0.9)
Missing lesion measurement data	22 (6.6)	24 (7.2)
Missing temperature data	37 (11.1)	32 (9.6)
Systemic concomitant antibiotics potentially effective against baseline pathogen	4 (1.2)	6 (1.8)

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; FA=free acid; ITT=intent-to-treat
Notes: n=number of patients in the specific category; N=number of patients in the Analysis Set. Missing temperature data includes temperature measurements collected outside the prespecified time period (48 - 72 hours). A patient may have more than 1 reason for nonresponse.

An additional analysis defining early clinical response as ≥20% reduction in lesion size as the endpoint (the same as the primary endpoint from Study TR701-113 and in the final October 2013 guidance) was performed. The response rates were similar in the tedizolid

phosphate (78.0%) and linezolid (76.1%) groups in this analysis, with the lower limit of the 95% CI greater than -10%, thus demonstrating non-inferiority. The results are shown in Table 26. In contrast to the primary efficacy outcome, the primary reason for an early clinical outcome of nonresponder was that the patient had less than a 20% decrease from baseline in lesion area. A total of 7% of patients in both treatment groups had missing data such that the primary outcome could not be determined.

Table 26. Study TR701-112: Additional Analysis - Early Clinical Response at the 48 - 72 Hour Visit 20% Decrease from Baseline in Lesion Area (ITT Analysis Set)

Response	Tedizolid (N=332) n (%)	Linezolid (N=335) n (%)	Difference (%)	95% CI for Difference
Responder	259 (78.0)	255 (76.1)	1.9	(-4.5, 8.3)
Non-responder or missing data	73 (22.0)	80 (23.9)		
Non-responder	50 (15.1)	56 (16.7)		
<20% decrease in lesion area	47 (14.2)	52 (15.5)		
Systemic concomitant antibiotics potentially effective against baseline pathogen	3 (0.9)	6 (1.8)		
Missing data	23 (6.9)	24 (7.2)		

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; ITT=intent-to-treat
Notes: n=number of patients in the specific category; N=number of patients in the Analysis Set.
Reasons for non-response are not mutually exclusive.
Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group.

Early clinical response at the 48-72 Hour Visit by baseline fever status was similar in both treatment groups but the outcome rates were lower in afebrile than febrile patients. Approximately 80% of afebrile patients had an early clinical response in both treatment groups where as 76.8% of tedizolid phosphate febrile patients and 73% of linezolid febrile patients were considered to be responders.

Early clinical response by type of infection was generally similar in the tedizolid phosphate and linezolid groups in the ITT Analysis Set (Table 27). Small differences were noted between groups; however, these were not consistent across infection type. Overall, early clinical response by type of infection was seen in approximately 75% to 86% of patients in the tedizolid phosphate group and approximately 72% to 86% in the linezolid group, with cellulitis/erysipelas patients having the lowest responder rates in both treatment groups.

Some differences were noted between groups in early clinical response by geographic region (Table 27). Early clinical response was seen in a higher percentage of patients treated with tedizolid phosphate in Europe (84.9% tedizolid phosphate vs 74.5% linezolid), while early response was seen in a higher percentage of patients treated with linezolid in Latin America (75.0% linezolid vs 66.7% tedizolid phosphate). There was little difference between groups in early clinical response in North America (78.9% tedizolid phosphate and 80.6% linezolid).

Table 27. Study TR701-112: Early Clinical Response at the 48-72 Hour Visit by Fever Status, Type of Infection and Geographic Region (ITT Analysis Set)

Strata	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)	Difference (%)	95% CI for Difference
Baseline Fever				
Presence	43/56 (76.8)	46/63 (73.0)	3.8	(-12.1, 19.2)
Absence	221/276 (80.1)	220/272 (80.9)	-0.8	(-7.5, 5.9)
Type of Infection				
Cellulitis/erysipelas	101/135 (74.8)	100/139 (71.9)	2.9	(-7.6, 13.3)
Major cutaneous abscess	80/100 (80.0)	84/98 (85.7)	-5.7	(-16.4, 4.9)
Wound infection	83/97 (85.6)	82/98 (83.7)	1.9	(-8.5, 12.3)
Region				
North America	213/270 (78.9)	216/268 (80.6)	-1.7	(-8.5, 5.1)
Latin America	6/9 (66.7)	9/12 (75.0)	-8.3	(-46.8, 30.0)
Europe	45/53 (84.9)	41/55 (74.5)	10.4	(-5.1, 25.6)

Abbreviations: CI=confidence interval; ITT=intent-to-treat; N=number of patients in the Analysis Set; n=number of patients in the specific category; N1=number of patients in the stratum for the Analysis Set.
Notes: Percentages are calculated as 100 × (n/N1). 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen. Difference (%)=responder rate for the TR-701 FA treatment group minus linezolid treatment group.

6.3.5 Secondary Endpoints

Sustained Clinical Response

Sustained clinical response at the EOT Visit was observed in a similar percentage of patients in the tedizolid phosphate and linezolid groups in the ITT Analysis Set (69.3% and 71.9%, respectively; treatment difference -2.6%; 95% CI: -9.6%, 4.2%) and in the CE-EOT Analysis Set (80.2% and 81.1%, respectively; treatment difference -0.9%; 95% CI: -7.7%, 5.4%) (Table 28). The lower limit of the 95% CI was greater than -10%, for sustained clinical response at the EOT Visit in the ITT and CE-EOT Analysis Sets.

Table 28. Study TR701-112: Sustained Clinical Response at the EOT Visit (ITT and CE-EOT Analysis Sets)

Analysis Set Response	Tedizolid Phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
ITT, N	**332**	**335**		
Clinical success	230 (69.3)	241 (71.9)	-2.6	(-9.6, 4.2)
Clinical failure or indeterminate	102 (30.7)	94 (28.1)		
Clinical failure	60 (18.1)	61 (18.2)		
Indeterminate	42 (12.7)	33 (9.9)		
CE-EOT, N	**273**	**286**		
Clinical success	219 (80.2)	232 (81.1)	-0.9	(-7.7, 5.4)
Clinical failure	54 (19.8)	54 (18.9)		

Abbreviations: CE=clinically evaluable; CI=confidence interval; EOT=end of therapy; ITT=intent-to-treat; N=number of patients in the specified Analysis Set; n=number of patients in the specific category.
Notes: Percentages are calculated as 100 × (n/N).
95% CI is adjusted for stratification factor of presence/absence of fever at baseline using the method of Miettinen and Nurminen.
Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group.

A total of 18.1% of patients in the tedizolid phosphate group and 18.2% of patients in the linezolid group were clinical failures for sustained clinical response in the ITT Analysis Set (Table 28). The primary reasons for clinical failure were patient pain reported by the physician (9.6% of tedizolid phosphate patients and 11.3% of linezolid patients) and nonresponder status at the 48 to 72 Hour Visit (8.1% of tedizolid phosphate patients and 10.1% of linezolid patients [who were defined as failures for this outcome]) (Table 29). It should be noted that neither of these criteria were included in the definition of the efficacy outcome at the EOT Visit in the draft 2010 FDA guidance issued after the SPA agreement for TR701-112 (FDA Guidance ABSSSI 2010).

Table 29. Study TR701-112: Reasons for Clinical Failure at the EOT Visit (ITT Analysis Set)

Reasons for Clinical Failure	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)
Temperature at EOT >37.6 °C	0	2 (0.6)
No decrease from baseline in primary ABSSSI lesion size	1 (0.3)	8 (2.4)
Clinical assessment of tenderness worse than mild	3 (0.9)	11 (3.3)
Investigator assessment of patient pain	32 (9.6)	38 (11.3)
Systemic concomitant antibiotics potentially effective against baseline pathogen	3 (0.9)	1 (0.3)
TEAE leading to study drug discontinuation and additional antibiotic therapy to treat ABSSSI	1 (0.3)	2 (0.6)
Additional antibiotic therapy for primary lesion	11 (3.3)	10 (3.0)
Unplanned major surgical intervention due to study drug failure	3 (0.9)	3 (0.9)
Osteomyelitis after baseline	0	0
Incision and drainage of ABSSSI site	7 (2.1)	5 (1.5)
Death within 28 days of first study drug dose	0	0
Nonresponder at the 48-72 hour visit	27 (8.1)	34 (10.1)

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; EOT=end of therapy; ITT=intent-to-treat; N=number of patients in the Analysis Set; n=number of patients in the specific category; TEAE=treatment-emergent adverse event.
Notes: A patient may have more than 1 reason for clinical failure.

When the additional analysis was conducted of the secondary outcome defined with failures at 48 to 72 hour visit not carried forward, and pain (present/absent) removed from the responder definition (consistent with the draft FDA guidance document, August 2010), the lower limit of the 95% CI was greater than -10%, for clinical response at the EOT for both the ITT and CE-EOT Analysis Sets as shown in Table 30.

Table 30. Study TR701-112: Additional Analysis - Clinical Response at the EOT Visit (ITT and CE-EOT Analysis Sets)

Analysis Set Response	Tedizolid Phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
ITT, N	**332**	**335**		
Clinical success	289 (87.0)	294 (87.8)	-0.8	(-5.8, 4.4)
Clinical failure or indeterminate	43 (13.0)	41 (12.2)		
Clinical failure	19 (5.7)	20 (6.0)		
Indeterminate	24 (7.2)	21 (6.3)		
CE-EOT, N	**273**	**286**		
Clinical success	258 (94.5)	272 (95.1)	-0.6	(-4.5, 3.2)
Clinical failure or indeterminate	15 (5.5)	14 (4.9)		
Clinical failure	15 (5.5)	13 (4.5)		
Indeterminate	0	1 (0.3)		

Abbreviations: CE=clinically evaluable; CI=confidence interval; EOT=end of therapy ITT=intent-to-treat; N=number of patients in the specified analysis set; n=number of patients in the specific category.
Notes: Percentages are calculated as 100 × (n/N).
95% CI is adjusted for stratification factor of presence/absence of fever at baseline using the method of Miettinen and Nurminen. Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group.

Investigator Assessment of Clinical Response

Clinical success rates at the PTE Visit based on the Investigators assessment were similar in the tedizolid phosphate and linezolid groups in the ITT Analysis Set (85.5% and 86.0%, respectively; treatment difference -0.5%; 95% CI: -5.8%, 4.9%) and in the CE-PTE Analysis Set (94.6% and 95.4%, respectively; treatment difference -0.8%; 95% CI: -4.6%, 3.0%). For each of these secondary analyses, the lower limit of the 95% CI was above -10% for each outcome measure (Table 31). The primary reason for clinical failure was that the patient received an additional antibiotic for treatment of the primary lesion (Table 32). Only 1 patient was a failure due to an unplanned surgical intervention. A total of 9.9% of patients in both treatment groups had an indeterminate response which was comprised primarily of patients who were lost to follow-up.

Table 31. Study TR701-112: Investigator's Assessment of Clinical Response at the PTE Visit (ITT and CE-PTE Analysis Sets)

Analysis Set Response	Tedizolid phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
ITT, N	**332**	**335**		
Clinical success	284 (85.5)	288 (86.0)	-0.5	(-5.8, 4.9)
Clinical failure or indeterminate	48 (14.5)	47 (14.0)		
Clinical failure	15 (4.5)	14 (4.2)		
Indeterminate	33 (9.9)	33 (9.9)		
CE-PTE, N	**279**	**280**		
Clinical success	264 (94.6)	267 (95.4)	-0.8	(-4.6, 3.0)
Clinical failure	15 (5.4)	13 (4.6)		

Abbreviations: CE=clinically evaluable; CI=confidence interval; ITT=intent-to-treat; N=number of patients in the specific analysis set; n=number of patients in the specific category; PTE=post-therapy evaluation.
Notes: Percentages are calculated as 100 × (n/N).
Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group (ITT and CE-PTE Analysis Sets).
95% CI is adjusted for stratification factor of presence/absence of fever at baseline using the method of Miettinen and Nurminen.

Table 32. Study TR701-112: Reasons for Clinical Failure at the PTE Visit (ITT Analysis Set)

	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)
Number of clinical failures for investigator assessment of clinical response	15 (4.5)	14 (4.2)
Additional antibiotic therapy for primary lesion	14 (4.2)	12 (3.6)
Unplanned major surgical intervention due to study drug failure	1 (0.3)	0
Osteomyelitis after baseline	1 (0.3)	0
Persistent gram-positive pathogen bacteremia	0	0
TEAE leading to study drug discontinuation and additional antibiotic therapy to treat ABSSSI	1 (0.3)	2 (0.6)
Death within 28 days of first study drug dose	0	0

Abbreviations: TEAE = Treatment-emergent adverse event; N = Number of patients in the ITT Analysis Set; n = Number of patients in the specific category.
Notes: Percentages are calculated as 100 x (n/N; A patient may have more than one reason for clinical failure.

Clinical Response by Pathogen at the PTE Visit

Review of the clinical success based on the Investigator's assessment at the PTE Visit by key baseline pathogen from the primary ABSSSI site or blood culture showed that >85%

of patients had a clinical successfor all Gram-positive aerobes reported at baseline in the microITT Analysis Set, including the most common pathogens, *S. aureus* and *S. pyogenes*. The percentage of patients with a favorable response was similar in both treatment groups (Table 33).

Table 33. Study TR701-112: Investigator Assessment of Clinical Success at the PTE Visit by Selected Baseline Pathogen (microITT Analysis Set)

Baseline Pathogen	Tedizolid Phosphate (N = 209)		Linezolid (N = 209)	
	N1	Clinical Success n (%)	N1	Clinical Success n (%)
Gram-positive Organisms (aerobes)	**207**	**176 (85.0)**	**205**	**179 (87.3)**
S. aureus	171	148 (86.5)	175	157 (89.7)
MRSA	88	75 (85.2)	90	77 (85.6)
MSSA	83	73 (88.0)	87	82 (94.3)
PVL *S. aureus*	97	83 (85.6)	102	86 (84.3)
S. pyogenes	8	7 (87.5)	4	4 (100)
S. anginosus-milleri group	15	11 (73.3)	15	12 (80.0)
E. faecalis	5	3 (60.0)	0	0
E. faecium	1	0	2	2 (100)
S. haemolyticus	4	4 (100)	3	3 (100)
S. lugdunensis	3	3 (100)	2	1 (50.0)
S. agalactiae	9	8 (88.9)	5	3 (60.0)
S. dysgalactiae	1	1 (100)	0	0
Gram-positive Organisms (anaerobes)	3	2 (66.7)	8	4 (50.0)

Abbreviations: microITT=microbiological intent-to-treat; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-sensitive *S. aureus*; N=number of patients in the analysis set; n=number of patients in the specific category; N1=number of patients in the Analysis Set with the baseline pathogen; PTE=post-therapy evaluation; PVL=Panton-Valentine Leukocidin.
Notes: Percentages are calculated as 100 × (n/N1).

6.3.6 Summary of Clinical Response

A summary of the efficacy analyses from Study TR701-112 is shown in Table 34. Tedizolid phosphate administered once daily for 6 days is non-inferior to linezolid administered twice daily for 10 days for the primary efficacy analysis of early clinical response. Results for key secondary outcomes (clinical response at the EOT Visit and Investigator's assessment of response at the PTE Visit) support the results seen for the primary analysis (Prokocimer 2013).

Table 34. Study TR701-112: Summary of Clinical Response and Key Additional Analyses at the 48 - 72 Hour Visit, EOT and PTE

Efficacy Outcome Measure Additional Analysis	Analysis Set	Tedizolid Phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
Programmatic Assessment of Early Clinical Response at the 48 to 72 Hour Visit (cessation of lesion spread and apyrexia)[a]	ITT	264 (79.5)	266 (79.4)	0.1	(-6.1, 6.2)
≥20% decrease from baseline in lesion area [c]	ITT	259 (78.0)	255 (76.1)	1.9	(-4.5, 8.3)
Sustained Clinical Response at EOT [a]	ITT	230 (69.3)	241 (71.9)	-2.6	(-9.6, 4.2)
Failures at 48 - 72 Hour Visit not carried forward, pain removed from definition [b]		289 (87.0)	294 (87.8)	-0.8	(-5.8, 4.4)
Sustained Clinical Response at EOT [a]	CE-EOT	219 (80.2)	232 (81.1)	-0.9	(-7.7, 5.4)
Failures at 48 - 72 Hour Visit not carried forward, pain removed from definition [b]		258 (94.5)	272 (95.1)	-0.6	(-4.5, 3.2)
Investigator Assessment of Clinical Response at PTE[abc]	ITT	284 (85.5)	288 (86.0)	-0.5	(-5.8, 4.9)
Investigator Assessment of Clinical Response at PTE[abc]	CE-PTE	264 (94.6)	267 (95.4)	-0.8	(-4.6, 3.0)

Abbreviations: CE=clinically evaluable; CI=confidence interval; EOT=end of therapy; n=number of patients in the specific category; PTE=post-treatment evaluation
[a]per 2010 SPA agreement
[b]per August 2010 draft FDA Guidance
[c]per October 2013 FDA Guidance
Notes: N=number of patients in the Analysis Set; n=number of patients in a specified category; Percentages are calculated as 100 × (n/N). 95% CI is adjusted for stratification factor of presence/absence of fever at baseline using the method of Miettinen and Nurminen.
Difference (%)=responder rate for the TR-701 FA treatment group minus linezolid treatment group.

6.4 Study TR701-113

6.4.1 Patient Disposition

Study drug completion rates were high in both groups; 92.5% of patients in the tedizolid phosphate group and 91.0% of patients in the linezolid group completed study drug treatment. Study completion rates were also high in both groups; 94.3% of patients in the tedizolid phosphate group and 91.6% of patients in the linezolid group completed the study.

Table 35 shows the specific patient disposition data for the ITT Analysis Set for TR701-113.

Table 35. Study TR701-113: Patient Disposition (ITT Analysis Set)

	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=334) n (%)
Patients randomized but did not receive drug	1 (0.3)	7 (2.1)
Patients completed study drug	307 (92.5)	304 (91.0)
Patients prematurely discontinued study drug	24 (7.2)	23 (6.9)
Primary reason for study drug discontinuation		
Adverse event	1 (0.3)	4 (1.2)
Treatment failure	9 (2.7)	2 (0.6)
Patient withdrew consent	4 (1.2)	5 (1.5)
Patient lost to follow-up	5 (1.5)	9 (2.7)
At request of Sponsor or Investigator	2 (0.6)	1 (0.3)
Staphylococcus aureus bacteremia	0	0
Patient requires prohibited medication	0	2 (0.6)
Abnormal liver function tests	0	0
Gram-negative infection	0	0
Other	3 (0.9)	0
Patients completed study	313 (94.3)	306 (91.6)
Patients prematurely discontinued from the study	19 (5.7)	28 (8.4)
Primary reason for study discontinuation		
Patient randomized but did not receive study drug	1 (0.3)	7 (2.1)
Patient withdrew consent	6 (1.8)	5 (1.5)
Patient lost to follow-up	11 (3.3)	14 (4.2)
At request of Sponsor or Investigator	0	1 (0.3)
Other	1 (0.3)	1 (0.3)

Abbreviations: ITT=intent-to-treat; N=number of patients in the Analysis Set; n=number of patients in the specific category.

