CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205436Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205435 and 205436
Priority or Standard	Priority
Submit Date(s)	October 18, 2014
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Division / Office	DAIP/OAP/OND/CDER
Reviewer Name(s)	Sheral Patel, M.D. Shrimant Mishra, M.D., M.P.H.
Review Completion Date	June 9, 2014
Established Name	Tedizolid phosphate (TR-701/FA)
(Proposed) Trade Name	Sivextro
Therapeutic Class	Oxazolidinone
Applicant	Cubist Pharmaceuticals, acquirer of Trius Therapeutics, Inc.
Formulation(s)	Oral and Intravenous
Dosing Regimen	Oral tablet: 200 mg once daily for 6 days Lyophilized powder for intravenous (IV) injection: 200 mg once daily for 6 days
Indication(s)	Acute bacterial skin and skin structure infections
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Tedizolid phosphate should be approved, at a dose of 200 mg oral or intravenous once daily for 6 days, for treatment of acute bacterial skin and skin structure infection (ABSSSI) caused by susceptible organisms in adults.

Two Phase 3 studies demonstrated that the difference between treatment effect for tedizolid phosphate compared to linezolid met the prespecified noninferiority margin for the primary endpoint for each trial, and tedizolid phosphate performed similarly to the comparator on important secondary endpoints. However, there is a lack of information regarding treatment efficacy in certain populations (neutropenic and pediatric individuals) as well as in individuals infected with particular pathogens. This should be addressed in labeling by either eliminating language claiming efficacy in these areas or addition of language describing the paucity of information to evaluate efficacy in those particular subgroups.

Based on the safety review of the clinical data presented by the Applicant, we recommend that tedizolid phosphate be approved for the treatment of acute bacterial skin and skin structure infections caused by susceptible organisms in adults.

1.2 Risk Benefit Assessment

From an efficacy perspective, the overall risk benefit profile is positive. ABSSSI is a serious infection, and tedizolid phosphate demonstrated similar efficacy as its comparator in two randomized, double blinded, multicenter phase 3 studies in this indication. Importantly, tedizolid phosphate appeared to have similar efficacy to the comparator using both the new primary endpoints recommended by the Agency (lesion measurements at 48-72 hrs.) as well as older traditional endpoints (investigator assessments at PTE). Moreover, the drug can be given once a day for a short dosing duration of 6 days, and it needs no dose adjustment for the various subgroups studied.

The observation that the study drug's activity relies significantly upon the presence of neutrophils is concerning, particularly as neutropenic subjects were not included in the Phase 3 trials. At the very least, labeling should limit or caution against use in this population; testing tedizolid phosphate's activity in this population is likely to be deemed unethical. until further investigation/clinical experience is acquired. Whether these findings imply decreased efficacy in other immunocompromised states beyond neutropenia is unclear.

There is also little data at this time to support use in pediatric subjects, including adolescents. Pediatric enrollment in Phase 3 studies was negligible, and PK studies in adolescents highlighted an increased tedizolid phosphate Cmax, the safety implications of which are unclear. Further studies are needed before use in this population can be indicated

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Subgroup analysis on the primary endpoint highlighted possible decreased efficacy, relative to the comparator, in potentially vulnerable subgroups, such as diabetics, the elderly, subjects with lesion size ≥ 1000 cm^2, obese subjects, etc. However, most of these findings could not be replicated from study to study or from earlier to later time points, and the subgroups themselves were generally small, thus limiting interpretation. Given the uncertainty surrounding these findings, any discussion of this in labelling is likely unwarranted at this time, as is any PMR/PMC (see discussion below).