6.4.2 IV and Oral Dosing Exposure

Total exposure to active study drug: Of the 332 patients in the tedizolid phosphate group, 331 patients were included in the Safety Analysis Set, and the majority (313 patients [94.6%]) received 5 to 6 doses of tedizolid phosphate. Of the 334 patients in the linezolid group, 327 patients were included in the Safety Analysis Set, and the majority (295 patients [90.2%]) received 19 to 20 doses of linezolid (Table 36).

IV and Oral: The majority of patients in the tedizolid phosphate and linezolid groups received both IV and oral study drug (80.7% and 82.3%). A total of 19.3% and 17.7% of patients in the tedizolid phosphate and linezolid groups received only IV therapy. Continuation of IV drug through the full period of drug administration generally reflected standard medical practice at the clinical site. About two-thirds of patients switched to oral therapy after one day of IV therapy.

Table 36. Study TR701-113: IV and Oral Drug Exposure (Safety Analysis Set)

Number of doses	Tedizolid Phosphate (N=331) n (%)	Linezolid (N=327) n (%)
Number of active oral or IV drug doses		
1-2 doses	7 (2.1)	NA
3-4 doses	8 (2.4)	NA
5-6 doses	313 (94.6)	NA
>6 doses	3 (0.9)	NA
1-4 doses	NA	6 (1.8)
5-8 doses	NA	8 (2.4)
9-12 doses	NA	5 (1.5)
13-18 doses	NA	12 (3.7)
19-20 doses	NA	295 (90.2)
>20 doses	NA	1 (0.3)
Received:		
Oral and IV Study Drug	267 (80.7)	269 (82.3)
Only IV Study Drug	64 (19.3)	58 (17.7)
Days to Oral Switch, N1	267	269
<1 day	0 (0)	2 (0.7)
1 day	170 (63.7)	171 (63.6)
2 day	48 (18.0)	41 (15.2)
3 day	28 (10.5)	30 (11.2)
4 day	12 (4.5)	7 (2.6)
≥5 days	9 (3.4)	18 6.7)

Abbreviations: IV=Intravenous
Notes: N=Number of patients in the Safety Analysis Set. n=Number of patients in the specific category. Percentages are calculated as 100 x (n/N).

6.4.3 Demographics and Baseline Characteristics

Of the 666 patients enrolled in Study TR701-113, 65.9% were male and the mean age was 45.6 years (range 15 to 89 years), most patients were White (85.1%). The geographical distribution of enrolled patients in TR701-113 shows that 47% of enrolled patients were in North America (314 patients), followed by 34% from Europe (223 patients), followed by 14% from South Africa (94 patients), 4% from Latin American (26 patients) and the remaining 1% from Australia and New Zealand (9 patients).

Demographics and baseline characteristics of patients in Study TR701-113 are summarized for the ITT Analysis Set in Table 37.

Table 37. Study TR701-113: Demographics and Baseline Characteristics (ITT Analysis Set)

Characteristic	Statistic	Tedizolid Phosphate (N=332)	Linezolid (N=334)
Sex			
Female	n (%)	107 (32.2)	120 (35.9)
Male	n (%)	225 (67.8)	214 (64.1)
Age (years)	Mean	45.6	45.6
	SD	15.79	15.57
Age group			
<65 years	n (%)	289 (87.0)	301 (90.1)
≥65 to ≤75 years	n (%)	32 (9.6)	19 (5.7)
>75 years	n (%)	11 (3.3)	14 (4.2)
Ethnicity: Hispanic or Latino	n (%)	67 (20.2)	63 (18.9)
Race			
White	n (%)	285 (85.8)	282 (84.4)
Asian	n (%)	4 (1.2)	7 (2.1)
Black or African American	n (%)	38 (11.4)	37 (11.1)
Native Hawaiian or Other Pacific Islander	n (%)	2 (0.6)	1 (0.3)
American Indian or Alaskan Native	n (%)	3 (0.9)	4 (1.2)
Other	n (%)	0	3 (0.9)
Region			
North America	n (%)	156 (47.0)	158 (47.3)
Latin America	n (%)	13 (3.9)	13 (3.9)
Europe	n (%)	112 (33.7)	111 (33.2)
South Africa	n (%)	48 (14.5)	46 (13.8)
Australia & New Zealand	n (%)	3 (0.9)	6 (1.8)
BMI (kg/m^2)	n	332	334
	Median	27.0	27.4
	Min, Max	14.23, 69.88	14.75, 56.24

Abbreviations: BMI=body mass index; ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation
Notes: N=number of patients in the Analysis Set; n=number of patients in the specific category. Percentages are calculated as 100 × (n/N).

The most common ABSSSI relevant medical history (reported in ≥20% of patients in either treatment group) in the ITT Analysis Set were current or recent IV drug use (19.9% tedizolid phosphate, 22.2% linezolid) and Hepatitis C positive at baseline (20.2 for tedizolid phosphate, 24.9% for linezolid) (Table 38). A similar percentage of patients in both groups (9.6% tedizolid phosphate, 12.3% linezolid) had a history of diabetes mellitus.

Table 38. Study TR701-113: ABSSSI Relevant Medical History (ITT Analysis Set)

Characteristic	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=334) n (%)
Hospitalization during treatment	140 (42.2)	143 (42.8)
Antibacterials (within 4-30 days of randomization)	14 (4.2)	12 (3.6)
Hepatitis C positive at baseline	65 (20.2)	80 (24.9)
HIV positive	8 (2.4)	7 (2.1)
Current or recent IV drug use	66 (19.9)	74 (22.2)
Diabetes mellitus	32 (9.6)	41 (12.3)

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; FA=free acid; HIV=human immunodeficiency virus; ITT=intent-to-treat; IV=intravenous; N=number of patients in the Analysis Set; n=number of patients in the specific category
Notes: Percentages are calculated as 100 × (n/N).

Most patients enrolled in Study TR701-113 had cellulitis/erysipelas (50.0% tedizolid phosphate, 50.3% linezolid), fewer had major cutaneous abscess (20.5% tedizolid phosphate, 20.4% linezolid) and wound infection (29.5% tedizolid phosphate, 29.3% linezolid). A maximum of 30% of the enrolled population were to have major cutaneous abscess. Most infections occurred on the leg or arm. There were no differences between treatment groups in the type and location of infections in the ITT Analysis Set. The type and location of ABSSSIs are summarized for the ITT Analysis Set in Table 39.

Table 39. Study TR701-113: Type and Location of ABSSSI (ITT Analysis Set)

Characteristic	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=334) n (%)
Type of ABSSSI infection		
Cellulitis/erysipelas	166 (50.0)	168 (50.3)
Major cutaneous abscess	68 (20.5)	68 (20.4)
Wound infection	98 (29.5)	98 (29.3)
Superficial incisional surgical site infection	5 (1.5)	3 (0.9)
Post-traumatic wound	93 (28.0)	95 (28.4)
Anatomical site		
Head	15 (4.5)	15 (4.5)
Neck	2 (0.6)	5 (1.5)
Chest	9 (2.7)	8 (2.4)
Abdomen	12 (3.6)	7 (2.1)
Back	4 (1.2)	5 (1.5)
Groin	11 (3.3)	12 (3.6)
Buttock	22 (6.6)	28 (8.4)
Shoulder	8 (2.4)	5 (1.5)
Axillary	14 (4.2)	10 (3.0)
Hand	31 (9.3)	20 (6.0)
Arm	103 (31.0)	105 (31.4)
Leg	124 (37.3)	131 (39.2)
Foot	22 (6.6)	21 (6.3)

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; e-CRF=electronic case report form; ITT=intent-to-treat
Notes: N=number of patients in the Analysis Set; n=number of patients in the specific category. Percentages are calculated as 100 × (n/N). A patient may have multiple anatomical sites as long as they are contiguous. If the primary infection is present on both anatomical sides (eg, left and right), the site is counted only once. Data drawn from e-CRFs. Type of ABSSSI infection is actual from the CRF rather than the infection used for randomization, if different.

The population studied had severe infections. The key marker of severity of the skin infections treated was the size of the lesion area. Overall (for all infection types), the median surface area (erythema + induration + edema) at baseline was 231.3 cm^2 in the tedizolid phosphate group and 238.6 cm^2 in the linezolid group for the ITT Analysis Set. Two patients in the tedizolid phosphate group were enrolled with a lesion area of <75 cm^2 due to an error at the site.

Adjacent lymphadenopathy, a marker of dissemination of the infection beyond the primary lesion was the sign most frequently seen (70.8% tedizolid and 70.4% linezolid), followed by WBC ≥10,000 cells/mm^3 or <4000 cells/mm^3 (53.0% tedizolid and 45.2% linezolid. Temperature ≥38°C was also noted in 31.0% and 29.0% of patients in the tedizolid phosphate and linezolid groups, respectively. A summary of the severity of infection at baseline for Study 113 is shown in Table 40.

Table 40. Study TR701-113: Baseline Regional and Systemic Symptoms of Infection (ITT Analysis Set)

Regional/Systemic Sign of Infection	Tedizolid Phosphate N=332	Linezolid N=334
Lesion area, cm^2, median (range)	231.3 (22.5, 2711.24)	238.6 (76, 5220)
Lymphadenopathy, n (%)		
Lymphadenopathy	235 (70.8)	235 (70.4)
Lymph node tenderness	230 (69.3)	229 (68.6)
Lymph node increase in volume or palpable	231 (69.6)	229 (68.6)
WBC ≥10,000 cells/mm^3 or <4000 cells/mm^3, n (%)	176 (53.0)	151 (45.2)
Immature neutrophils >10%, N1, n (%)	328, 53 (16.2)	327, 40 (12.2)
Temperature ≥38°C (fever), n (%)	103 (31.0)	97 (29.0)

Abbreviations: ITT=intent-to-treat; max=maximum; min=minimum;; N1=number of patients in this specific in the Analysis Set; n=number of patients in the specific category; WBC=white blood cell
Notes: Percentages are calculated as 100 × (n/N). Baseline is the last assessment made before first dose of study drug.

A Gram-positive pathogen was isolated from the primary infection site at baseline in approximately 59% of patients in both groups and most pathogens isolated were Gram-positive aerobes (97.5% tedizolid phosphate and 98.5% linezolid). The most common pathogen isolated was *S. aureus* (80.2% tedizolid phosphate and 82.7% linezolid) with MRSA accounting for 26.9% and 27.7% of infections in the tedizolid phosphate and linezolid groups, respectively and MSSA accounting for 53.3% and 55.0% of infections in the tedizolid phosphate and linezolid groups, respectively (Table 41). *S. pyogenes* was reported in 12.7% and 7.9% of infections in the tedizolid phosphate and linezolid groups, respectively. Other Gram-positive aerobes and anaerobes were each reported in <10% of patients in either treatment group.

Table 41. Study TR701-113: Pathogenic Organisms from Baseline Primary ABSSSI Site or Blood Culture by Genus and Species (microITT Analysis Set)

Pathogenic Organism	TR-701 FA (N=197) n (%)	Linezolid (N=202) n (%)
Gram-positive organisms (aerobes)	**192 (97.5)**	**199 (98.5)**
S. aureus	158 (80.2)	167 (82.7)
MRSA	53 (26.9)	56 (27.7)
MSSA	105 (53.3)	111 (55.0)
PVL S. aureus	93 (47.2)	78 (38.6)
S. pyogenes	25 (12.7)	16 (7.9)
S. anginosus-milleri group	15 (7.6)	12 (5.9)
S. intermedius	7 (3.6)	10 (5.0)
S. constellatus	7 (3.6)	2 (1.0)
S. milleri	1 (0.5)	0
E. faecalis	5 (2.5)	4 (2.0)
S. lugdunensis	1 (0.5)	5 (2.5)
S. agalactiae	0	5 (2.5)
Gram-positive organisms (anaerobes)	**7 (3.6)**	**5 (2.5)**
Gram-negative organisms (aerobes)	**3 (1.5)**	**1 (0.5)**
Gram-negative organisms (anaerobes)	**0**	**1 (0.5)**

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; FA=free acid; microITT=microbiological intent-to-treat; MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*; N=number of patients in the Analysis Set; n=number of patients in the specific category; PVL=Panton-Valentine Leukocidin, PVL *S. aureus* refers to PVL positive status in *S. aureus*

Notes: Percentages are calculated as 100 × (n/N). Patients with the same pathogen isolated from multiple specimens are counted only once for that pathogen. Patients with the same pathogen identified from both the blood and primary ABSSSI cultures are counted only once. Patients with both MRSA and MSSA are counted only once in overall *S. aureus* row, and untyped *S. aureus* pathogens are only counted in the overall *S. aureus* row.

6.4.4 Primary Endpoint: Early Clinical Response

Early clinical response at the 48 - 72 Hour Visit was observed in 85.2% of patients in the tedizolid phosphate group and 82.6% of patients in the linezolid group in the ITT Analysis Set (treatment difference 2.6%; 95% CI: -3.0%, 8.2%). The lower limit of the 95% CI was greater than -10%, which was the predefined requirement for non-inferiority. Based on these results, tedizolid phosphate was non-inferior to linezolid for the primary efficacy outcome of early clinical response. Primary endpoint data for TR701-113 is shown in Table 42.

A total of 14.8% of patients in the tedizolid phosphate group and 17.4% of patients in the linezolid group were nonresponders or missing data in the ITT Analysis Set. The primary reasons for the early clinical outcome of nonresponder was a <20% reduction in the primary ABSSSI lesion area (12.0% of tedizolid phosphate patients and 12.3% of linezolid patients). Missing lesion measurements were found in 1.5% of tedizolid phosphate patients and 4.2% of linezolid patients.

Table 42. Study TR701-113: Primary Efficacy Analysis - Early Clinical Response at the 48 - 72 Hour Visit (ITT Analysis Set)

Response	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=334) n (%)	Difference (%)	95% CI for Difference
Responder	283 (85.2)	276 (82.6)	2.6	(-3.0, 8.2)
Nonresponder or missing data	49 (14.8)	58 (17.4)		
Nonresponder	44 (13.3)	44 (13.2)		
<20% decrease in lesion area	40 (12.0)	41 (12.3)		
Systemic concomitant antibiotics potentially effective against baseline pathogen	7 (2.1)	6 (1.8)		
Missing data	5 (1.5)	14 (4.2)		

Abbreviations: CI=confidence interval; ITT=intent-to-treat
Notes: N=number of patients in the Analysis Set; n=number of patients in the specific category. Percentages are calculated as 100 × (n/N). Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group. 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen. Reasons for nonresponse are not mutually exclusive.

Early clinical response by by baseline fever status and type of infection was generally similar in the TR-701 FA and linezolid groups in the ITT Analysis Set (Table 43). Small differences were noted between type of infection groups; however, these were not consistent across infection type. Overall, early clinical response by type of infection was seen in approximately 81.1% to 91.1% of patients in the tedizolid phosphate group and approximately 80.0% to 90.4% in the linezolid group. Patients with cellulitis/erysipelas and the lowest early clinical response rates in both groups.

Early clinical response was similar in both treatment groups in the 2 highest enrolling regions, North America (82.1% tedizolid phosphate and 82.9% linezolid) and Europe (92.9% tedizolid phosphate and 89.2% linezolid) (Table 43). Some differences were noted between groups in early clinical response in the other 3 regions (Latin America, South Africa, and Australia/New Zealand); however, this may be due to fewer patients being enrolled in these regions.

Table 43. Study TR701-113: Early Clinical Response at the 48-72 Hour Visit by Baseline Fever, Type of Infection and Geographic Region (ITT Analysis Set)

Strata	Tedizolid Phosphate (N=332) n/N1 (%)	Linezolid (N=334) n/N1 (%)	Difference (%)	95% CI for Difference
Baseline Fever				
Presence	96/103 (93.2)	89/97 (91.8)	1.4	(-6.3, 9.5)
Absence	187/229 (81.7)	187/237 (78.9)	2.8	(-4.5, 10.0)
Type of Infection				
Cellulitis/erysipelas	137/169 (81.1)	138/171 (80.7)	0.4	(-8.1, 8.8)
Major cutaneous abscess	64/73 (87.7)	66/73 (90.4)	-2.7	(-13.6, 7.9)
Wound infection	82/90 (91.1)	72/90 (80.0)	11.1	(0.8, 21.7)
Region				
North America	128/156 (82.1)	131/158 (82.9)	-0.8	(-9.4, 7.6)
Latin America	11/13 (84.6)	12/13 (92.3)	-7.7	(-36.9, 21.6)
Europe	104/112 (92.9)	99/111 (89.2)	3.7	(-4.1, 11.7)
South Africa	39/48 (81.3)	31/46 (67.4)	13.9	(-3.9, 31.2)
Australia/New Zealand	1/3 (33.3)	3/6 (50.0)	-16.7	(-66.9, 47.6)

Abbreviations: CI=confidence interval; ITT=intent-to-treat; N=number of patients in the Analysis Set; n=number of patients in the specific category; N1=number of patients in the stratum for the Analysis Set
Notes: Percentages are calculated as 100 × (n/N1). 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen. Difference (%)=responder rate for the TR-701 FA treatment group minus linezolid treatment group. A responder is defined as having at least 20% reduction from baseline in lesion area.

6.4.5 Secondary Endpoints

Clinical Response at the EOT Visit

Clinical response at the EOT Visit was observed in a similar percentage of patients in the tedizolid phosphate and linezolid groups in the ITT Analysis Set (87.0% and 88.0%, respectively; treatment difference -1.0%; 95% CI: -6.1%, 4.1%) and in the CE-EOT Analysis Set (89.5% and 93.6%, respectively; treatment difference -4.1%; 95% CI: -8.8%, 0.3%). The lower limit of the 95% CIs were greater than -10% for clinical response at the EOT Visit in the ITT and CE-EOT Analysis Sets (Table 44).

A total of 9.9% of patients in the tedizolid phosphate group and 7.2% of patients in the linezolid group were clinical failures for clinical response at the EOT Visit in the ITT Analysis Set (Table 45). The primary reasons for clinical failure were tenderness worse than mild (4.8% of tedizolid phosphate patients and 2.1% of linezolid patients) and additional antibiotic therapy for the primary lesion (3.9% of tedizolid phosphate patients and 1.8% of linezolid patients).

Table 44. Study TR701-113: Sustained Clinical Response at the EOT Visit (ITT and CE-EOT Analysis Sets)

Analysis Set Response	Tedizolid phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
ITT, N	**332**	**334**		
Clinical success	289 (87.0)	294 (88.0)	-1.0	(-6.1, 4.1)
Clinical failure or indeterminate	43 (13.0)	40 (12.0)		
Clinical failure	33 (9.9)	24 (7.2)		
Indeterminate	10 (3.0)	16 (4.8)		
CE-EOT, N	**304**	**299**		
Clinical success	272 (89.5)	280 (93.6)	-4.1	(-8.8, 0.3)
Clinical failure	32 (10.5)	19 (6.4)		

Abbreviations: CE=clinically evaluable; CI=confidence interval; EOT=end of therapy; ITT=intent-to-treat; N=number of patients in the specified Analysis Set; n=number of patients in the specific category
Notes: Percentages are calculated as 100 × (n/N). 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen. Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group.

Table 45. Study TR701-113: Reasons for Clinical Failure at the EOT Visit (ITT Analysis Set)

Reasons for Clinical Failure	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=334) n (%)
Number of clinical failures for clinical response	33 (9.9)	24 (7.2)
Temperature at EOT >37.6 deg C	1 (0.3)	0
No decrease from baseline in primary ABSSSI lesion size (surface area, length, or width)	10 (3.0)	6 (1.8)
Clinical assessment of tenderness worse than mild	16 (4.8)	7 (2.1)
Persistent purulent drainage from wound infection at same or greater intensity than baseline	0	0
Systemic concomitant antibiotics potentially effective against baseline pathogen	5 (1.5)	8 (2.4)
TEAE leading to study drug discontinuation and additional antibiotic therapy to treat ABSSSI	1 (0.3)	4 (1.2)
Additional antibiotic therapy for primary lesion	13 (3.9)	6 (1.8)
Unplanned major surgical intervention due to study drug failure	7 (2.1)	3 (0.9)
Osteomyelitis after baseline	0	0
Incision and drainage of ABSSSI site	11 (3.3)	6 (1.8)
Death within 28 days of first infusion of study drug	1 (0.3)	1 (0.3)

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; FA=free acid; ITT=intent-to-treat
Notes: n=number of patients in the specific category; N=number of patients in the Analysis Set. Missing temperature data includes temperature measurements collected outside the prespecified time period (48 to 72 hours). A patient may have more than 1 reason for nonresponse.

Investigator Assessment of Clinical Response

The clinical success rates at the PTE Visit based on the Investigators assessment were similar in the tedizolid phosphate and linezolid groups for Investigator assessments of clinical response at the PTE Visit in the ITT Analysis Set (88.0% and 87.7%, respectively; treatment difference 0.3%; 95% CI: -4.8%, 5.3%) and in the CE-PTE Analysis Set (92.4% and 96.1%, respectively; treatment difference -3.7%; 95% CI: -7.7%, 0.2%). For each of these secondary analyses, the lower limit of the 95% CI was above -10%. The primary reason for clinical failure was that the patient received an additional antibiotic for the primary lesion (Table 47). Only 2 patients were failures due to an unplanned surgical intervention. A total of 5.4% of patients in the tedizolid phosphate group and 9.0% of patients in the linezolid group had indeterminate response which consisted primarily of patients who were lost to follow-up.

Table 46. Study TR701-113: Investigator Assessment of Clinical Response at the PTE Visit (ITT and CE-PTE Analysis Sets)

Analysis Set Response	Tedizolid phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
ITT, N	332	334		
Clinical success	292 (88.0)	293 (87.7)	0.3	(-4.8, 5.3)
Clinical failure or indeterminate	40 (12.0)	41 (12.3)		
Clinical failure	22 (6.6)	11 (3.3)		
Indeterminate	18 (5.4)	30 (9.0)		
CE-PTE, N	290	280		
Clinical success	268 (92.4)	269 (96.1)	-3.7	(-7.7, 0.2)
Clinical failure	22 (7.6)	11 (3.9)		

Abbreviations: CE=clinically evaluable; CI=confidence interval; ITT=intent-to-treat; N=number of patients in the specific Analysis Set; n=number of patients in the specific category; PTE=post-therapy evaluation
Notes: Percentages are calculated as 100 × (n/N).
Difference (%)=clinical success rate for the Tedizolid Phosphate treatment group minus linezolid treatment group (ITT and CE-PTE Analysis Sets). 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen.

Table 47. Study TR701-113: Reasons for Clinical Failure at the PTE Visit (ITT Analysis Set)

	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=334) n (%)
Number of clinical failures for investigator assessment of clinical response	22 (6.6)	11 (3.3)
Additional antibiotic therapy for primary lesion	19 (5.7)	8 (2.4)
Unplanned major surgical intervention due to study drug failure	2 (0.6)	0
Osteomyelitis after baseline	0	0
Persistent gram-positive pathogen bacteremia	1 (0.3)	0
TEAE leading to study drug discontinuation and additional antibiotic therapy to treat ABSSSI	1 (0.3)	4 (1.2)
Death within 28 days of first infusion	1 (0.3)	1 (0.3)

Clinical Response By Pathogen at the PTE Visit

Review of the clinical success based on the Investigator's assessment at the PTE Visit by key baseline pathogen from the primary ABSSSI site or blood culture showed that >87% of patients had a clinical success for all Gram-positive aerobes reported at baseline in the microITT Analysis Set, including the most common pathogens, *S. aureus* and *S. pyogenes*. The percentage of patients with a favorable response was similar in both treatment groups and similar results were observed in the ME Analysis Set (Table 48).

Table 48. Study TR701-113: Investigator Assessment of Clinical Success at the PTE Visit by Key Baseline Pathogen (microITT Analysis Set)

Baseline Pathogen	Tedizolid Phosphate (N=197)		Linezolid (N=202)	
	N1	Clinical Success n (%)	N1	Clinical Success n (%)
Gram-positive organisms (aerobes)	**192**	**168 (87.5)**	**199**	**176 (88.4)**
S. aureus	158	143 (90.5)	167	146 (87.4)
MRSA	53	43 (81.1)	56	42 (75.0)
MSSA	105	100 (95.2)	111	104 (93.7)
PVL *S. aureus*	93	82 (88.2)	78	64 (82.1)
S. pyogenes	25	23 (92.0)	16	15 (93.8)
S. anginosus group	15	10 (66.7)	12	12 (100.0)
E. faecalis	5	4 (80.0)	4	4 (100.0)
S. lugdunensis	1	1 (100.0)	5	5 (100.0)
S. agalactiae	0	0	5	5 (100.0)
Gram-positive organisms (anaerobes)	**7**	**5 (71.4)**	**5**	**4 (80.0)**

Abbreviations; microITT = microbiological intent-to-treat; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*; N=number of patients in the Analysis Set; n=number of patients in the specific category; N1=number of patients in the Analysis Set with the baseline pathogen; PTE=post-therapy evaluation; PVL=Panton-Valentine Leukocidin
Notes: Percentages are calculated as isolated from multiple specimens are counted only once for that pathogen.

6.4.6 Summary of Efficacy

A summary of the efficacy analyses from Study TR701-113 is shown in Table 49. Tedizolid phosphate administered once daily for 6 days is non-inferior to linezolid administered twice daily for 10 days for the primary efficacy outcome of early clinical response. Results for each of the key secondary outcomes (clinical response at the EOT Visit and Investigator's assessment at the PTE Visit) support the results seen for the primary analysis.

Table 49. Study TR701-113: Summary of Clinical Response at the 48 - 72 Hour Visit, EOT and PTE

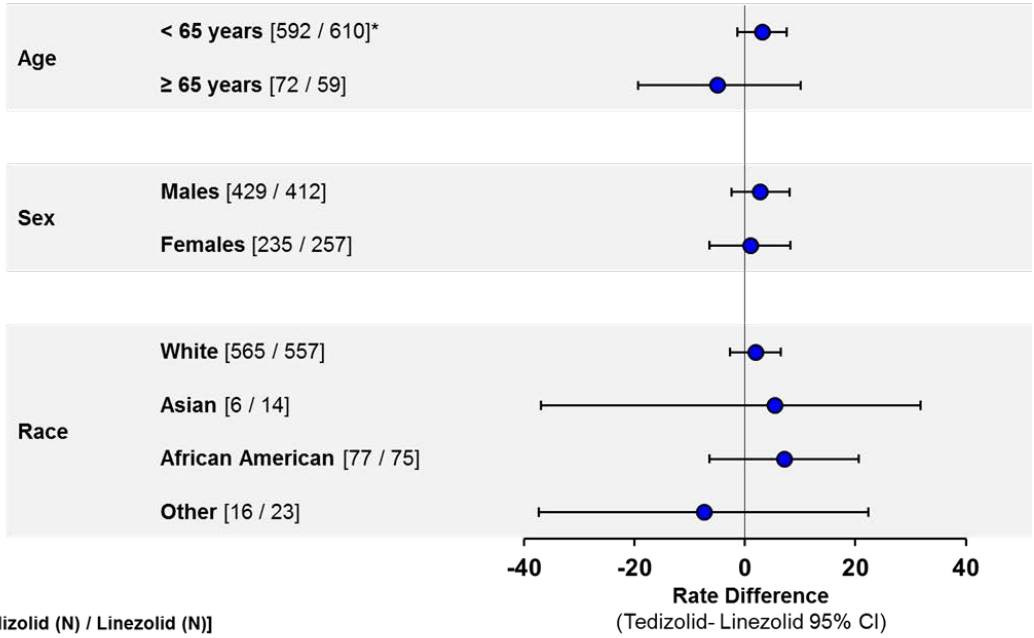
Efficacy Outcome Measure	Analysis Set	Tedizolid Phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
Programmatic Determination of Early Clinical Response at the 48 - 72 Hour Visit (>20% reduction in lesion size)[b]	ITT	283 (85.2)	276 (82.6)	2.6	(-3.0, 8.2)
Sustained Clinical Response at EOT[a]	ITT	289 (87.0)	294 (88.0)	-1.0	(-6.1, 4.1)
Sustained Clinical Response at EOT[a]	CE-EOT	272 (89.5)	280 (93.6)	-4.1	(-8.8, 0.3)
Investigator Assessment of Clinical Response at PTE[b]	ITT	292 (88.0)	293 (87.7)	0.3	(-4.8, 5.3)
Investigator Assessment of Clinical Response at PTE[b]	CE-PTE	268 (92.4)	269 (96.1)	-3.7	(-7.7, 0.2)

Abbreviations: ITT=intent-to-treat; CE=clinically evaluable; CI=confidence interval; EOT=end of therapy; n=number of patients in the specific category; PTE=post-treatment evaluation
Notes: N=number of patients in the Analysis Set; n=number of patients in a specific category; Percentages are calculated as 100 × (n/N). 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen. Difference (%)=responder rate for the tedizolid phosphate treatment group minus linezolid treatment group.
[a]Per draft 2010 FDA Guidance
[b]Per ABSSSI 2013 FDA Guidance

6.5 Pooled Subgroup Analysis for Primary Endpoint for Phase 3 Trials

Efficacy (≥20% reduction in lesion area) analyses by subgroups were conducted in the combined Phase 3 patients (Studies TR701-112 and TR701-113) in the ITT Analysis Set. The treatment differences and associated 95% confidence intervals for subgroups defined by age, sex and race in Figure 11. A similar percentage of patients in these subgroups were early clinical responders in the tedizolid phosphate and linezolid groups.

Figure 11. Pooled Studies: Subgroup Analysis of Primary Endpoint (≥20% Reduction in Lesion Size): Demographics (ITT Analysis Set)



CI=Confidence Interval

Early clinical response rates by BMI show no difference between the tedizolid and linezolid groups except for low and high BMI groups (Table 50). The numbers of patients in the low BMI group is too small to make any conclusions. Baseline characteristics including age, sex, country, clinical syndrome, IV drug use, and diabetes, as well as severity characteristics including baseline lesion area, lymphadenopathy, leukocytosis/leukopenia, fever, and bands in the high BMI groups in the two treatment groups were examined. There were no differences between the tedizolid phosphate and linezolid groups with respect to these baseline factors, except 74.1% of tedizolid phosphate patients and 53.8% of linezolid patients in the BMI≥40 group had cellulitis. As shown in Table 27 for study TR701-112 and Table 43 for study TR701-113, patients with cellulitis, regardless of treatment group, had a lower outcome rate as compared with patients with abscess or wound infection. However, the numbers in the BMI≥40 group were small, limited the usefulness of adjusted analyses. Drug exposure was also examined and in patients with BMI values <30, 30-35, >35 this was found to be similar. In patients with BMI 35-<40, a lower response was seen in tedizolid treated patient in study 112 only, not in study 113. Patients with BMI >40 were only recruited in study 113. A review of patients who were non-responders provided no apparent explanation for the numerical differences in the early clinical response rate between the 2 treatment groups.

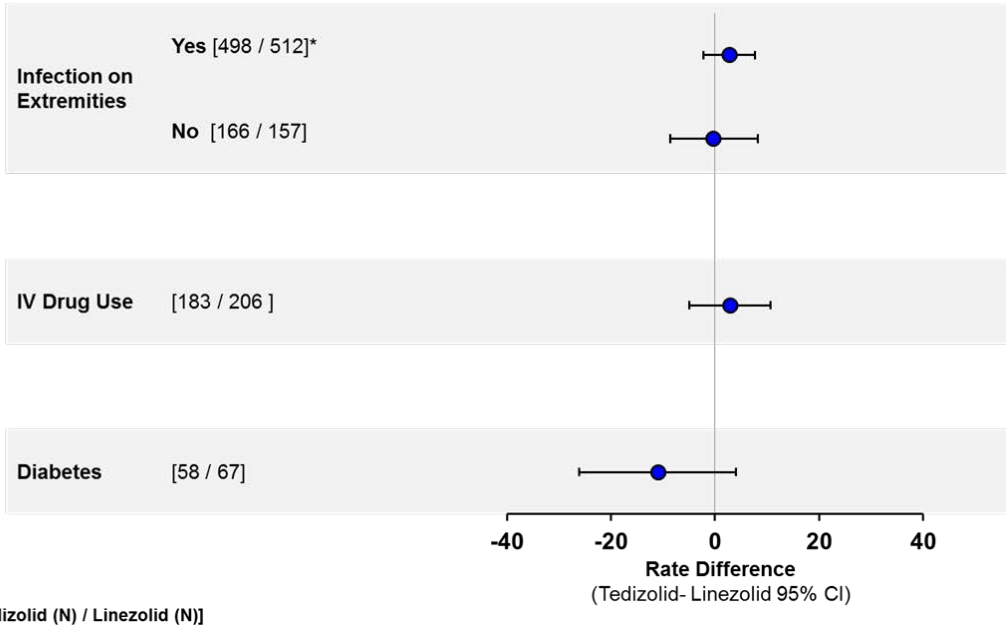
Table 50. Pooled Studies: Subgroup Analysis of Primary Endpoint (≥20% Reduction in Lesion Size): BMI (ITT Analysis Set)

BMI range	Tedizolid Phosphate (200 mg) n/N (%)	Linezolid (1200 mg) n/N (%)	Rate Difference[a] (CI)
BMI <18.5	10/12 (83.3)	4/8 (50.0)	42.4 (-4.0, 73.5)
18.5≤BMI<25	195/219 (89.0)	183/227 (80.6)	8.6 (2.0, 15.3)
25≤BMI<30	184/233 (79.0)	160/202 (79.2)	-0.3 (-7.9, 7.5)
30≤BMI<35	84/105 (80.0)	111/146 (76.0)	-4.3 (-6.4, 14.3)
35≤BMI<40	53/68 (77.9)	52/60 (86.7)	-8.9 (-22.2, 4.8)
BM≥40[b]	16/27 (59.3)	21/26 (80.8)	-21.5 (-44.3, 3.5)

Abbreviation: BMI=body mass index
Note: n is the number of patients with a 20% reduction in lesion size; N is the total number of patients for that BMI range
[a]Difference is the weight treatment difference (weighted by study) and the CI is adjusted for study.
[b]BMI ≥40 only in study 113.

The treatment difference and 95% confidence intervals for early clinical response by relevant medical history is provided in Figure 12. Response rates were similar between the treatment groups based on location of infection, and IV drug use. For diabetes, patients on tedizolid phosphate had a numerically lower response rate as compared with patients on linezolid. There is overlap between the diabetic and obese populations and as with the high BMI groups, no apparent explanation could be found for the numerical difference. Median tedizolid AUC was slightly lower in subjects with diabetes with a high degree of overlap in the range of exposures and was similar with or without obesity as a comorbidity.

Figure 12. Pooled Studies: Subgroup Analysis of Primary Endpoint (≥20% Reduction in Lesion Size) by Medical History (ITT Analysis Set)

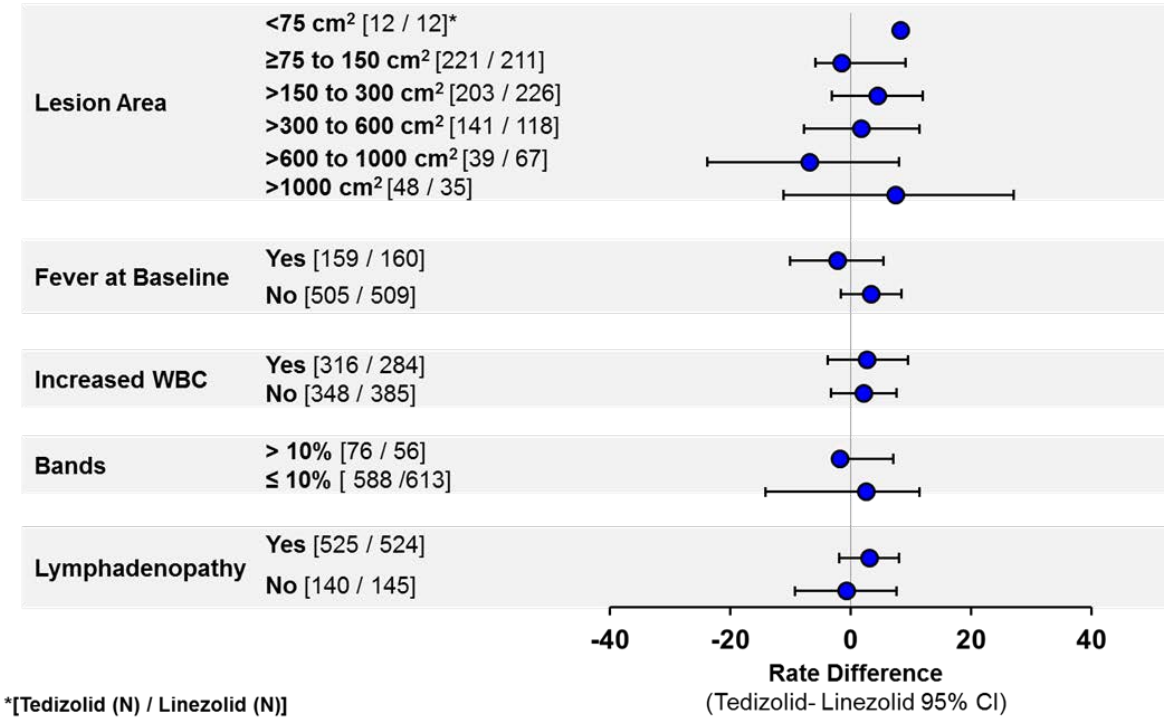


*[Tedizolid (N) / Linezolid (N)]

CI=confidence interval; IV=intravenous

The treatment difference and 95% confidence intervals for early clinical response by characteristics defining severity is provided in Figure 13. Response rates were similar between the treatment groups based on infection lesion area, presence or absence of fever at baseline, and the presence or absence of increased WBCs, bands and infection-associated lymphadenopathy. In patients with bacteremia at baseline, 100% of patients who received tedizolid phosphate (11/11) and 69% of patients who received linezolid (11/16) were responders based on clinical response at the 48-72 Hour Visit and had negative cultures or were presumed to have negative cultures. In tedizolid-treated patients, *S. aureus* bacteremia was caused by MRSA in 2 patients and by MSSA in 4 patients.