Based on the data submitted, tedizolid phosphate has a favorable safety profile for approval for the treatment of acute bacterial skin and skin structure infections caused by susceptible organisms in adults at a dosage of 200 mg orally or intravenously once daily for six days. The most common treatment emergent adverse events occurring at ≥2% incidence for both tedizolid phosphate and linezolid were diarrhea, nausea, vomiting, abscess, cellulitis, dizziness and headache. In the Phase 3 trials, the incidence of diarrhea, nausea and vomiting were numerically lower in the tedizolid phosphate versus linezolid arm. At the proposed dose and duration (200 mg oral/intravenous once daily for 6 days), tedizolid phosphate does not appear to influence QT prolongation, hepatotoxicity, or renal toxicity. Review of the available clinical data suggest that tedizolid phosphate, at the proposed dose (200 mg po/IV once daily) and duration (6 days), was similar to the comparator, linezolid, with respect to potential class specific toxicities such as peripheral and ophthalmic neuropathy, myelosuppression, lactic acidosis, convulsions and hypoglycemia. It should be noted that the Phase 3 studies are of limited benefit in assessing toxicities noted to occur with prolonged administration (myelosuppression or peripheral and optic neuropathy) or that may occur relatively infrequently (lactic acidosis, convulsions, hypoglycemia). Nonclinical and Phase 1 studies suggest that the risk of MAO-related drug interactions and serotonergic syndrome may be less likely with tedizolid phosphate versus linezolid in healthy adults. Conclusions regarding safety in patient subpopulations such as patients < 18 years old, the elderly as well as neutropenic, renally impaired and diabetic individuals cannot be made because of limited data available. Furthermore, additional studies would be required in patients using tedizolid phosphate at different doses and durations of treatment for other indications such as osteomyelitis or septic arthritis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division of Risk Management in the Office of Medication Error Prevention and Management reviewed the application and determined that a Postmarket Risk and Evaluation Strategy (REMS) for the management of the risks associated with tedizolid was not recommended. This recommendation was based on the available safety data and a safety profile consistent with linezolid, which does not have a REMS.

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1.4 Recommendations for Postmarket Requirements and Commitments

Standard division post marketing requirements, including surveying for developing resistance to tedizolid phosphate over a five year period, should be recommended as well the development and conduct of studies in pediatric populations, as required by the Pediatric Research and Equity Act (PREA).

Tedizolid phosphate did appear to perform more poorly in certain subgroups with regards to efficacy. However, as discussed above, there is considerable uncertainty regarding these findings in terms of whether they represent a statistical variation or whether they represent some deficiency with the drug itself (such as the proposed dose and duration). It is unclear whether a PMR/PMC to evaluate tedizolid phosphate's ability to treat ABSSSI in such patient subpopulations, including the elderly or diabetics, would be useful. Such a study might include evaluating tedizolid phosphate vs. a comparator or comparing two different dosing durations of tedizolid phosphate in certain high risk groups. However, the Applicant may have no significant incentive to conduct this study, and there could be statistical issues in interpreting the results. For example, if only a small sample size was evaluated, it could be difficult to draw any definitive conclusions. While observational studies may have increased feasibility, interpretation of data arising from such studies also could be limited. Alternatively, no PMR/PMC could be recommended and this could simply be monitored through the usual Agency mechanisms (AERS, PADER reports, etc.), however it is unlikely that adverse event reporting would frequently include subjects who seemed to do poorly with the drug. Given the above considerations, it is likely best to forego any PMR/PMC related to this issue and instead learn from clinical experience. Also, when considering risk to such vulnerable subjects in approving the current dosing regimen, it is reasonable to assume that in a real world setting, many of the subjects in these subgroups would end up being treated off-label for slightly longer durations than what was studied if they did not appear to improve after six days.

From the safety perspective, tedizolid phosphate and linezolid had a similar safety profile overall; however the numbers were too small to make definitive conclusions in subgroups.

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2 Introduction and Regulatory Background

2.1 Product Information

Tedizolid phosphate (proposed trade name SIVEXTRO)is an oxazolidinone prodrug that is converted *in vivo* by phosphatases to the microbiologically active moiety tedizolid (TR700), (**Figure 2.1-1**). Tedizolid interacts with the 50S subunit of the bacterial ribosome as a protein synthesis inhibitor.

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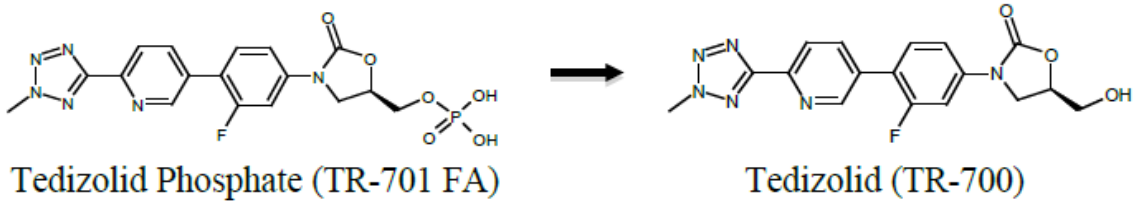
Figure 2.1-1: Chemical Structures of Tedizolid Phosphate and Tedizolid



Source: Applicant's submission 2.5 Clinical Overview, Figure 1.