Figure 13. Pooled Studies: Subgroup Analysis of Primary Endpoint (>20% Reduction in Lesion Size) by Infection Characteristics (ITT Analysis Set)



CI=Confidence Interval

6.6 Pooled Percent Reduction in Lesion Area at the EOT and PTE Visits

Percent reduction in lesion area at the EOT and PTE Visits in the CE-PTE Analysis Set is provided in Table 51 for those patients who have lesion measurements at these time points. At the EOT Visit, about 81% of patients in both treatment groups have achieved a ≥90% reduction in lesion area, with another 7% showing an 80-<90% reduction in lesion area. By the PTE Visit, nearly all patients, 95.4% in the tedizolid phosphate group and 96.1% of patients in the linezolid group have at least a 90% reduction in lesion area. When clinical cure was assessed by the Investigator at the PTE Visit, 94.8%) tedizolid phosphate-treated patients were assessed as a clinical success and comparably, 95.4% linezolid-treated patients were assessed as a clinical success. Thus, when evaluating clinical response at PTE based on lesion area (Table 51) or the Investigator's judgment (92.4 %vs 96.1%), the same conclusion regarding clinical success is reached.

Table 51. Percent Reduction in Lesion Area at EOT and PTE - CE-PTE Analysis Set

Measurement Visit	Tedizolid Phosphate (200 mg) n/N (%)	Linezolid (1200 mg) n/N (%)
EOT, N1	**563**	**560**
Any increase	7 (1.2)	8 (1.4)
0-<5% decrease	2 (0.4)	1 (0.2)
5-<10% decrease	2 (0.4)	0 (0)
10-<15% decrease	1 (0.2)	1 (0.2)
15-<20% decrease	0 (0)	0 (0)
20-<30% decrease	4 (0.7)	4 (0.7)
30-<40% decrease	7 (1.2)	4 (0.7)
40-<50% decrease	3 (0.5)	8 (1.4)
50-<60% decrease	6 (1.1)	6 (1.1)
60-<70% decrease	14 (2.5)	9 (1.6)
70-<80% decrease	20 (3.6)	18 (3.2)
80-<90% decrease	41 (7.3)	39 (7.0)
>=90% decrease	456 (81.0)	462 (82.5)
PTE N1	**540**	**542**
Any increase	0 (0)	0 (0)
0-<30% decrease	0 (0)	0 (0)
30-<40% decrease	2 (0.4)	2 (0.4)
40-<50% decrease	3 (0.6)	2 (0.4)
50-<60% decrease	1 (.2)	0 (0)
60-<70% decrease	5 (0.9)	4 (0.7)
70-<80% decrease	1 (.2)	4 (0.7)
80-<90% decrease	13 (2.4)	9 (1.7)
>=90% decrease	515 (95.4)	521 (96.1)

6.7 Concordance Between Early Response and Clinical Success at PTE Visit

The concordance analysis of the early clinical response at 48-72 hours and clinical success at PTE visit (Day 18-25) is provided for data pooled across both treatment groups and studies as shown in Table 52. The analysis is presented for patients in the ITT Analysis Set and thus, includes patients with missing data at either the 48-72 Hour Visit or the PTE Visit. Concordance is defined as the percentage of patients who are both an early responder and assessed by the investigator as a clinical cure plus the percentage of patients were both an early non-responder and assessed by the investigator as a clinical failure plus the percentage of patients that were an indeterminate at both time points.

Concordance between early clinical response and Investigator's assessment at the post therapy evaluation was 80.5%. A total of 92.5% (993/1073) of patients who were an early clinical responder were also a success at the PTE Visit, illustrating that an early positive response is a good indicator of success at a later time point. However, 18.0% (35/194) of patients who were an early failure were also a failure at PTE.

A total of 11% of patients were non-responders at 48 - 72 hours and were assessed by the investigator as a clinical success. This result is expected since the outcomes at these time points may evaluate different processes with the early time point measuring the drug effect and the later time point also reflecting the natural history of the disease.

Table 52. Pooled Studies: Concordance of Early Clinical Response and Investigators Assessment at PTE visit (ITT Analysis Set)

	Early Clinical Response			
Investigator's Assessment of Clinical Cure at PTE	**Clinical Success n (%)**	**Clinical Failure n (%)**	**Indeterminate n (%)**	Total N
Clinical Success	**993 (74.5)**	146 (11.0)	18 (1.4)	1157
Clinical Failure	24 (1.8)	**35 (2.6)**	3 (0.2)	62
Indeterminate	56 (4.2)	13 (1.0)	**45 (3.4)**	114
Total N	1073	194	66	1333

7 TEDIZOLID PHOSPHATE SAFETY

7.1 Summary of Safety Experience with Tedizolid Phosphate

- Generally similar safety profile in Phase 3 studies for tedizolid phosphate compared to linezolid
- No unexpected safety signals were observed
- The most common treatment-emergent adverse events in controlled Phase 3 clinical studies with tedizolid phosphate were nausea, headache and diarrhea
- Three deaths occurred in the tedizolid phosphate clinical development program; 2 in patients receiving tedizolid phosphate and 1 in a patient receiving linezolid. All death cases had significant co-morbidities upon study entry
- A thorough QT study with tedizolid phosphate at therapeutic (200 mg) a supra-therapeutic dose (1200 mg) demonstrated no evidence of QT prolongation with tedizolid
- Overall, when considering the incidence of patients with substantially abnormal values, the hematologic effects in patients treated with tedizolid phosphate were similar to those observed with linezolid therapy. However, a lower incidence of patients with low platelet counts (<LLN) was consistently observed in tedizolid treated patients. A similar trend was observed for hemoglobin and ANC.
- There was no evidence of ophthalmologic or peripheral neurologic toxicities detected in the tedizolid phosphate group by both systematic integrated safety data analysis and special ophthalmologic and neurologic studies conducted in the program
- Nonclinical studies and a human volunteer drug-drug interaction studies did not identify any evidence of tedizolid phosphate interaction with MAOIs, serotonergic or vasopressor agents

7.2 Overall Safety Experience with Tedizolid Phosphate

The complete tedizolid phosphate safety database comprises data from 1050 patients enrolled in Phase 2/3 clinical trials and 438 subjects (437 unique subjects) enrolled in Phase 1 clinical trials, including both oral and IV administration routes (Table 53). Healthy volunteers and patients received tedizolid phosphate as single oral administrations of 50 to 1200 mg, multiple oral administrations of 200 to 400 mg per day for up to 21 days, single IV infusions ranging from 50 to 400 mg, and multiple IV infusions of 200 or 300 mg per day for up to 7 days.

Table 53. Duration of Treatment with Tedizolid Phosphate ≥200 mg at the Indicated Phase of Drug Development

Number of Treatment Days	Phase 1 Studies	Phase 2 Studies	Phase 3 Studies
0-3 days	281	20	32
4-6 days	26	230	628
7-10 days	99	138	3
>10 days	31	0	0

Comparative safety data from the controlled Phase 3 studies with tedizolid phosphate and the active comparator linezolid showed a comparable adverse event profile. The occurrence of TEAEs, severe TEAEs, serious TEAEs, TEAE leading to drug discontinuation and TEAE with the outcome of death were very similar between the tedizolid phosphate 200 mg once per day treated patients compared to the linezolid 600 mg twice daily treated patients in the Phase 3 studies in the development program.

7.3 Treatment-Emergent Adverse Events

The most common adverse reactions occurring in patients receiving tedizolid phosphate in the pooled Phase 3 clinical trials were nausea, headache, diarrhea and vomiting. The most common adverse events leading to discontinuations for both treatments being gastrointestinal disorders at a rate of 0.3% in the tedizolid phosphate group and 0.5% in the linezolid group (see Section 7.5.1).

The incidence of adverse events grouped by System Organ Class (SOC) occurring in Phase 2 and Phase 3 studies in the tedizolid phosphate program permits analysis by study and by dosage of tedizolid phosphate. These data are shown in Table 54.

Overall the incidence of AE was similar between studies. Slight differences were observed in the Phase 3 Study TR701-112 where the incidence in 4 SOCs showed a >2 percentage point difference between the treatment groups. For GI Disorders, the incidence in the tedizolid phosphate group was lower than in the linezolid group (16.6% and 26.0%, respectively) and this pattern was consistent for the preferred terms nausea (8.8% and 14.3%, respectively) and vomiting (3.0% and 6.3%, respectively).

In the second Phase 3 Study TR701-113, incidence in the GI Disorders SOC was lower in the tedizolid phosphate group compared with the linezolid group (16.0% and 20.5%,

respectively) and a similar pattern was seen in the preferred term nausea (8.2% and 11.0%, respectively). However, the lower incidence observed in the GI Disorders SOC and the preferred term nausea was consistent in both studies, despite approximately 20% of patients in Study TR701-113 who continued to receive IV therapy for the full course.

When examining other SOCs, there were numerical imbalances in TEAE rates noted. For the Infections and Infestations; Skin and Subcutaneous Tissue; and Respiratory, Thoracic and Mediastinal Disorders (RTMD) SOC from Study TR701-112, incidence in the tedizolid phosphate group was higher than in the linezolid group (15.4% and 11.0%, 8.2% and 6.0%, 3.6% and 1.2%, respectively). The difference in incidence between treatment groups in TR701-113 study was either <2 percentage points for all other SOCs or >2 percentage points lower in the tedizolid phosphate group (RTMD SOC, 1.8% in the tedizolid phosphate group and 4.3% in the linezolid group). No individual preferred terms emerged as a notable difference between the treatment groups.

Table 54. TEAEs (≥2%) for Phase 2 and 3 Studies

System Organ Class / Preferred Term	Study TR701-104			Study TR701-112		Study TR701-113		Study TR701-126
	Tedizolid Phosphate 200 mg (N=63) n (%)	Tedizolid Phosphate 1 300 mg (N=63) n (%)	Tedizolid Phosphate 400 mg (N=62) n (%)	Tedizolid Phosphate 200 mg (N=331) n (%)	Linezolid 1200 mg (N=335) n (%)	Tedizolid Phosphate 200 mg (N=331) n (%)	Linezolid 1200 mg (N=327) n (%)	Tedizolid Phosphate 200 mg (N=200) n (%)
Gastrointestinal Disorders	19 (30.2)	25 (39.7)	28 (45.2)	55 (16.6)	87 (26.0)	53 (16.0)	67 (20.5)	44 (22.0)
Nausea	10 (15.9)	13 (20.6)	13 (21.0)	29 (8.8)	48 (14.3)	27 (8.2)	36 (11.0)	22 (11.0)
Diarrhoea	7 (11.1)	3 (4.8)	6 (9.7)	15 (4.5)	18 (5.4)	11 (3.3)	17 (5.2)	13 (6.5)
Vomiting	7 (11.1)	7 (11.1)	6 (9.7)	10 (3.0)	21 (6.3)	11 (3.3)	17 (5.2)	9 (4.5)
Toothache	2 (3.2)	1 (1.6)	0	0	0	3 (0.9)	2 (0.6)	1 (0.5)
Abdominal Pain	1 (1.6)	2 (3.2)	0	4 (1.2)	3 (0.9)	1 (0.3)	1 (0.3)	2 (1.0)
Constipation	0	2 (3.2)	1 (1.6)	5 (1.5)	5 (1.5)	4 (1.2)	1 (0.3)	4 (2.0)
Dry Mouth	0	2 (3.2)	2 (3.2)	1 (0.3)	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.5)
Dyspepsia	0	2 (3.2)	1 (1.6)	2 (0.6)	6 (1.8)	2 (0.6)	2 (0.6)	0
Infections And Infestations	14 (22.2)	12 (19.0)	15 (24.2)	51 (15.4)	37 (11.0)	40 (12.1)	41 (12.5)	27 (13.5)
Abscess	6 (9.5)	7 (11.1)	7 (11.3)	21 (6.3)	15 (4.5)	14 (4.2)	11 (3.4)	8 (4.0)
Skin Infection	4 (6.3)	2 (3.2)	2 (3.2)	0	2 (0.6)	0	0	0
Nasopharyngitis	2 (3.2)	1 (1.6)	0	0	1 (0.3)	1 (0.3)	3 (0.9)	0
Cellulitis	2 (3.2)	0	2 (3.2)	8 (2.4)	8 (2.4)	9 (2.7)	6 (1.8)	9 (4.5)
Vulvovaginal Mycotic Infection	1 (1.6)	1 (1.6)	0	0	2 (0.6)	2 (0.6)	7 (2.1)	1 (0.5)
Folliculitis	0	1 (1.6)	2 (3.2)	3 (0.9)	0	0	1 (0.3)	2 (1.0)
Fungal Infection	0	1 (1.6)	2 (3.2)	1 (0.3)	2 (0.6)	0	2 (0.6)	0
Nervous System Disorders	11 (17.5)	12 (19.0)	8 (12.9)	36 (10.9)	33 (9.9)	30 (9.1)	36 (11.0)	19 (9.5)
Headache	5 (7.9)	11 (17.5)	7 (11.3)	21 (6.3)	19 (5.7)	20 (6.0)	22 (6.7)	7 (3.5)
Dizziness	4 (6.3)	1 (1.6)	0	8 (2.4)	7 (2.1)	5 (1.5)	7 (2.1)	7 (3.5)
Dysgeusia	2 (3.2)	0	0	0	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.5)
Somnolence	1 (1.6)	0	1 (1.6)	4 (1.2)	1 (0.3)	2 (0.6)	4 (1.2)	5 (2.5)
Skin And Subcutaneous Tissue Disorders	7 (11.1)	7 (11.1)	4 (6.5)	27 (8.2)	20 (6.0)	24 (7.3)	22 (6.7)	12 (6.0)
Skin Lesion	3 (4.8)	2 (3.2)	1 (1.6)	1 (0.3)	1 (0.3)	1 (0.3)	0	2 (1.0)
Pruritus	1 (1.6)	2 (3.2)	1 (1.6)	4 (1.2)	9 (2.7)	0	1 (0.3)	1 (0.5)
Pruritus Generalised	1 (1.6)	1 (1.6)	0	5 (1.5)	3 (0.9)	7 (2.1)	5 (1.5)	1 (0.5)
Rash	0	2 (3.2)	2 (3.2)	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	0

Table 54. TEAEs (≥2%) for Phase 2 and 3 Studies (*Continued*)

System Organ Class / Preferred Term	Study TR701-104			Study TR701-112		Study TR701-113		Study TR701-126
	Tedizolid Phosphate 200 mg (N=63) n (%)	Tedizolid Phosphate 300 mg (N=63) n (%)	Tedizolid Phosphate 400 mg (N=62) n (%)	Tedizolid Phosphate 200 mg (N=331) n (%)	Linezolid 1200 mg (N=335) n (%)	Tedizolid Phosphate 200 mg (N=331) n (%)	Linezolid 1200 mg (N=327) n (%)	Tedizolid Phosphate 200mg (N=200) n (%)
General Disorders And Administration Site Conditions	6 (9.5)	5 (7.9)	6 (9.7)	13 (3.9)	15 (4.5)	24 (7.3)	25 (7.6)	14 (7.0)
Fatigue	3 (4.8)	1 (1.6)	1 (1.6)	1 (0.3)	5 (1.5)	8 (2.4)	7 (2.1)	3 (1.5)
Chills	2 (3.2)	1 (1.6)	0	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	4 (2.0)
Pain	2 (3.2)	2 (3.2)	2 (3.2)	0	0	0	3 (0.9)	1 (0.5)
Pyrexia	0	0	2 (3.2)	2 (0.6)	0	2 (0.6)	3 (0.9)	2 (1.0)
Psychiatric Disorders	3 (4.8)	7 (11.1)	6 (9.7)	9 (2.7)	4 (1.2)	10 (3.0)	4 (1.2)	3 (1.5)
Insomnia	1 (1.6)	4 (6.3)	1 (1.6)	6 (1.8)	2 (0.6)	4 (1.2)	3 (0.9)	3 (1.5)
Sleep Disorder	0	2 (3.2)	0	0	0	1 (0.3)	0	0
Respiratory, Thoracic And Mediastinal Disorders	3 (4.8)	6 (9.5)	7 (11.3)	12 (3.6)	4 (1.2)	6 (1.8)	14 (4.3)	6 (3.0)
Oropharyngeal Pain	1 (1.6)	1 (1.6)	2 (3.2)	1 (0.3)	2 (0.6)	0	3 (0.9)	1 (0.5)
Rhinorrhoea	1 (1.6)	2 (3.2)	1 (1.6)	1 (0.3)	0	0	3 (0.9)	0
Cough	0	3 (4.8)	2 (3.2)	3 (0.9)	0	3 (0.9)	4 (1.2)	0
Blood And Lymphatic System Disorders	2 (3.2)	0	0	1 (0.3)	0	5 (1.5)	1 (0.3)	1 (0.5)
Lymphadenopathy	2 (3.2)	0	0	1 (0.3)	0	0	0	0
Cardiac Disorders	2 (3.2)	1 (1.6)	1 (1.6)	6 (1.8)	6 (1.8)	3 (0.9)	2 (0.6)	1 (0.5)
Tachycardia	2 (3.2)	1 (1.6)	1 (1.6)	2 (0.6)	4 (1.2)	0	0	0
Investigations	1 (1.6)	5 (7.9)	2 (3.2)	6 (1.8)	6 (1.8)	2 (0.6)	5 (1.5)	0
Blood Pressure Increased	1 (1.6)	4 (6.3)	2 (3.2)	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)	0
Metabolism And Nutrition Disorders	1 (1.6)	2 (3.2)	3 (4.8)	7 (2.1)	7 (2.1)	9 (2.7)	7 (2.1)	2 (1.0)
Decreased Appetite	1 (1.6)	2 (3.2)	2 (3.2)	0	1 (0.3)	0	0	1 (0.5)

Abbreviations: N=number of patients in the Safety Analysis Set; n=number of patients with the specified adverse event

An analysis of TEAEs experienced by various subgroups in the Phase 3 controlled studies is shown in Table 55. In this table, the incidence of any 1 or more TEAEs is shown for each group.

The subgroups examined include the demographic characteristics of age, sex, race, and BMI, and underlying disease characteristics relating to renal function, hepatic function, and diabetes.

Overall, for demographic patient subgroups, the incidence of any 1 or more TEAEs was similar between tedizolid phosphate and linezolid treatment groups. Dissimilarities were observed when the number of patients in the subgroup was small, such as for the Asian race.

Table 55. Incidence of Treatment-emergent Adverse Events by Subgroup - Phase 3 Studies

	Tedizolid Phosphate (200 mg) (N=662)		Linezolid (1200 mg) (N=662)	
Subgroup	**N1**	**n (%)**	**N1**	**n (%)**
All patients	662	283 (42.7)	662	286 (43.2)
<65 years	590	260 (44.1)	603	267 (44.3)
≥65 years	72	23 (31.9)	59	19 (32.2)
≥75 years	24	9 (37.5)	25	8 (32.0)
Male	429	179 (41.7)	408	164 (40.2)
Female	233	104 (44.6)	254	122 (48.0)
White	563	256 (45.5)	555	250 (45.0)
Black or African American	77	23 (29.9)	71	21 (29.6)
Asian	6	1 (16.7)	14	7 (50.0)
Other	16	3 (18.8)	22	8 (36.4)
Underweight (BMI <18.5 kg/m^2)	12	2 (16.7)	7	4 (57.1)
Normal/Overweight (BMI ≥18.5 to <30 kg/m^2)	450	194 (43.1)	426	171 (40.1)
Obese (BMI >30 kg/m^2)	200	87 (43.5)	229	111 (48.5)
Normal/Mild Renal Impairment	633	270 (42.7)	612	273 (44.6)
Moderate/Severe Renal Impairment*	20	11 (55.0)	29	8 (27.6)
Normal Hepatic Function	474	202 (42.6)	443	183 (41.3)
Hepatic Impairment[+]	14	3 (21.4)	12	5 (41.7)
Hepatic Disease[S]	175	78 (44.6)	209	98 (46.9)
Diabetes	58	26 (44.8)	67	32 (47.8)
No diabetes	604	257 (42.5)	595	254 (42.7)

Abbreviations: N=number of patients in the Safety Analysis Population; n=number of patients in the specified category; N1=number in the subgroup and is used as the denominator to calculate percentage
*Renal impairment: based on estimated creatinine clearance at baseline; moderate/severe impairment defined as creatinine clearance <60 mL/min.
[+]Hepatic impairment: defined as Child=Pugh score of ≥7 (B, or C).
[S]Hepatic disease: defined as ALT or AST >2 × upper limit of normal (ULN) at baseline or positive for Hepatitis C at baseline.

7.4 Mortality

There were 3 serious adverse events resulting in deaths in the tedizolid phosphate development program. All deaths occurred in the Phase 3 studies. Two deaths occurred in patients receiving tedizolid phosphate; one death occurred in a patient receiving linezolid. There was no temporal association of the events to study drug dosing. The 2 deaths in the tedizolid phosphate group were in patients with significant co-morbidities and therefore not unexpected. The single linezolid death occurred in a HIV patient during a time of low CD4+ cell count (49 cells/mm^3). A brief description of each death case is found in Table 56. The complete narratives for all death cases are found in Appendix 2.

Table 56. Death Cases – Tedizolid Phosphate Development Program

Patient ID	Age	Sex	Country	Treatment	Preferred Term	AE Onset Date (Relative Study Day)	Date of Death
TR701-112-342-605	86	M	Peru	Tedizolid Phosphate 200 mg	Septic shock	(b) (6) (55)	(b) (6)
TR701-113-444-230	33	F	South Africa	Linezolid 1200 mg	Meningitis tuberculous	(b) (6) (14)	(b) (6)
TR701-113-451-258	84	M	South Africa	Tedizolid Phosphate 200 mg	Myocardial infarction	(b) (6) (11)	(b) (6)

Abbreviations: AE=adverse event

7.5 Serious Adverse Events

Overall, the incidence of serious adverse events (SAEs) in the Phase 3 studies was similar between treatment groups with 1.8% of patients in the tedizolid phosphate group and 2.0% of patients in the linezolid group experiencing a SAE. Similarly, in the Phase 2 studies, 1.8% of enrolled patients (tedizolid phosphate treated) experienced a SAE.

Two SAEs were reported in the Phase 1 program. A case of mild appendicitis occurred in Study TR701-107. This SAE occurred on Day 22 after the subject received 7 infusions of 200 mg tedizolid phosphate. The second SAE in Phase 1 was a severe extradural abscess that occurred 13 days after a subject in Study TR701-124 (control subject in Hepatic Impairment study) had received a single oral administration of 200 mg tedizolid phosphate.

A summary of all SAEs in the Phase 3 studies is found in Table 57.

Table 57. Serious Adverse Events: Phase 3 Controlled Studies

System Organ Class Preferred Term	Tedizolid Phosphate (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
Number (%) of Patients with at least 1 SAE:	**12 (1.8)**	**13 (2.0)**
Infections and infestations	**6 (0.9)**	**4 (0.6)**
Abscess	1 (0.2)	0
Pneumonia	2 (0.3)	0
Septic Shock	2 (0.3)	0
Staphylococcal Infection	1 (0.2)	0
Cellulitis	0	2 (0.3)
Endophthalmitis	1 (0.2)	0
Urinary Tract Infection	1 (0.2)	1 (0.2)
Meningitis Tuberculous	0	1 (0.2)
Cardiac disorders	**2 (0.3)**	**2 (0.3)**
Cardiac Arrest	1 (0.2)	0
Myocardial Infarction	1 (0.2)	0
Acute Coronary Syndrome	0	1 (0.2)
Acute Myocardial Infarction	0	1 (0.2)
Gastrointestinal disorders	**2 (0.3)**	**0**
Upper Gastrointestinal Haemorrhage	1 (0.2)	0
Vomiting	1 (0.2)	0
Metabolism & nutrition disorders	**2 (0.3)**	**1 (0.2)**
Dehydration	1 (0.2)	0
Diabetes Mellitus	1 (0.2)	0
Diabetic Ketoacidosis	0	1 (0.2)
Investigations	**1 (0.2)**	**1 (0.2)**
Weight Decreased	1 (0.2)	0
Blood Glucose Increased	0	1 (0.2)
Nervous system disorders	**1 (0.2)**	**0**
VIIth Nerve Paralysis	1 (0.2)	0
Psychiatric disorders	**0**	**2 (0.3)**
Suicidal Ideation	0	1 (0.2)
Alcoholic Psychosis	0	1 (0.2)
Major Depression	0	1 (0.2)
Renal and urinary disorders	**1 (0.2)**	**0**
Nephrolithiasis	1 (0.2)	0
Vascular disorders	**1 (0.2)**	**1 (0.2)**
Hypertension	1 (0.2)	0
Thrombophlebitis Superficial	0	1 (0.2)
Immune system disorders	**0**	**1 (0.2)**
Anaphylactic Reaction	0	1 (0.2)
Pregnancy, puerperium & perinatal conditions	**0**	**1 (0.2)**
Abortion Spontaneous	0	1 (0.2)

Abbreviations: N=number of patients in the Safety Analysis Set; SAE=serious adverse event.

Serious adverse events reported in the Phase 2 portion of the tedizolid phosphate development program are shown in Table 58.

Table 58. Serious Adverse Events: Phase 2 Studies

System Organ Class Preferred Term	Uncontrolled Studies Tedizolid Phosphate ≥ 200 mg (N=388)
Number (%) of Patients with at least 1 Serious Adverse Event:	**7 (1.8)**
Infections and infestations	**4 (1.0)**
Abscess	2 (0.5)
Staphylococcal Infection	1 (0.3)
Cellulitis	1 (0.3)
Thrombophlebitis Septic	1 (0.3)
Hepatobiliary disorders	**1 (0.3)**
Cholecystitis Acute	1 (0.3)
Psychiatric disorders	**1 (0.3)**
Suicidal Ideation	1 (0.3)
Respiratory, thoracic & mediastinal disorders	**1 (0.3)**
Haemoptysis	1 (0.3)

Abbreviations: N=number of patients in the Safety Analysis Set.

7.5.1 Study Drug Discontinuations due to Adverse Events

In the Phase 3 studies, the incidence of discontinuation of the study drug due to a TEAE was low and similar between groups (0.5% tedizolid phosphate and 0.9% linezolid). Each event was a singular occurrence except for nausea (3 patients), vomiting (3), and headache (2) in the linezolid group. These data are shown in Table 59.

Two patients in the Phase 2 studies discontinued tedizolid phosphate treatment due to TEAEs of thrombophlebitis septic and drug hypersensitivity.

In Phase 1 studies, incidence of subjects who discontinued the study drug was 3.4% and 2.3% in the tedizolid phosphate group and placebo groups, respectively. Events leading to discontinuation in Phase 1 for the tedizolid phosphate group were predominantly in the General Disorders and Administrative Site Conditions SOC, and all were singular events except infusion site pain, swelling, and erythema; palpitations and vomiting. Events in the placebo group leading to study drug discontinuation were 1 subject each for infusion site pain, infusion site swelling, and vaginitis bacterial.

Table 59. Discontinuation of Study Drug due to TEAE: Phase 3 Studies

System Organ Class Preferred Term	Tedizolid Phosphate (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Any patients with treatment-emergent adverse event leading to discontinuation of study drug:	3 (0.5)	6 (0.9)
Gastrointestinal Disorders	**2 (0.3)**	**3 (0.5)**
Abdominal Discomfort	1 (0.2)	0
Diarrhoea	1 (0.2)	0
Vomiting	1 (0.2)	3 (0.5)
Nausea	0	3 (0.5)
Infections And Infestations	**1 (0.2)**	**0**
Osteomyelitis	1 (0.2)	0
Immune System Disorders	**0**	**1 (0.2)**
Anaphylactic Reaction	0	1 (0.2)
General Disorders & Administration Site Conditions	**0**	**1 (0.2)**
Pain	0	1 (0.2)
Pyrexia	0	1 (0.2)
Eye Disorders	**0**	**1 (0.2)**
Visual Acuity Reduced	0	1 (0.2)
Nervous System Disorders	**0**	**2 (0.3)**
Headache	0	2 (0.3)
Psychiatric Disorders	**0**	**1 (0.2)**
Restlessness	0	1 (0.2)

Abbreviations: N=number of subjects in the Safety Analysis Set; n=number of subjects in the specified category
Note: A subject with an event coding to the same System Organ Class (SOC) or Preferred Term (PT) on more than 1 occasion is only counted 1 time for that SOC and PT.

7.6 Clinical Laboratory Effects of Tedizolid Phosphate

7.6.1 Hematology Clinical Laboratory Effects: Phase 3 Studies

An analysis was performed on the combined Phase 3 data to evaluate absolute neutrophil counts (ANC), hemoglobin values, and platelet counts at different time points/periods in the treatment course. The incidence of abnormal values (<LLN) was analyzed using data from all patients in the Safety Analysis Set with nonmissing data (N1) at the summarized time point/period and using data from all patients in the Safety Analysis Set with nonmissing data and a normal value at baseline (N2). The incidence of substantially

abnormal (SA) values was analyzed in a subset of patients with nonmissing data at both baseline and for the summarized time point/period (N3). SA was defined as <75% of LLN for platelet or hemoglobin values normal at baseline, or <75% of LLN and <75% of baseline for values abnormal at baseline; for ANC, SA was defined as <50% of LLN for normal baseline values; or <50% of LLN and <50% of baseline for abnormal baseline ANC values.

Abnormal hematologic laboratory data from patients in the controlled studies with tedizolid phosphate and linezolid are summarized in Table 60. The incidence of ANCs <LLN was low overall, and lower in all patients in the Safety Analysis Set (N1) in the tedizolid phosphate group than in the linezolid group at all four time points/periods. When excluding data from patients with abnormal or missing ANCs at baseline (N2), the pattern followed a similar trend. The incidence of substantially abnormal ANC values was <1% in both groups at all time points/periods (N3).

For hemoglobin, the incidence of values <LLN in all patients in Safety Analysis Set (N1) was slightly lower in the tedizolid phosphate group compared with the linezolid group at all four time points/periods. When excluding data from patients with abnormal or missing hemoglobin values at baseline (N2), the pattern followed a similar trend. The incidence of substantially abnormal hemoglobin values was similar in both treatment groups at all time points/periods (N3).

The incidence of platelet counts <LLN in all patients in the Safety Analysis Set (N1) was low overall and was lower in the tedizolid phosphate group compared with the linezolid group at all four time points/periods. Notably, in the linezolid group, there was an increasing incidence of platelet counts <LLN in all patients in the Safety Analysis Set (from 5.6% to 10.8%) when comparing the two time points (Day 7-9 to Day 11-13) and this change was greater than the change in the tedizolid phosphate group between the same two time points (from 3.2% to 4.9%). When excluding data from patients with abnormal or missing hemoglobin values at baseline (N2), the pattern followed a similar trend. The incidence of substantially abnormal platelet counts in the linezolid group increased (from 0.8% to 1.8%) but was stable in the tedizolid phosphate group (0.8% to 0.8%) over the 2 time points (Day 7-9 to Day 11-13). A direct comparison of platelet counts <LLN at the last dose of active drug shows a similar pattern, with an incidence of platelet counts <LLN of 3.7% in the tedizolid phosphate group and 10.8% in the linezolid group (N1). Over the period from post-baseline through the last dose of active drug, the incidence of platelet counts<LLN was lower for all patients in the tedizolid phosphate group compared with the linezolid group (6.4% and 12.6%, in the N1 set, respectively). When excluding data from patients with an abnormal or missing platelet values at baseline (N2), the pattern followed a similar trend. The incidence of substantially abnormal platelet values was similar in both treatment groups (N3) at all time points/periods.

Table 60. Incidence of Abnormal ANC, Hemoglobin Values and Platelet Counts: Phase 3 Studies

Parameter	Time Point/Period		Tedizolid Phosphate (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
ANC	Study Day 7-9	<LLN, N1	9/536 (1.7)	15/427 (2.8)
		<LLN, N2	4/479 (0.8)	12/471 (2.5)
		SA, N3	1/484 (0.2)	1/476 (0.2)
	Study Day 11-13	<LLN, N1	10/537 (1.9)	17/516 (3.3)
		<LLN, N2	7/479 (1.5)	11/458 (2.4)
		SA, N3	0/483 (0)	2/463 (0.4)
	Last Dose of Active Drug	<LLN, N1	8/526(1/5)	16/499(3.2)
		<LLN, N2	4/472 (0.8)	11/445 (2.5)
		SA, N3	2/477 (0.4)	2/450 (0.4)
	Any Post-Baseline through Last Dose of Active Drug	<LLN, N1	12/618(1.9)	29/617(4.7)
		<LLN, N2	8/547 (1.5)	21/542 (3.9)
		SA, N3	2/552 (0.4)	3/547 (0.5)
Hemoglobin	Study Day 7-9	<LLN, N1	169/574 (29.4)	187 /562 (33.3)
		<LLN, N2	45/386 (11.7)	45/348 (12.9)
		SA, N3	0/541 (0)	0/527 (0)
	Study Day 11-13	<LLN, N1	162/560 (28.9)	172/553 (31.1)
		<LLN, N2	44/373 (11.8)	43/341 (12.6)
		SA, N3	1/527 (0.2)	1 /516(0.2)
	Last Dose of Active Drug	<LLN, N1	168/564 (29.8)	175/538 (32.5)
		<LLN, N2	44/378 (11.6)	43/328 (13.1)
		SA, N3	1/535 (0.2)	1/503(0.2)
	Any Post-Baseline through Last Dose of Active Drug	<LLN, N1	254/632 (40.2)	282/633 (44.5)
		<LLN, N2	82/418 (19.6)	90/392 (23.0)
		SA, N3	1/594 (0.2)	2/589 (0.3)
Platelets	Study Day 7-9	<LLN, N1	18/554 (3.2)	31/551 (5.6)
		<LLN, N2	9/471 (1.9)	9/462 (1.9)
		SA, N3	4/509 (0.8)	4/504 (0.8)
	Study Day 11-13	<LLN, N1	27/552 (4.9)	58/537 (10.8)
		<LLN, N2	16/466 (3.4)	31/453 (6.8)
		SA, N3	4/501 (0.8)	9/491 (1.8)
	Last Dose of Active Drug	<LLN, N1	20/546 (3.7)	56/520 (10.8)
		<LLN, N2	12/466 (2.6)	28/439 (6.4)
		SA, N3	5/504 (1.0)	5/477 (1.0)
	Any Post-Baseline through Last Dose of Active Drug	<LLN, N1	40/627 (6.4)	79/626 (12.6)
		<LLN, N2	18/527 (3.4)	38/521 (7.3)
		SA, N3	7/571 (1.2)	11/569 (1.9)

Abbreviations: ANC=absolute neutrophil count; LLN=lower limit of normal; N=number of patients in the Safety Analysis Set; N1=all patients in the Safety Analysis Set with nonmissing data for the summarized time period (including patients with missing, normal, or abnormal baseline values); N2=Number of patients in the Safety Analysis Set with nonmissing data for the summarized time period and with normal baseline values; SA=Substantially Abnormal; N3=Number of patients with normal and abnormal nonmissing baseline values and a value at the summarized visit; SA for platelet or hemoglobin values is defined as 75% of LLN for values normal at baseline, or <75% of LLN and <75% of baseline for platelet or hemoglobin values abnormal at baseline; SA for ANC is defined as <50% of LLN for values normal at baseline; or <50% of LLN and <50% of baseline for ANC values abnormal at baseline; n=number of patients in the specified category.

Increases of ≥2 toxicity grades from baseline to the worst post-baseline result were infrequent in both the tedizolid phosphate and linezolid treatment groups. The shift in toxicity grade from baseline to worst treatment period value for hematology laboratories

is shown in Table 61. The treatment period was defined as the time period through 3 days after the end of treatment, ie, 6 days of tedizolid treatment and the Day 7-9 visit or 10 days of linezolid treatment and the Day 11-13 visit. Low platelet values during this time period appear to be isolated and sporadic abnormalities. Subsequent values were within normal range or near baseline values for each patient.

Table 61. Toxicity Grade Shift (≥2) from Baseline to Worst Treatment Period Value in Hematology Parameter: Phase 3 Studies

	Tedizolid Phosphate (200 mg)		Linezolid (1200 mg)	
Parameter	**N**	**n (%)**	**N**	**n (%)**
Hemoglobin	599	2 (0.3)	593	2 (0.3)
Leukocytes	580	5 (0.9)	577	3 (0.5)
Neutrophils	556	1 (0.2)	551	5 (0.9)
Platelets	575	2 (0.4)	573	3 (0.5)

Abbreviations: N=number of patients with nonmissing data at both baseline and the summarized time period; n=number of patients for each toxicity grade at baseline.
Note: The treatment period evaluated for tedizolid phosphate spanned 9 days (6 days of treatment and the Day 7-9 visit). The treatment period evaluated for linezolid spanned 13 days (10 days of treatment and the Day 11-13 visit).

7.6.2 Chemistry Clinical Laboratory Effects: Phase 3 Studies

The incidence of substantially abnormal chemistry values (worst post-baseline results) occurring in more than 1 patient is shown in Table 62.