The drug is an NME, and the Applicant is seeking an indication of Acute Bacterial Skin and Skin Structure Infections caused by susceptible strains of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA], methicillin-susceptible [MSSA]), *Streptococcus pyogenes*, *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*), and *Enterococcus faecalis.* Tedizolid phosphate is to be dosed as a once a day 200mg IV or oral medication for 6 days; the Applicant is proposing the drug be administered in subjects (b) (4) The drug is purported to inhibit bacterial translation of susceptible organisms. Moreover, the Applicant purports that tedizolid phosphate is safer than its class comparator with regards to myelosuppressive, neuropathic (optic and peripheral), and drug-drug interaction effects.

2.2 Tables of Currently Available Treatments for Proposed Indications

Given the inclusion of MRSA in the proposed indication of tedizolid phosphate, relevant comparator drugs include daptomycin, intravenous vancomycin, linezolid, tygecycline, telavancin, ceftaroline, and clindamycin among others.

2.3 Availability of Proposed Active Ingredient in the United States

The drug is currently not marketed in the US or worldwide.

2.4 Important Safety Issues With Consideration to Related Drugs

Several safety issues exist for the only drug approved in the oxazolidinone drug class, linezolid (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=6e70e63b-bfd5-478d-a8ee-8ba22c9efabd#nlm43685-7). These safety concerns include optic and peripheral neuropathy, myelosuppression, MAO related drug interactions, serotonin syndrome, lactic acidosis, convulsions and hypoglycemia. Some of the safety concerns associated with linezolid occur with longer duration of exposure. For example, peripheral and optic neuropathy have been

reported primarily in patients treated with linezolid for more than 28 days and myelosuppression is a particular concern in patients taking linezolid for more than two weeks. In cases of myelosuppression where the outcome was known, affected hematology parameters returned to pre-treatment levels after linezolid was discontinued. Potential increases in blood pressure have been seen in patients receiving linezolid and concomitant medications such as directly and indirectly acting sympathomimetic agents, vasopressive agents, and dopaminergic agents. Patients taking linezolid who develop lactic acidosis may have repeated episodes of nausea and vomiting. Some patients who experience convulsions while taking linezolid had a history of, or risk factors for, seizures reported. Symptomatic hypoglycemia has been reported in patients with diabetes mellitus receiving linezolid while taking concomitant insulin or oral hypoglycemic agents.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The US Congress approved the Generating Antibiotic Incentives Now Act of 2011 to encourage the development of products to treat, prevent, detect, and diagnose antibiotic-resistant pathogens. Under the Qualified Infectious Disease Product (QIDP) and qualifying pathogen provisions of this Act, tedizolid phosphate, IV and oral forms, for the treatment of ABSSSI and hospital-acquired pneumonia/ventilator-associated pneumonia were granted the QIDP designation in January 2013.

Previous characterization of skin and skin structure infections fell into two categories, uncomplicated skin and skin structure infections (uSSSI) and complicated skin and skin structure infections (cSSSI). Uncomplicated skin and skin structure infections included simple abscesses, impetiginous lesions, furuncles and cellulitis. Complicated skin and skin structure infections involved deeper tissues which may require surgical intervention (such as extensive cellulitis/ erysipelas or major cutaneous abscess) as well as infected wounds, ulcers or burns.

In October 2013, FDA issued a new guidance where ABSSSI includes cellulitis/erysipelas, wound infection, and major cutaneous abscess with a minimum lesion surface area of approximately 75 cm^2. With the new definition of ABSSSI, where surface area is a criterion, mild infections which may not require treatment are excluded. The guidance also recommended that clinical response should be based on the percent reduction in the lesion size at 48 to 72 hours compared to baseline. The guidance defines a clinical response as a ≥ 20% reduction compared to baseline.

A timeline of relevant activities/meetings is as follows:

> **Oct. 2009**- The End of Phase 2 meeting was held. At this meeting, the division requested a special ophthalmic toxicity substudy in humans, requested longer nonclinical optic and peripheral neuropathy studies, and agreed to a safety database of roughly 1200 subjects.

Feb. 2010- At this meeting, there was a discussion of potential endpoints for study 112 with no agreement made.

May 2010- At this meeting, a general agreement was reached on what study 112's primary endpoint should be (fever and no spread of lesion as well as NI margin).

June 2010- SPA agreement issued for study 112.

Jan. 2011- SPA for study 112 altered to remove required quota on febrile and wound subjects.

Aug. 2011- agreement for study 113 SPA; this initial agreement was based on a primary endpoint of no lesion spread and absence of fever at 48-72 hrs with a 10% NI margin.

Dec. 2012- New SPA issued with a 20% reduction in lesion size at the 48-72 hr. visit designated the primary endpoint in study 113.

Jan 2013- QIDP Granted for ABSSSI and HABP/VABP.

May 2013- Pre NDA meeting held that included discussion on how to file/submit application.

June 2013- Pediatric Study Plan discussed.

It should be noted that the change in endpoint for Study 113 was the result of a Foundation for the National Institutes of Health 2012 recommendation to use such an endpoint in ABSSSI studies.

2.6 Other Relevant Background Information

This new molecular entity was taken to the Anti-Infective Drug Advisory Committee for consideration on March 31, 2014. Details are provided in Section 9.3.

The drug is not approved in foreign countries.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant submitted the NDA application in accordance with the electronic format defined in the M4 International Conference on Harmonisation (ICH) Common Technical Document (CTD). Datasets were submitted per Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format. The submission included all clinical study reports and datasets. Relevant case reports forms for patients with a serious adverse event including death were submitted.

There were several issues with the datasets submitted for the safety analyses necessitating multiple and repeated information requests during the review. A brief description of a few of the dataset issues are highlighted below. This is not a comprehensive list.

1.) *Nomenclature for unique subject identifiers*: There was inconsistent nomenclature for unique subject identifiers between the two Phase 3 trials, TR701-112 and TR701-113. The Applicant was requested to resubmit datasets where there was truly a unique subject Identifier variable in both tabulations and analysis datasets to allow for pooled safety analyses to be completed.

2.) *Parsing errors of resubmitted datasets*: Resubmitted datasets included single double quotes in the SAS label. Special characters in the SAS labels or variable names typically lead to errors. The Applicant was requested to resubmit datasets for the safety analyses without these special characters.

3.) *Inconsistent use of units for laboratory results*: Different dataset variables were used in the tabulation and analysis datasets. This included inconsistent use of laboratory results reported in Standard International or US Conventional units. The Applicant was requested to re-submit datasets to consistently include the laboratory results in US Conventional units with Conventional Normal Range variables Upper Limit and Lower Limit in the ISS datasets.

4.) *Snellen Visual Acuity Results dataset errors*: In the course of the review, missing variables were noted in the Snellen Visual Acuity Results. The Applicant resubmitted this dataset for analysis.

Dataset issues led to significant challenges with the safety review. The numerous information requests required during this priority review resulted in a compressed amount of time to conduct safety analyses.

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3.2 Compliance with Good Clinical Practices

Per the Applicant, International Conference on Harmonisation and Good Clinical Practice regulations were followed in the country in which each study was conducted. During the course of the NDA review cycle, the Applicant reported three sites from Study TR701-112 with GCP violations (sites 120, 121, and 122). Audit reports from these sites were submitted for review. All 18 patients from the three clinical sites with GCP violations were included in the safety analyses.

Please see the final inspection reports issued by Division of Scientific Investigation (DSI) for further information (Note: currently not all inspection reports have been finalized at the time of this review).

Four study sites were chosen for inspection, primarily due to study enrollment numbers (OSI's site inspection tool was utilized in this process). Of the four sites, 3 were domestic and one was an international site in Russia. Due to factors outside of Agency control (namely a tense current U.S. –Russia diplomatic relationship), access to the Russian site has been prohibited; it is unlikely to be inspected before the PDUFA goal date if at all. Brief discussion findings at the other 3 sites are discussed below.

Site #1 (Dr. Green): This has preliminarily received a VAI designation by DSI. At this site, minor problems were noted including not maintaining photographs for certain visits in the source document or the CRF and not recording symptoms (such as fluctuance, pain, erythema) accurately for 5 patients at a particular visit in the CRF. Also, two adverse events were not reported in the CRF (upper respiratory infection; chest rash). Overall, it appeared that these mistakes occurred at particular visits only, may have involved symptoms not used in primary or secondary endpoints, or involved supplemental evidence (photographs).