In the phase 3 studies, the incidence of substantially abnormal values for most analytes was <1% in both treatment groups. The incidence of substantially abnormal ALT values was similar in the tedizolid phosphate and linezolid groups, 3.9% and 3.1%, respectively. The incidence of substantially abnormal AST values was also similar in the tedizolid phosphate and linezolid groups, 2.6% and 2.8%, respectively. The incidence of substantially abnormal results in the phase 3 studies (both treatment arms) was consistent with the results observed in the Uncontrolled Studies groups

Hy's Law laboratory criteria were used to identify patients in the development program with a pattern of hepatic test abnormalities consistent with drug-induced liver toxicity. A patient met the Hy's Law Laboratory Criteria if they had the following laboratory test results collected during a single visit: ALT or AST >3× ULN, and total bilirubin >2× ULN, and alkaline phosphatase <2× ULN.

One patient in Study TR701-113, who received linezolid 1200 mg, met Hy's Law laboratory criteria: Patient TR701-113-141-437 had ALT, AST, and bilirubin values at baseline (Day -1) that were Grade 0, and on Day 1 were Grades 2, 3, and 3, respectively. No TEAEs related to these findings was reported.

Table 62. Incidence of Substantially Abnormal Chemistry Test Values for the Worst Post-baseline Result: Phase 2 and 3 Studies

Parameter	Uncontrolled Studies	Controlled Studies	
	Tedizolid phosphate ≥200 mg (N=388) n/N1 (%)	Tedizolid phosphate (200 mg) (N=662) n/N1 (%)	Linezolid (1200 mg) (N=662) n/N1 (%)
Alanine Aminotransferase	10/378 (2.6)	25/646 (3.9)	20/643 (3.1)
Alkaline Phosphatase	1/379 (0.3)	1/646 (0.2)	0/644 (0)
Aspartate Aminotransferase	7/378 (1.9)	17/646 (2.6)	18/643 (2.8)
Bilirubin	0/379 (0)	0/646 (0)	1/644 (0.2)
Blood urea nitrogen	0/185 (0)	0/322 (0)	1/324 (0.3)
Creatinine	1/379 (0.3)	1/646 (0.2)	3/644 (0.5)

Abbreviations: N=Number of patients in Safety Analysis Set; N1=Number of patients with nonmissing data at the summarized visit; n=Number of patients in each category
Note: Criteria to determine substantially abnormal values are defined in the ISS SAP.

7.7 Special Safety Topics

7.7.1 Neurologic and Ophthalmologic Safety Assessments

From the published clinical and postmarketing experience, optic and peripheral neuropathy AEs are associated with prolonged treatment with linezolid and other agents that inhibit protein synthesis. These risks were thoroughly investigated in tedizolid phosphate clinical studies per the FDA's request and guidance. Routine neurologic examinations were performed in all studies, targeted examinations in selected studies, and specialized ophthalmic and neurologic examinations were performed in the Phase 1 studies TR701-101 and TR701-110 in 96 subjects at therapeutic and supratherapeutic doses.

There were only two abnormal neurologic findings in Phase 1, 2, and 3 Studies that included extensive neurologic examinations. The first was patient TR701-113-143-606 in the linezolid treatment group, who had a history of chronic back pain and experienced decreased sensation in the left lower extremity at a neurologic examination on Study Day 16. The second was subject TR701-105-001-007 in the Phase 1 Study TR701-105, who had strabismus recorded during cranial nerve examinations on Study Days 16 and 23, but also had abnormal lateral gaze since birth recorded as medical history and abnormal lateral gaze identified in a general physical examination on Day 1.

On Snellen Visual Acuity examinations, there were no clinically significant differences in results between treatment groups in the Phase 3 controlled studies to suggest optic nerve toxicity.

In the Phase 3 studies, most patients had improvement or no change in visual acuity in both eyes in the tedizolid phosphate and linezolid groups at the 48 to 72 hour (89.5%,

90.0%, respectively), EOT (90.8%, 85.9%, respectively), and PTE (89.2%, 85.3%, respectively) Visits. In an analysis of the worst post-baseline status, most patients in the tedizolid phosphate and linezolid groups experienced improvement or no change in both eyes (80.4%, 79.2%, respectively). Few patients experienced worsening by 1 category in one (10.5%, 10.9%, respectively) or two (8.4%, 8.9%, respectively) eyes. Even fewer patients experienced worsening by 2 or more categories in one eye (0.3%, 0.3%, respectively) or worsening by 2 or more categories in one eye and 1 category the other eye (0.3%, 0.7%, respectively).

In addition, Study TR701-110 was designed to evaluate ophthalmic and neurologic safety in 72 healthy subjects receiving oral 200 mg tedizolid phosphate once daily for 10 days. Extensive ophthalmic and neurologic assessments were performed. Ophthalmic assessments included optical coherence tomography, best corrected distance visual acuity, dilated fundoscopy, color vision testing, slit lamp examination, visual field testing, and optic nerve photographs. Neurologic assessments included cranial nerve, sensory, motor, reflex, coordination, and gait evaluations. No findings suggestive of optic or peripheral neuropathy were observed. All subjects had normal neurological examinations at all assessment time points. There were no clinically meaningful changes in ophthalmic examinations and no subject had an abnormal ophthalmic assessment that was considered clinically significant at any time point. An external expert in drug-induced optic nerve toxicity reviewed the TR701-110 baseline and post-baseline ophthalmologic examination data and found no evidence of optic neuropathy.

Additionally, results from a multiple-dose 21-day study (TR701-101) of oral 200, 300, or 400 mg tedizolid phosphate once daily showed that TR-701 was well tolerated over the 21-day dosing period with no signs of optic or peripheral neuropathy. Ophthalmic assessments included visual acuity, color acuity, visual field, slit lamp, dilated fundoscopy examination, and optic nerve photographs in that study.

There were also no signals for peripheral neuropathy or optic nerve disorders from a systematic review of TEAEs using standardized MedDRA queries. These data showed that 10 (1.5%) patients in the tedizolid phosphate group and 6 (0.9%) in the linezolid group experienced at least 1 TEAE included in the peripheral neuropathy SMQ. Similarly, a review for potential events suggesting optic nerve disorders was performed using an SMQ. There were 2 TEAEs identified by the optic nerve disorder SMQ reported in the tedizolid phosphate group in the phase 2/3 studies, and 1 case in the phase 1 group, which were transient episodes of visual acuity reduced (1 event) and visual impairment (2 events). The identified events reported in the tedizolid phosphate group were mild, generally transient, and most were associated with a spontaneous resolution; none were considered evidence of neurotoxicity on medical review.

Of note, there was one case of VIIth cranial nerve paralysis reported as an SAE requiring treatment in a patient receiving tedizolid phosphate in Study TR701-112 (patient TR701-112-128-665). On Day 10 (day of final study drug administration, 4 days from last active drug administration), the subject experienced left facial droop and weakness. On Day 25, a right facial droop and weakness developed. Notably, severe nausea and vomiting occurred on Day 24 requiring hospitalization on Day 33. Given the temporal

association, the neurologic symptoms could be connected with the GI events of *C. jejuni* infection (potential differential diagnostic with Guillain-Barré syndrome). Further evaluations, including a brain MRI, were not diagnostic. No eye/optic TEAEs were reported. While symptoms improved significantly over time, the event was considered ongoing at last contact (approximately 4 months after onset).

9-Month Neuropathy Study in Rats

Because of previous neuropathology findings in a 6-month study in rats and in post-marketing experience with linezolid (Zyvox® Labeling Instructions), a special repeat dose 9-month neuropathology study was conducted with tedizolid phosphate in pigmented rats. This study had interim evaluations at 1, 3, 6, (with a 3 month recovery group) and 9 months and used sensitive morphologic evaluation of perfusion-fixed tissue. Tissues assessed included brain, eyes (includes retina and uveal tract), optic tract/nerves, spinal cord, peripheral/central nerves (includes sciatic nerve), and skeletal muscle. No treatment-related neuropathology effects, either functional or histopathological, were seen in this study at plasma exposures up to 8.4 fold greater than those seen at the human therapeutic dose.

7.7.2 Drug-Drug Interactions

A comprehensive nonclinical evaluation of potential drug-drug interactions with tedizolid phosphate dosage forms and various transporters and drug metabolizing enzymes was performed. No potential for inhibition or induction of drug metabolizing enzymes was revealed in in vitro studies with tedizolid phosphate and the active metabolite, tedizolid. Tedizolid is the only circulating metabolite of tedizolid phosphate.

Drug interactions with the monoamine oxidase inhibitors (MAOI) are known to occur with linezolid and have led to a labeled contraindication for this antibiotic. The development program for tedizolid phosphate included systematic exploration of the potential for a similar drug-drug interaction to occur. FDA provided guidance and advices on study designs.

Nonclinical and clinical studies assessed the potential for tedizolid to interact with central or peripheral MAO and to elicit a clinically meaningful pharmacodynamic response. Linezolid and tedizolid phosphate are nonselective, reversible MAO inhibitors when assayed in vitro with endogenous or expressed human MAO_A or MAO_B; this activity could potentially increase local and circulating concentrations of neurotransmitter substrates of MAO in vivo. Although use of certain medications (SSRI, SNRI, tricyclic antidepressants, MAOI, triptans, and other medications with potential adrenergic or serotonergic activity) were reasons for exclusion in all studies, a total of 10 patients in the Safety Analysis Set from Phase 2/3 studies received these medications without evidence of serotonin syndrome. In phase 2/3 studies, 7 patients reported TEAEs, 3 reported the TEAEs before beginning the serotonergic medication (citalopram or trazodone). TEAEs with onset on or after the day that the other 4 patients began treatment with an antidepressant did not meet Hunter's criteria for serotonin syndrome.

Rare, sporadic cases of serotonin syndrome have been associated with linezolid treatment, usually in combination with MAOIs or other antidepressants, reflecting increased central serotonergic activity. A prospective clinical study comparative to linezolid to assess central serotonergic potentiation is not ethical or practical. Extensive nonclinical studies with tedizolid phosphate, utilizing a murine behavioral model of central serotonergic activity to assess inhibition of brain MAO (Flanagan 2013) showed no evidence for central MAO inhibition at tedizolid exposure levels equivalent to 30-fold the human equivalent exposure at a therapeutic dose of tedizolid phosphate (200 mg/kg). In the same model, linezolid at a dose (50 mg/kg) with exposure similar to a human therapeutic dose of 600 mg twice daily demonstrated a positive signal for increased serotonergic activity, comparable to fluoxetine, the positive control used in the evaluations.

Two Phase 1 double-blind crossover studies evaluated the potential of tedizolid phosphate at steady state to inhibit MAO in vivo (Flanagan 2013). Study TR701-114 evaluated the potential for tedizolid to interact with oral pseudoephedrine (PSE); administration of tedizolid phosphate did not potentiate the vasopressor effect of PSE, and there was no meaningful PK interaction between PSE and tedizolid phosphate. Study TR701-105 assessed the potential for tedizolid phosphate to alter sensitivity to oral tyramine relative to placebo. In this study, the geometric mean ratio (placebo: tedizolid phosphate) of the tyramine dose required to elicit this response was 1.33 (90% CI 1.05, 1.69), less than the tyramine sensitivity ratio published for linezolid (3.48; Antal 2001) and similar to what would be expected in patients receiving placebo (1.5; Goren 2010). These results indicate no clinically relevant increases in tyramine sensitivity occur with tedizolid phosphate when compared with placebo.

The integrated analysis evaluated the association of TEAEs of blood pressure increased or hypertension with concomitant medications during tedizolid phosphate administration and for patterns of TEAEs associated with particular concomitant medications or classes. A clinical review of the data was performed and no evidence of drug interaction was identified.

7.7.3 Thorough QT Study

The cardiac safety and thorough QTc study, TR701-115, evaluated tedizolid phosphate for the potential for QT interval prolongation at therapeutic (200 mg) and supratherapeutic (1200 mg) doses. Healthy adult subjects received a single administration of each study drug in a randomized sequence crossover design: tedizolid phosphate 200 mg (N=44), tedizolid phosphate1200 mg (N=46), moxifloxacin (N=47), and placebo (N=44). Cardiac electrophysiology was analyzed by a centralized reading of blinded data from Holter monitors for continuous ECG recording from 1 hour pre-dose to 23 hours post-dose. Tedizolid phosphate had no effect on heart rate, atrioventricular conduction, or cardiac depolarization as measured by PR, QRS, QTcB, and QTcF interval duration. Tedizolid phosphate did not prolong the QT interval relative to placebo when evaluated by time-matched or time-averaged QTcF values; the positive control, moxifloxacin, confirmed assay sensitivity.

7.8 Summary of Safety Experience with Tedizolid Phosphate

The tedizolid phosphate development program included 19 clinical studies with 438 research subjects and 1050 patients with active infections participating in the trials. The range of tedizolid phosphate dosages administered in the clinical program was from 50 mg to 1200 mg.

The most common adverse events observed in the tedizolid phosphate treatment group in Phase 3 studies were nausea, headache and diarrhea. For both Phase 3 studies combined, only 3/662 tedizolid phosphate patients and 6/662 linezolid patients discontinued study drug due to TEAEs.

There were 3 deaths in the Phase 3 development program. Two deaths occurred in patients receiving tedizolid phosphate; one death occurred in a patient receiving linezolid. All 3 deaths occurred in patients with significant co-morbidities.

In tedizolid treated patients, there was a consistent trend for a lower incidence of hematologic abnormalities (values below the lower limit of normal) in the Phase 3 trials, in comparison with linezolid. However, likely due to the short duration of therapy for both agents, there were no difference in the incidence of patients with substantially abnormal hematological values.

Tedizolid phosphate does not prolong the QTc interval in healthy volunteers at supratherapeutic levels.

Neurologic effects were rare with tedizolid phosphate and the active comparator in the Phase 3 program and there were no ophthalmologic toxicities detected in the tedizolid phosphate group by special assessments and through systematic reviews of TEAEs in the integrated safety analysis. To further evaluate this potential risk, a robust 9-month placebo-controlled rat neurotoxicology study showed no evidence of functional or optic and peripheral neuropathologic lesions at systemic exposures of tedizolid phosphate equivalent to up to 8-fold that observed in human at the therapeutic dose of 200 mg once daily.

Nonclinical studies and two human volunteer drug-drug interaction studies did not identify any evidence for tedizolid phosphate to interact with MAOIs or vasopressor agents.

8 BENEFIT/RISK DISCUSSION

In general, the majority of ABSSSI are caused by Gram-positive pathogens such as *S. aureus*, including methicillin-resistant *S aureus* (MRSA) and *S. pyogenes*.

Currently, the only approved agent for the treatment of ABSSSI that allows an IV to oral switch option without necessitating a change in antibiotic is linezolid. The incidence of drug-resistant organisms such as MRSA has reached a level of significant concern. Unfortunately, linezolid resistance due to the plasmid borne *cfr* gene appears to be spreading across the globe (Bonilla 2010; Sánchez Garcia 2010; Cai 2012).

Tedizolid phosphate is a highly effective antibiotic for the treatment of ABSSSI. Robust evidence from 2 double-blind controlled and randomized clinical trials has shown tedizolid phosphate to be as effective over 6 days as linezolid over 10 days, an established FDA-approved and marketed antibiotic for the same indication.

Based on clinical studies, there does not appear to be a need to adjust the dosage of tedizolid phosphate in patients with renal or hepatic impairment or any other special patient populations investigated.

Compared to linezolid, tedizolid phosphate offers the clear advantage of once-daily dosing and a significantly shorter treatment course than linezolid (6 versus 10 to 14 days) for the treatment of ABSSSI.

Overall the identified risks associated with clinical use of tedizolid phosphate are not unlike what is known for linezolid. However, rates of treatment-emergent GI adverse events as well as the effects on clinical hematology laboratory parameters for tedizolid phosphate were reduced as compared to linezolid.

Intensive neurologic and ophthalmologic investigations did not detect any evidence of neurotoxicity associated with tedizolid phosphate when administered for up to 21 days. Moreover, the absence of neuropathic signal was further supported by results from a 9 month rat neurotoxicity study where no evidence of drug-related neurotoxicity was observed on detailed assessments.

A potentially important advantage of tedizolid phosphate over linezolid is in the area of drug-drug interaction risks with MAOIs/serotonergic agents and vasopressor agents. Nonclinical data from a mouse head twitch model supports a low probability of rare, but potentially significant interactions with serotonergic agents by inhibition of MAO by tedizolid phosphate. More common hypertensive effects associated with MAO inhibition were tested clinically. A direct, clinical drug-drug interaction study with tedizolid phosphate and a vasopressor agent did not show evidence for an interaction. These data suggest that a clinically significant interaction is unlikely to occur when tedizolid phosphate is administered with vasopressors. A Phase 1 interaction study with tyramine led to similar conclusions. Thus, the potential for tedizolid interaction with MAOIs, serotonergic agents, vasopressor agents or with foods with high tyramine content is low.

A low therapeutic dose providing a low systemic exposure, a favorable PK profile (modest accumulation over time, low intersubject variability and linear PK) and short course of therapy (6 days) appear to collectively contribute to the favorable therapeutic index of tedizolid phosphate.

9 CONCLUSIONS

In the population of patients with ABSSSI, tedizolid phosphate 200 mg, once daily for 6 days was shown to be non-inferior to linezolid 600 mg, twice daily for 10 days. Phase 3 studies were conducted under Special Protocol Assessments with the FDA and in agreement with all applicable published regulatory guidance current at the time of study

conduct. Each of the two Phase 3 trials showed noninferiority of tedizolid phosphate versus linezolid for the primary endpoints with consistently supportive secondary analysis and robust additional analyses.

Tedizolid phosphate was associated with an adverse event profile very similar to the marketed active comparator, linezolid, though tedizolid phosphate does appear to provide an enhanced safety margin on hematological parameters, drug-drug interaction and neurologic function. Special FDA-requested studies with tedizolid phosphate to explore the potential for neurological toxicity, including extensive ophthalmologic examinations, did not detect significant effects. Moreover, the risks associated with MAO inhibition appear to be minimal, if any.

If approved, tedizolid phosphate would be a viable alternative to linezolid as effective agent with an established safety profile and a distinct advantage of once daily use for a 6 day course of therapy in all adult and adolescent patients with ABSSSI.