Site #2 (Kingsley): This site has preliminarily received a designation of VAI. Issues included 3 subjects using prohibited medications (Neosporin four days prior to enrollment, concomitant metronidazole, and use of Toradol on enrollment). Importantly, twenty-three of 43 patients who completed the 48-72 hour visit had temperature measurements prior to the 48 hours after randomization. Though this is important in terms of trial conduct and assessment of the primary endpoint, its effect is minimized by study 113 (which did not have a temperature parameter in the endpoint), as well as secondary endpoints in both studies which assessed efficacy at later time points. The Applicant noted that getting temperature measurements at particular time points proved to be burdensome and difficult.

Site # 3 (Mehra): This site has preliminarily received a designation of VAI. Issues included having identical photographs for screening and the 48-72 hr. visit and not reporting a tachycardia event for 3 patients. Also, one subject was classified as a success on the crf

though he/she was classified as a failure on the source document. Eight subjects were randomized into the clinical syndrome of "major abscess" but then reclassified as a "wound infection" on CRF. Overall, it appears errors in endpoint assessment were limited and issues with adverse event reporting involved an adverse event of minor concern and which can be investigated further by analyzing vital signs data. Difficulty in interpreting whether a subject had particular clinical syndrome is a shortcoming of the study as a whole and not just limited to this site. In fact DSI notes that officially "*for TR701-112, there were 21 cases reclassified out of 667 patients randomized. For TR701-113, there were a 43 cases reclassified of 666 patients randomized. DAIP is aware of the reclassifications."*

Applicant Inspection: No issues were noted at the Applicant site visit, which included evaluation of monitoring reports related to the Russia site.

Despite the above inspections, the Applicant reported that it had found cGCP violations at three different sites. Please note the discussion in section 3.2. For its part, DSI plans to inspect these sites and recommends performing sensitivity analyses with and without the sites included.

Upon its own internal review, the Applicant noted that 3 sites, sites 120, 121, and 122 in Study TR701-112, did not appear to adhere to accepted cGCP practices. In particular, it was noted that were deficiencies in source documents (including multiple and hard to interpret corrections, lack of source documentation, etc.) that did not allow for proper corroboration of eCRF data. Moreover, these sites appeared to have poor management and operating practices including inadequate training, poor maintenance of documentation, poor storage of documents, and poorly understood delegation of authority. Also, in some instances, infection types were reclassified without proper documentation as to the reason for this. Though the Applicant concluded that subjects at these sites were in general properly screened and randomized, received proper treatment, and followed the protocol, due to issues with source documentation, it was recommended to exclude these subjects from efficacy analyses. These sites only enrolled 18 subjects, and the statistical reviewer has performed most Study 112 analyses using the ITT population exclusive of these subjects; these analyses did not appear to change the overall study conclusions. Given this finding, in this review, the ITT population has been evaluated as a whole (these subjects were not excluded from analyses). As noted above, DSI has not inspected these sites yet (b) (4) and has recommended sensitivity analyses excluding these subjects.

3.3 Financial Disclosures

The Applicant disclosed no financial interests on Form 3454 (box 1) for the vast majority of investigators involved in its Phase 1 and 2 studies and all of its Phase 3 studies. For one Phase 1 investigator (b) (6) and (b) (6) Phase 2 investigators (b) (6) the Applicant submitted Form 3454 (box 3), stating that though no financial disclosures were apparent at the initiation of the respective studies, one year follow up

information could not be obtained. For one investigator [redacted] (b) (6) it was noted that he received monies for Applicant-related but study-unrelated work (nonclinical studies; work on a tedizolid phosphate advisory board). His monies totaled $275,000 though all but $1,500 was paid to his employer [redacted] (b) (6) He received an honoraria of $1,500. The Applicant noted that [redacted] (b) (6) consults for multiple pharmaceutical companies and is not an Applicant shareholder. It is unlikely that the submitted financial disclosures should affect the evaluation of study drug efficacy, particularly given that the primary evaluation of efficacy is derived from the Phase 3 trials (for which no disclosures were noted).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the CMC review by Dr. Rajiv Agarwal for further details.

4.2 Clinical Microbiology

Please see the Clinical Microbiology review by Dr. Avery Goodwin for further details, including discussion of the in vitro activity of tedizolid phosphate against various pathogens and its resistance profile.

4.3 Preclinical Pharmacology/Toxicology

Please see the Pharmacology-Toxicology review by Dr. James Wild for details. Key safety findings from the preclinical studies follow.