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11 APPENDICES

Appendix 1. Inclusion and Exclusion Criteria for Phase 3 Studies

Study TR701-112: Selection of Study Population

Inclusion Criteria

1. Males or females ≥18 years old

2. ABSSSI meeting at least 1 of the clinical syndrome definitions listed below and requiring systemic oral antibiotic therapy. Local symptoms must have started within 7 days before the Screening Visit.
   a. Cellulitis/erysipelas defined as a diffuse skin infection, characterized by all of the following within 24 hours:

   - Rapidly spreading areas of erythema of a minimum total lesion surface area of 75 cm^2
   - No collection of pus apparent upon visual examination (diagnosis still consistent with cellulitis/erysipelas if pus is collected from the lesion)
   - At least 1 of the following signs of infection:
     - Induration
     - Localized warmth
     - Pain or tenderness on palpation
     - Swelling
   - At least 1 of the following regional or systemic signs of infection:
     - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
     - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
     - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
     - >10% immature neutrophils

b. Major cutaneous abscess defined as an infection characterized by a collection of pus apparent upon visual examination spreading within the dermis or deeper that is accompanied by all of the following within 24 hours:

- Erythema extending at least 5 cm in the shortest distance from the peripheral margin of the abscess (specified in Protocol Amendments 3 and 4) and with a minimum total lesion surface area of 75 cm^2
- At least 1 of the following signs of infection:
  - Fluctuance
    - Incision and drainage (I&D) required
    - Purulent or seropurulent drainage
    - Localized warmth
    - Pain or tenderness on palpation
- At least 1 of the following regional or systemic signs of infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils

c. Wound Infection defined as an infection of any apparent break in the skin characterized by the following:

- Superficial incision surgical site infection (SSI) meeting all of the following criteria:
  - Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered)
  - Involves only the skin or subcutaneous tissue around the incision, does not involve fascia
  - Occurs within 30 days after procedure

- Original surgical incision ≥3 cm
- Purulent drainage (spontaneous or therapeutic) with surrounding erythema extending at least 5 cm in the shortest distance from the peripheral margin of the wound (specified in Protocol Amendments 3 and 4) and with a minimum total lesion surface area of 75 cm^2
- At least 1 of the following regional or systemic signs of infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils

- Post-traumatic wound (including penetrating trauma [needle, nail, knife]) characterized by all of the following within 24 hours:
  - Purulent drainage (spontaneous or therapeutic) with surrounding erythema extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2
  - At least 1 of the following regional or systemic signs of infection:
    - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
    - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
    - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
    - >10% immature neutrophils

3. Suspected or documented Gram-positive infection from baseline Gram stain or culture. The microbiological sample must have been collected using a valid sampling technique such as an aspirate, biopsy, incision, deep swab, etc. A superficial swab is not acceptable. Specimens for culture are required for abscesses and wounds at Screening; cellulitis specimens are to be collected according to standard practice at the site

4. Able to give informed consent and willing to comply with all required study procedures

Exclusion Criteria

1. Uncomplicated skin and skin structure infections such as furuncles, minor abscesses (area of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, and minor wound infections (eg, stitch abscesses)

2. Infections associated with, or in close proximity to, a prosthetic device

3. Severe sepsis or septic shock

4. Known bacteremia

5. ABSSSI due to or associated with any of the following:

    - Suspected or documented gram-negative pathogens in patients with cellulitis/erysipelas or major cutaneous abscess that require an antibiotic with specific gram-negative coverage. Patients with wound infections where gram-negative adjunctive therapy is warranted may be enrolled if they meet the other eligibility criteria

    - Diabetic foot infections, gangrene, or perianal abscess

    - Concomitant infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)

    - Infected burns

    - Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous)

    - Any evolving necrotizing process (ie, necrotizing fasciitis)

    - Infected human or animal bites. However, arthropod (eg, insects, spiders, "bugs") bites are allowed; these are not considered animal bites in this study

    - Infections at vascular catheter sites or involving thrombophlebitis

    - Incision SSI with any of the following characteristics:

        - Follows clean-contaminated surgery (urgent or emergency case that is otherwise clean, elective opening of respiratory, gastrointestinal, biliary, or genitourinary tract with minimal spillage [eg, appendectomy] not encountering infected urine or bile; minor technique break)

            - Follows contaminated surgery (nonpurulent inflammation; gross spillage from gastrointestinal tract; entry into biliary or genitourinary tract in the

presence of infected bile or urine; major break in technique; chronic open wounds to be grafted or covered)

- Follows dirty surgery (purulent inflammation [eg, abscess]; preoperative perforation of respiratory, gastrointestinal, biliary, or genitourinary tract)

- Extends into the fascial or muscle layers, organs, or spaces

6. Use of antibiotics as follows:

   - Systemic antibiotic with Gram-positive cocci activity for the treatment of any infection within 96 hours before Dose 1 of study drug

   - Patients who failed prior therapy for the primary infection site are also excluded from enrollment

   - Topical antibiotic on the primary lesion except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound

7. Administration of linezolid within 30 days before Dose 1

8. Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome [AIDS])

9. Receiving chronic systemic immunosuppressive therapy such as prednisone doses ≥20 mg per day for ≥3 of the last 12 months OR therapies that in the Investigator's judgment could predispose to opportunistic infections

10. Receiving treatment for active tuberculosis

11. Last known CD4 count <200 cells/mm^3 in patients with AIDS

12. Current or anticipated neutropenia with absolute neutrophil count (ANC) <1000 cells/mm^3

13. Severe renal disease defined as creatinine clearance (CrCl) <30 mL/min estimated by the Cockcroft-Gault formula *OR* requirement for peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration

14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5 upper limit of normal (ULN) OR moderate to severe hepatic disease with Child-Pugh score ≥7 defined by the following:

    - Presence of ascites upon examination

    - Evidence of encephalopathy upon examination

- Total bilirubin ≥2 mg/dL
- Serum albumin ≤3.5 g/dL
- Prothrombin time (PT) ≥4 seconds longer than control, or international normalized ratio (INR) ≥1.7

15. Significant or life-threatening condition or organ or system condition or disease (eg, endocarditis, meningitis) that would confound or interfere with the assessment of the ABSSSI

16. Morbid obesity with body mass index (BMI) ≥40 kg/m^2

17. Triptan treatment for migraine headaches within 3 years

18. ECG finding of QTc interval >500 msec

19. In patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or thyrotoxicosis, the use of the following medications within 2 days before Dose 1 or planned use through the EOT Visit:

    - Systemic directly and indirectly acting sympathomimetic agents (eg, pseudoephedrine, phenylpropanolamine), vasopressive agents (eg, epinephrine, norepinephrine), or dopaminergic agents (eg, dopamine, dobutamine). Use of a small amount of a vasoconstrictor (eg, lidocaine containing epinephrine) during a local surgical procedure (eg, I&D) is allowed

20. Use of the following medications within 14 days before Dose 1 or planned use through the EOT Visit:

    - Monoamine oxidase A and B (MAOA and MAOB) inhibitors (eg, phenelzine, isocarboxazid)
    - Serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and serotonin 5-hydroxytryptamine (5-HT1) receptor agonists (triptans), meperidine, or buspirone

21. High tyramine diet

22. Women who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel], or male partner sterilization [excluding women ≥2 years postmenopausal or surgically sterile])

23. Treatment with investigational medicinal product within 30 days before Dose 1

24. Investigational device present, or removed <30 days before Dose 1, or presence of device-related infection

25. Previous inclusion in the TR-701 FA or TR-701 development program

26. Hypersensitivity to oxazolidinones or any component in the formulation

27. If aztreonam adjunctive therapy is required in patients with wound infections, history of hypersensitivity to ceftazidime or any component of the aztreonam formulation

28. For patients with wound infections, history of hypersensitivity to metronidazole or any component of the formulation, if metronidazole adjunctive therapy is required

29. Patients who the Investigator considers unlikely to adhere to the protocol, comply with study drug administration, or complete the clinical study

Study TR701-113: Inclusion Criteria

1. Males or females ≥12 years old

2. Adequate venous access for a minimum of 2 IV doses of study drug

3. ABSSSI meeting at least 1 of the clinical syndrome definitions listed below and requiring IV antibiotic therapy. Local symptoms must have started within 7 days before the Screening Visit
   - **a. Cellulitis/erysipelas** defined as a diffuse skin infection, characterized by all of the following within 24 hours:
     - Rapidly spreading areas of erythema, edema, and/or induration of a minimum total lesion surface area of 75 cm^2
     - No collection of pus apparent upon visual examination (diagnosis still consistent with cellulitis/erysipelas if pus is collected from the lesion)
     - At least 2 of the following signs of infection:
       - Erythema
       - Induration
       - Localized warmth
       - Pain or tenderness on palpation
       - Swelling/edema
     - At least 1 of the following regional or systemic signs of infection:
       - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI

- Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
- WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
- >10% immature neutrophils

b. Major cutaneous abscess defined as an infection characterized by a collection of pus apparent upon visual examination spreading within the dermis or deeper that is accompanied by all of the following within 24 hours:

- Erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the abscess and with a minimum total lesion surface area of 75 cm^2
- At least 1 of the following signs of infection:
  - Fluctuance
  - Incision and drainage required
  - Purulent or seropurulent drainage
  - Localized warmth
  - Pain or tenderness on palpation
- At least 1 of the following regional or systemic signs of infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils

c. Wound infection defined as an infection of any apparent break in the skin characterized by the following:

- Superficial incision surgical site infection meeting all of the following criteria:
  - Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, GI, biliary, and genitourinary tracts not entered)
  - Involves only the skin or subcutaneous tissue around the incision, does not involve fascia
  - Occurs within 30 days after procedure
  - Original surgical incision ≥3 cm

- Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2

- At least 1 of the following regional or systemic signs of infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils

- Post-traumatic wound (including penetrating trauma [needle, nail, knife]) characterized by all of the following within 24 hours:

  - Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2

- At least 1 of the following regional or systemic signs of infection:
  - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
  - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
  - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
  - >10% immature neutrophils

4. Suspected or documented Gram-positive infection from baseline Gram stain or culture. The microbiological sample must have been collected using a valid sampling technique such as an aspirate, biopsy, incision, deep swab, etc. A superficial swab is not acceptable. Specimens for culture are required for abscesses and wounds at Screening; cellulitis specimens are to be collected according to standard practice at the site

5. Able to give informed consent and willing to comply with all required study procedures

Exclusion Criteria

1. Uncomplicated skin and skin structure infections such as furuncles, minor abscesses (area of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, and minor wound infections (eg, stitch abscesses)

2. Infections associated with, or in close proximity to, a prosthetic device

3. Severe sepsis or septic shock

4. Known bacteremia at time of Screening

5. ABSSSI due to or associated with any of the following:

    - Suspected or documented gram-negative pathogens in patients with cellulitis/erysipelas or major cutaneous abscess that require an antibiotic with specific gram-negative coverage. Patients with wound infections where gram-negative adjunctive therapy is warranted may be enrolled if they meet the other eligibility criteria

    - Diabetic foot infections, gangrene, or perianal abscess

    - Concomitant infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)

    - Infected burns

    - Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous)

    - Any evolving necrotizing process (ie, necrotizing fasciitis)

    - Infected human or animal bites. However, arthropod (eg, insects, spiders, "bugs") bites are allowed; these are not considered animal bites in this study

    - Infections at vascular catheter sites or involving thrombophlebitis

    - Incision surgical site infection with any of the following characteristics:
        - Follows clean-contaminated surgery (urgent or emergency case that is otherwise clean, elective opening of respiratory, GI, biliary, or genitourinary tract with minimal spillage [eg, appendectomy] not encountering infected urine or bile; minor technique break)
        - Follows contaminated surgery (nonpurulent inflammation; gross spillage from GI tract; entry into biliary or genitourinary tract in the presence of

infected bile or urine; major break in technique; chronic open wounds to be grafted or covered)

- Follows dirty surgery (purulent inflammation [eg, abscess]; preoperative perforation of respiratory, GI, biliary, or genitourinary tract)
- Extends into the fascia or muscle layers, organs, or spaces

6. Use of antibiotics as follows:
   - Systemic antibiotic with Gram-positive cocci activity for the treatment of any infection within 96 hours before the first infusion of study drug
   - Patients who failed prior therapy for the primary infection site are also excluded from enrollment
   - Topical antibiotic on the primary lesion except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound
7. Administration of linezolid within 30 days before the first infusion of study drug
8. Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome [AIDS])
9. Receiving chronic systemic immunosuppressive therapy such as prednisone doses ≥20 mg per day for ≥3 of the last 12 months OR therapies that in the Investigator's judgment could predispose to opportunistic infections
10. Chronic (daily for the previous 30 days) use of antipyretic medication (eg, acetaminophen, paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs]). Low-dose aspirin (≤200 mg per day) for cardiovascular prophylaxis is allowed
11. Receiving treatment for active tuberculosis
12. Last known CD4 count <200 cells/mm^3 in patients with AIDS
13. Current or anticipated neutropenia with absolute neutrophil count (ANC) <1000 cells/mm^3
14. Severe renal disease defined as creatinine clearance (CrCl) <30 mL/min estimated by the Cockcroft-Gault formula OR requirement for peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration
15. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥8 × upper limit of normal (ULN) OR severe hepatic disease with Child-Pugh score >9 defined by the following:
    - Presence of ascites upon examination

- Evidence of encephalopathy upon examination
- Total bilirubin ≥2 mg/dL
- Serum albumin ≤3.5 g/dL
- Prothrombin time (PT) ≥4 seconds longer than control, or international normalized ratio (INR) ≥1.7

16. Significant or life-threatening condition or organ or system condition or disease (eg, endocarditis, meningitis) that would confound or interfere with the assessment of the ABSSSI

17. Triptan treatment for migraine headaches within 3 years

18. ECG finding of corrected QT interval >500 msec using Bazett's correction method (QTcB) or Fridericia's correction method (QTcF)

19. In patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or thyrotoxicosis, the use of the following medications within 2 days before the first infusion of study drug or planned use through the EOT Visit:

    - Systemic directly and indirectly acting sympathomimetic agents (eg, pseudoephedrine, phenylpropanolamine), vasopressive agents (eg, epinephrine, norepinephrine), or dopaminergic agents (eg, dopamine, dobutamine). Use of a small amount of a vasoconstrictor (eg, lidocaine containing epinephrine) during a minor surgical procedure under local anesthesia (eg, incision and drainage) is allowed

20. Use of the following medications within 14 days before the first infusion of study drug or planned use through the EOT Visit:

    - Monoamine oxidase A and B (MAO_A and MAO_B) inhibitors (eg, phenelzine, isocarboxazid)

    - Serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and serotonin 5-hydroxytryptamine (5-HT1) receptor agonists (triptans), meperidine, or buspirone

21. High tyramine diet

22. Women who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel], or male partner sterilization [excluding women ≥2 years postmenopausal or surgically sterile])

23. Treatment with investigational medicinal product within 30 days before the first infusion of study drug

24. Investigational device present, or removed <30 days before the first infusion of study drug or presence of device-related infection

25. Previous inclusion in the TR-701 FA or TR-701 development program

26. Hypersensitivity to oxazolidinones or any component in the formulation

27. If aztreonam adjunctive therapy is required in patients with wound infections, history of hypersensitivity to ceftazidime or any component of the aztreonam formulation

28. For patients with wound infections, history of hypersensitivity to metronidazole or any component of the formulation, if metronidazole adjunctive therapy is required

29. Patients who the Investigator considers unlikely to adhere to the protocol, comply with study drug administration, or complete the clinical study

Appendix 2. Narratives for Death Cases

Tedizolid Phosphate Group:

Patient TR701-113-451-258, an 84-year-old White male, initiated tedizolid phosphate treatment [redacted] for right leg cellulitis/erysipelas. The final study drug administration was 11 July 2012. Relevant medical history included myocardial infarction (MI; 2008); heart failure, hypertension, dyslipidemia, and chronic obstructive pulmonary disease (2008); coronary artery bypass (2010), and pulmonary hypertension (2012). Concomitant medications include furosemide, ramipril, bisoprolol, atorvastatin, amlodipine, and tamsulosin. The cellulitis was improving by Day 7.

On [redacted] the patient experienced a myocardial infarction and was transported to the hospital by ambulance. He was placed on mechanical ventilation due to cardiopulmonary failure and sedated. Medications included epinephrine, dobutamine, glyceryl trinitrate, furosemide, enoxaparin, pantoprazole, amiodarone, morphine, and prophylactic cefuroxime. Data from outside the database included laboratory values of myoglobin 475 µg/L (28-72 µg/L), troponin 405 ng/L (<14 ng/L), creatine kinase 271 IU/L (38-174 IU/L), creatine kinase-MB 15.7 µg/L (<4.9 µg/L), creatine kinase-MB to creatine kinase relative index 5.8% (0-2.5%), and lactate 5.3 mmol/L (0.5-2.2 mmol/L). On [redacted] laboratory values were troponin 419 ng/L and NT-pro brain natriuretic peptide 22,360 ng/L (<486 ng/L). The patient's condition continued to deteriorate with laboratory values [redacted] of troponin 1154 ng/L (0-50 ng/L), blood urea nitrogen 21.6 mmol/L, creatinine 263 µmol/L, and GFR 20 mL/min/1.73 m^2.

On [redacted] at 7:00 am supportive measures were discontinued and the patient died at approximately [redacted]. An autopsy was not performed.

Patient TR701-112-342-605, an 86-year-old Hispanic White male, initiated tedizolid phosphate treatment on [redacted] for left arm cellulitis. The final study drug administration was [redacted]. Relevant medical history included current/recent IV drug use, pneumonia (April and June 2011), chronic obstructive pulmonary disease, arterial hypertension, atrial fibrillation, chronic congestive heart failure, ischemic stroke, dementia, rigidity and tremor of arms and legs, and uninfected decubitus ulcers in the sacral region and in the back of the right thigh. Concomitant medications included digoxin, omeprazole, salmeterol/fluticasone, ipratropium bromide, enoxaparin, furosemide, fenoterol, and spironolactone.

On [redacted], approximately 21 days following the last study drug administration, the patient was admitted with pneumonia. The patient received norepinephrine, omeprazole, enoxaparin hydrocortisone, and fenoterol.

Data from outside the clinical database indicated oxygen saturation was 88%. There were diffuse rhonchi in bilateral lung fields. Leukocytes were 13,260 cells/mm^3 and arterial blood gas was pH 7.22, pO_2 66.0 mmHg, pCO_2 130 mmHg, and HCO_3^- 51.5 mmol/L with FiO_2 0.5. The patient received oxygen, IV meropenem 1 gram 3 times

daily, IV vancomycin 1 gram twice daily, and human albumin, methylprednisolone then prednisone, fluconazole, ranitidine, norepinephrine, hydrocortisone, fenoterol, and furosemide (for edema). Chest x-ray revealed consolidation in the lower lobe of the right lung. The patient was intubated.

The patient developed septic shock on [redacted], and mechanical ventilation and vasopressor support with norepinephrine was initiated. A tracheostomy was performed. On [redacted], the patient experienced cardiac arrest and underwent cardiopulmonary resuscitation. The patient received IV norepinephrine and atropine. On [redacted], creatine phosphokinase-MB was 14.19 UI/L (range 0-25 UI/L) and creatine phosphokinase 49.33 U/L (range 24-195 U/L). The cardiac arrest was assessed to be possibly related to respiratory failure and pneumonia. The patient's condition remained critical, with hypoxic encephalopathy, and vital functions were stabilized by vasopressors and mechanical ventilatory support. Respiratory tract cultures revealed growth of *Pseudomonas aeruginosa*.

On [redacted], the patient was hemodynamically stable without vasoactive drugs and with noted gradual improvement in neurological status. Meropenem and linezolid were discontinued and the patient was switched to IV ceftazidime 1 gram 3 times daily and magnesium sulfate. The patient was transferred to the Intermediate Care Unit on [redacted], awake and alert but still requiring mechanical ventilation. However, the patient's condition declined, renal dysfunction developed, and bilateral pulmonary infiltrates were noted by chest x-ray. On [redacted], respiratory secretions culture was positive for extended spectrum β-lactamase producing *Klebsiella*.

On [redacted], the patient developed septic shock with multiorgan failure. On [redacted], the patient received colloid and crystalloid fluid resuscitation, norepinephrine 0.41 µg/kg/min IV, dopamine 5.8 µg/kg/min IV, magnesium sulfate, methylprednisolone, omeprazole, vecuronium, fentanyl, and midazolam. The patient went into cardiac arrest; resuscitative measures were unsuccessful and the patient died. Immediate cause of death on the death certificate was septic shock.

Linezolid Group:

Patient 444-230/[redacted], a 33-year-old Black female, initiated linezolid treatment [redacted] for right lower leg cellulitis/erysipelas. The final study drug administration was 28 June 2012 (received Doses 1 through 18). Relevant medical history included human immunodeficiency virus (HIV) infection (diagnosed during hospitalization). Concomitant medications included acetaminophen/codeine for pain associated with the ABSSSI.

On 27 June 2012 the patient experienced mild nausea and vomiting and received metoclopramide, and on 29 June 2012 the patient received ciprofloxacin 500 mg twice for cellulitis.

Data from outside the database included the patient reporting a 3-day history [redacted] of progressive headache, nausea, and weakness, and the patient was

admitted. Symptoms included mild headache, slight confusion, dehydration, and sleepiness, with no overt signs of increased intracranial pressure or meningism. Temperature was 99.9°F. The patient received ceftriaxone 1 g twice daily for possible meningitis. Cerebral spinal fluid (CSF) from a lumbar puncture showed lymphocytes 188, neutrophils 182, protein 3.56 (reference ranges and units not provided), and was cryptococcus negative, HIV positive. Additional laboratory tests revealed the following: WBC count 8600 cells/mm^3, hemoglobin 9.8 g/dL, C-reactive protein 44 mg/L, CD4+ count 49 cells/mm^3, normal urea, and normal electrolytes. The patient received rifampicin, pyrazinamide, ethambutol and isoniazid for tuberculosis meningitis diagnosed based on the clinical presentation and CSF results. On (b) (6) the patient experienced a convulsion and received diazepam 5 mg IV. Later that day the patient was found dead in the hospital bed; no resuscitation was attempted. An autopsy was not performed.

The Investigator assessed the tuberculous meningitis as severe and not related to study drug.

Appendix 3. Definition of Trial Responder at EOT and PTE for Study TR701-112 and TR701-113

Study TR701-112

Criteria for Sustained Response at EOT (Day 11-12)

For the secondary outcome measure of sustained response at the EOT Visit, patients who were not defined programmatically as a clinical failure or an indeterminate were to be considered a clinical success.

Patients assessed as a nonresponder at the 48-72 Hour Visit were to be considered a clinical failure at the EOT Visit. Patients were to be programmatically defined as a clinical failure as outlined below:

- At the EOT Visit (Day 11) the patient meets any of the following:
    - Presence of fever >37.6°C (oral; Investigator reported) with no cause other than the primary skin infection
    - No decrease from baseline in the size of the primary ABSSSI lesion
    - Clinician assessment of tenderness worse than mild
    - Patient-reported presence of pain
- At any time from the first dose of study drug through the EOT Visit (Day 11), the patient meets any of the following:
    - Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
    - Treatment-emergent AE (TEAE) leading to discontinuation of study drug and patient required additional antibiotic therapy to treat the ABSSSI
    - Requires additional antibiotic therapy for treatment of the primary lesion
    - Unplanned major surgical intervention required due to failure of study drug (ie, amputation)
    - Developed osteomyelitis after baseline
    - For wounds and abscess: I&D of the ABSSSI site not planned before randomization and performed after Day 1
    - For cellulitis/erysipelas: I&D of the ABSSSI site after the 48-72 Hour Visit
    - Death (all-cause mortality) within 28 days of the first dose of study drug

Patients were to be programmatically defined as an indeterminate based on the criteria below:

- Osteomyelitis present at baseline
- Lost to follow-up prior to EOT (Day 11)
- For patients with cellulitis/erysipelas or major cutaneous abscess: gram-negative organism isolated at baseline that required a different antibiotic therapy
- For patients with wound infections: gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole
- Patient withdraws consent prior to the EOT Visit

Investigator's Assessment of Clinical Response Definitions at End of Therapy and Post-Therapy Evaluation Visits

Clinical Success

Meets the following three criteria:

- Resolution or near resolution of most disease-specific signs and symptoms
- Absence or near resolution of systemic signs of infection (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count), if present at baseline
- No new signs, symptoms, or complications attributable to the ABSSSI so no further antibiotic therapy is required for the treatment of the primary lesion

Clinical Failure

Any of the following:

- Requires additional antibiotic therapy for treatment of the primary lesion
- Unplanned major surgical intervention required due to failure of study drug (ie, amputation)
- Developed osteomyelitis after baseline
- Persistent Gram-positive pathogen bacteremia
- Treatment-emergent AE leading to discontinuation of study drug and patient required additional antibiotic therapy to treat the ABSSSI
- Death (all-cause mortality) within 28 days of first dose

Indeterminate

Study data are not available for the evaluation of efficacy for any reason including:

- Osteomyelitis present at baseline
- Lost to follow up

- Extenuating circumstances that preclude the classification of a clinical success or failure
- For patients with cellulitis/erysipelas or major cutaneous abscess: gram-negative organism isolated at baseline that required a different antibiotic therapy
- For patients with wound infections: gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole
- Patient withdraws consent

Study TR701-113

Criteria for Programmatic Clinical Response at EOT Visit (day 11-12)

Clinical Success

Patient meets any of the following at the EOT Visit (Day 11):

- Patient is afebrile (<37.7°C oral; Investigator reported) or the fever ≥37.7°C is attributable to a cause other than the primary skin infection
- Decrease from baseline in the size (area, length, and width) of the primary ABSSSI lesion
- Clinician assessment of tenderness of mild or absent
- No purulent drainage from a wound infection or the purulent drainage is of a lesser intensity than at Screening

Patient meets any of the following from the first infusion of study drug through the EOT Visit (Day 11)

- Did not receive any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
- Did not have a TEAE leading to discontinuation of study drug and required additional antibiotic therapy to treat the ABSSSI
- No additional antibiotic therapy for treatment of the primary lesion is required
- No unplanned major surgical intervention to the primary lesion
- Did not develop osteomyelitis after baseline
- For wounds and abscess: no incision and drainage of the ABSSSI site was performed after Day 1 unless it was planned before randomization
- For cellulitis/erysipelas: no incision and drainage of the ABSSSI site after the 48 72 Hour Visit

Clinical Failure

Patient meets any of the following at the EOT Visit (Day 11):

- Presence of fever ≥37.7°C (oral; Investigator reported) with no cause other than the primary skin infection
- No decrease from baseline in the size of the primary ABSSSI lesion (area, length, or width)
- Clinician assessment of tenderness worse than mild
- Persistent purulent drainage from a wound infection at the same or greater intensity as Screening

Patient meets any of the following at any time from the first infusion of study drug through the EOT Visit (Day 11):

- Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
- Treatment-emergent AE leading to discontinuation of study drug and patient required additional antibiotic therapy to treat the ABSSSI
- Requires additional antibiotic therapy for treatment of the primary lesion
- Unplanned major surgical intervention required due to failure of study drug (ie, amputation)
- Developed osteomyelitis after baseline
- For wounds and abscess: incision and drainage of the ABSSSI site not planned before randomization and performed after Day 1
- For cellulitis/erysipelas: incision and drainage of the ABSSSI site after the 48 72 Hour Visit
- Death (all-cause mortality) within 28 days of the first infusion of study drug

Indeterminate

- Osteomyelitis present at baseline
- Lost to follow up prior to EOT (Day 11)
- For patients with cellulitis/erysipelas or major cutaneous abscess: gram-negative organism isolated at baseline that required a different antibiotic therapy
- For patients with wound infections: gram-negative organism isolated at baseline that required a different antibiotic therapy other than aztreonam or metronidazole
- Patient withdraws consent prior to the EOT Visit

Investigator's Assessment of Clinical Response Definitions at End of Therapy and Post-Therapy Evaluation Visits

Please see Study TR701-112 definitions, criteria for Study TR701-113 are the same.

Appendix 4. Inclusion In or Exclusion from the CE-EOT Analysis Set and In or Exclusion from the CE-PTE Analysis Set for Studies TR701-112 and TR701-113

Clinically Evaluable (CE) Analysis Sets

Patients will be *included* in or *excluded* from the CE Analysis Sets based on the criteria listed below.

Diagnosis of ABSSSI

To be included in the CE-EOT and CE-PTE Analysis Sets, patients must meet the following protocol defined inclusion criteria that describe the ABSSSI:

ABSSSI meeting at least 1 of the clinical syndrome definitions listed below and requiring IV antibiotic therapy. Local symptoms must have started within 7 days before the Screening Visit.

- **Cellulitis/erysipelas** defined as a diffuse skin infection, characterized by all of the following within 24 hours:
    - Rapidly spreading areas of erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2
    - No collection of pus apparent upon visual examination (diagnosis still consistent with cellulitis/erysipelas if pus is collected from the lesion)
    - At least 2 of the following signs of infection:
    - Erythema
    - Induration
    - Localized warmth
    - Pain or tenderness on palpation
    - Swelling/edema

    - At least 1 of the following regional or systemic signs of infection:
        - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
        - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
        - White blood cell (WBC) count ≥10,000 cells/mm^3 or <4000 cells/mm^3
        - >10% immature neutrophils

- **Major cutaneous abscess** defined as an infection characterized by a collection of pus upon visual examination spreading within the dermis or deeper that is accompanied by all the following within 24 hours:
  - Erythema, edema and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the abscess and a minimum total lesion surface area of 75 cm^2
  - At least 1 of the following signs of infection:
    - Fluctuance
    - Incision and drainage required
    - Purulent or seropurulent drainage
    - Localized warmth
    - Pain or tenderness on palpation
  - At least 1 of the following regional or systemic signs of infection:
    - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
    - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
    - WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
    - >10% immature neutrophils
- Wound Infection defined as an infection of any apparent break in the skin characterized by the following:
  - Superficial incision surgical site infection (SSI) meeting all of the following criteria:
    - Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered)
    - Involves only the skin or subcutaneous tissue around the incision, does not involve fascia
    - Occurs within 30 days after procedure
    - Original surgical incision ≥3 cm
    - Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2
    - At least 1 of the following regional or systemic signs of infection:

- Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
- Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
- WBC count ≥10,000 cells/mm^3 or <4000 cells/mm^3
- >10% immature neutrophils

- Post traumatic wound (including penetrating trauma [needle, nail, knife]) characterized by all of the following within 24 hours:
  - Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound and with a minimum total lesion surface area of 75 cm^2
  - At least 1 of the following regional or systemic signs of infection:
    - Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
    - Fever, defined as body temperature ≥38°C (100.4°F) oral, ≥38.5°C (101.3°F) tympanic, or ≥39°C (102.2°F) rectal (observed by a health care provider)
    - WBC count ≥10,000 cells/mm3 or <4000 cells/mm3
    - >10% immature neutrophils

Prior Antibiotic Therapy

Patients who receive any systemic antibiotic therapy for the treatment of any infection or topical antibiotic on the primary lesion (except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound) within 96 hour before the first infusion of study drug are *excluded* from the CE-EOT and CE-PTE Analysis Sets, unless the antibiotic does not have activity against the baseline pathogen. Patients who were a failure on prior therapy are also *excluded* from the CE-EOT and CE-PTE Analysis Sets.

Concomitant Antibiotic Therapy

Patients who receive any systemic concomitant antibiotic therapy from the first infusion of study drug through EOT (Day 11) that is potentially effective against the baseline pathogen (other than adjunctive aztreonam and/or metronidazole in patients with wound infections) will be defined as a clinical failure for the secondary efficacy outcome measure of clinical response at the EOT Visit and thus, will be included in the CE-EOT Analysis Set. If a patient does not have a pathogen isolated at baseline and the systemic concomitant antibiotic received has Gram-positive activity, the patient will be defined as

a failure for the secondary efficacy outcome measure and will be included in the CE-EOT Analysis Set.

Patients who receive any systemic concomitant antibiotic therapy from the first infusion of study drug through the PTE Visit that is potentially effective against the baseline pathogen (other than adjunctive aztreonam and/or metronidazole in patients with wound infections) will be excluded from the CE-PTE Analysis Set, unless the patient is considered a clinical failure by the Investigator at EOT or PTE. Patients who do not have a pathogen isolated at baseline and receive an antibiotic with Gram-positive activity (from the first infusion of study drug through the PTE Visit) will also be excluded from the CE-PTE Analysis Set unless considered a failure by the Investigator at EOT or PTE.

Patients who receive a systemic concomitant antibiotic that is not effective against the baseline pathogen, or if no pathogen is isolated, and the antibiotic does not have Gram-positive activity, will be included in the CE-EOT and CE-PTE Analysis Sets.

In addition, patients must meet the following to be included in the CE Analysis Sets:

- Did not use any topical antibiotic (except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound) on the primary ABSSSI lesion from first infusion of study drug through EOT (CE-EOT Analysis Set) or the PTE Visit (CE-PTE Analysis Set)
- Antibiotics that will not interfere with the course of the ABSSSI are allowed and do not affect inclusion in the CE Analysis Sets: eg, metronidazole, norfloxacin nalidixic acid, pipemedic acid, oral vancomycin, antifungals, antivirals, topical antibiotics used for decontamination or in places other than the primary lesion.

Concomitant Surgical Procedures

Patients who receive an unplanned major surgical procedure such as amputation will be defined as a clinical failure for both the secondary outcome measure of clinical response at the EOT Visit and the Investigator's assessment of clinical outcome and thus, will be included in the CE Analysis Sets. Patients with a major cutaneous abscess or wound infection who have an unplanned (ie, not planned before randomization) incision and drainage (I&D) of the primary ABSSSI site more than 24 hours after the first dose of study drug will be defined as a clinical failure for the secondary outcome measure of clinical response at the EOT Visit and thus, will be included in the CE-EOT Analysis Set. Patients with cellulitis/erysipelas who have an I&D of the primary ABSSSI after 72 hours after the first infusion of study drug will be defined as a clinical failure for the secondary outcome measure of clinical response at the EOT Visit and thus, will be included in the CE-EOT Analysis Set.

All surgical procedures performed after the first dose of study drug will be reviewed by the Sponsor to determine whether the procedure potentially confounds the outcome and whether the patient should be excluded from either CE Analysis Set. Debridement, aspiration puncture or excision with or without skin grating will generally be acceptable and will not exclude a patient from the CE Analysis Sets.

Study Drug Therapy

Patients must meet all of the following to be included in the CE Analysis Sets:

- Received at least one dose of study drug and the correct study drug based on the randomization assignment
- Study personnel involved in the assessment of efficacy remained blinded to study treatment, unless a treatment limiting adverse event occurred which required emergency unblinding.
- Evaluable failure: The patient received the first 2 doses of active study drug (TR-701 FA group) or first 4 doses of active study drug (linezolid group) and the patient is a failure based on the secondary outcome of clinical response at the EOT Visit (CE-EOT Analysis Set) or the Investigator classifies the patient as a clinical failure (CE-PTE Analysis Set) unless the patient had a treatment limiting adverse event.
- Evaluable success: The patient received at least 5 doses of active study drug (TR-701 FA group) or at least 10 doses of active study drug (linezolid group) and the patient is a success based on the secondary outcome of clinical response at the EOT Visit (CE-EOT) or the Investigator classifies the patient as a clinical success at the EOT and PTE Visits (CE-PTE Analysis Set).

Clinical Outcome Assessment

Patients must meet the following to be included in the CE Analysis Sets:

- For the CE-EOT Analysis Set:
  - Completed the clinical response outcome assessment at the EOT Visit (ie, was not programmatically determined to be an indeterminate response)
  - The EOT Visit occurred on Study Day 11 (+2 days) or with 2 days after the last dose of study drug.
- For the CE-PTE Analysis Set:
  - Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the PTE Visit, unless the patient was defined as a clinical failure based on Investigator's assessment at the EOT Visit.
  - The PTE Visit occurred 7-14 days after the EOT Visit, unless the patient was considered to be a clinical failure based on the Investigator's assessment at the EOT Visit. If the patient did not have an EOT Visit, the PTE Visit must occur within 7-14 days of Study Day 11 (the protocol specified time point for the EOT Visit).

Baseline or Inter-Current Medical Events

Patients will be excluded from the CE Analysis Sets if the Investigator has documented in the e-CRF that they meet any one of the following protocol-defined exclusion criteria at baseline (ie, prior to randomization):

- Uncomplicated skin and skin structure infections (SSSIs) such as furuncles, minor abscesses (area of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, and minor wound infections (eg, stitch abscesses)
- Infections associated with, or in close proximity to, a prosthetic device
- Severe sepsis or septic shock
- ABSSSI due to or associated with any of the following:
- Suspected or documented gram-negative pathogens in patients with cellulitis/erysipelas or major cutaneous abscess that require an antibiotic with specific gram-negative coverage. Patients with wound infections where gram negative adjunctive therapy is warranted may be enrolled if they meet the other eligibility criteria
- Diabetic foot infections, gangrene, or perianal abscess
- Concomitant infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
- Infected burns
- Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous)
- Any evolving necrotizing process (ie, necrotizing fasciitis)
- Infected human or animal bites. However, arthropod (eg, insects, spiders, ‘bugs’) bites are allowed; these are not considered animal bites in this study.
- Infections at vascular catheter sites or involving thrombophlebitis
- Incision SSI with any of the following characteristics:
    - Follows clean contaminated surgery (urgent or emergency case that is otherwise clean, elective opening of respiratory, gastrointestinal, biliary, or genitourinary tract with minimal spillage [eg, appendectomy] not encountering infected urine or bile; minor technique break)
    - Follows contaminated surgery (nonpurulent inflammation; gross spillage from gastrointestinal tract; entry into biliary or genitourinary tract in the presence of infected bile or urine; major break in technique; chronic open wounds to be grafted or covered)

- Follows dirty surgery (purulent inflammation [eg, abscess]; preoperative perforation of respiratory, gastrointestinal, biliary, or genitourinary tract)
- Extends into the fascial or muscle layers, organs, or spaces
- Administration of any linezolid within 30 days before the first infusion of study drug
- Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome [AIDS])
- Chronic (daily for the previous 30 days) use of antipyretic medication (eg. Acetaminophen, paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDS]). Low dose aspirin for cardiovascular prophylaxis is allowed.
- Last known CD4 count <200 cells/mm^3 in patients with AIDS
- Current or anticipated neutropenia with ANC <1000 cells/mm^3
- Significant or life-threatening condition or organ or system condition or disease (eg, endocarditis, meningitis) that would confound or interfere with the assessment of the ABSSSI

Concomitant medical conditions will be reviewed by the Sponsor to determine whether these conditions potentially confound the secondary outcome(s), in which case the patient should be excluded from the CE-EOT or CE-PTE Analysis Sets.