4.3.1 Neurologic and ophthalmologic disorders

A 9-month vehicle-controlled rat neurotoxicology study suggested no evidence of functional or histopathologic optic or peripheral neuropathic lesions at systemic exposures equivalent to up to 8-fold that observed in humans at the therapeutic dose of 200 mg once daily. In addition, no functional nerve anomalies were observed through the 9-month assessment up to the maximum 8-fold clinical exposure.

4.3.2 Myelosuppression

Preclinical studies examined immunotoxicity. The results indicate that, at doses associated with TR-700 exposures 4 to 8 times the human therapeutic exposure, TR-701 is immunotoxic. However, results of the recovery study in the 3-month oral toxicology study indicate that the

immunotoxicity appears to be reversible. Because TR-701 was immunotoxic in animals studied at high doses, immune cells may require monitoring in patients if dosed at longer durations.

4.3.3 MAO related drug interactions and serotonergic syndrome

The effects of tedizolid phosphate and central serotonergic potentiation and blood pressure were examined in animal models. In a mouse head-twitch experiment and a tyramine-challenge experiment in rats, linezolid doses comparable to the human therapeutic dose produced positive results (increased head twitch or increased mean arterial pressure), but TR-701 doses associated with plasma TR-700 C_{max} and AUC values greatly exceeding the equivalent clinical therapeutic exposure values did not.

4.4 Clinical Pharmacology

Tedizolid phosphate is noted to have similar plasma exposures with IV and oral administration. Thus, a dose adjustment is not needed when transitioning from IV to oral therapy. Please see the Clinical Pharmacology review by Dr. Zhixia Yan and Dr. Fang Li for details including analysis of tedizolid phosphate's major pharmacodynamic parameters and ADME information. Important safety findings from the clinical pharmacology studies follow.

4.4.1 MAO-related drug interactions

Nonclinical and Phase 1 studies in healthy individuals suggest that potential MAO related drug-drug interactions with tedizolid phosphate may be less than that observed with linezolid. In nonclinical studies, a tyramine challenge in rats had no significant effect on mean arterial pressure. Results from Phase 1 studies, conducted to evaluate whether TR-701 FA potentiates sensitivity to tyramine (TR701-105) and the MAO-mediated pressor response to pseudoephedrine HCl (TR701-114), suggest that there is minimal drug-drug interaction in healthy individuals. MAO-related drug interactions were not assessed in Phase 2 and Phase 3 trials due to study design and patient exclusion criteria. Further data will be required to determine possible MAO related drug interactions in a clinically relevant population.

4.4.2 Serotonergic syndrome

Current prescribing information for linezolid indicates that patients taking drugs with serotonergic potential should take the drug only if no other therapies are available, and to discontinue serotonergic drugs and monitor for serotonergic syndrome. Data from a study examining serotonergic brain activity in a murine behavioral model suggest no increase in head twitch rates at TR701 exposures equivalent to 30 times the human therapeutic dose. In the Phase 2 and Phase 3 trials, patients taking concomitant serotonergic agents were excluded. In the few individuals taking concomitant $5HT_3$ antagonists in the Phase 3 trials, the incidence of

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treatment emergent adverse events were similar for tedizolid phosphate and linezolid, and were not characteristic of serotonin syndrome. Preliminary studies suggest that interactions with serotonergic potentiating drugs may be less than linezolid in healthy adults.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Phase 3 trials used for the efficacy evaluation are highlighted in the **Table 5.1 -1**..

Table 5.1-1: Highlights of Phase 3 Studies for Tedizolid Phosphate

Study 112	
Design	Randomized, double blind, active-controlled, multicenter, noninferiority trial Aug. 2010-Sept. 2011
Route/Dose/Duration	200mg tedizolid phosphate (oral) daily x 6 days 600mg linezolid bid (oral) x 10 days
Sites	81 sites in North America, Europe, and Latin America
Study Populations	ITT: Tedizolid phosphate: 332 Linezolid: 335 Safety: Tedizolid phosphate: 331Linezolid: 335 mITT: Tedizolid phosphate: 209 Linezolid: 209
Pediatric Enrollment	None
Primary Endpoint	Noninferiority (NI) in the early clinical response rate at 48-72 hours in ITT population; responder afebrile with no spread of lesion
Secondary Endpoint	♦ Clinical response at 48-72 hours that is sustained at EOT in the ITT and CE-EOT analysis sets ♦Investigator's assessment of clinical success at PTE in the ITT and CE-PTE analysis sets ♦Investigator's assessment of clinical response at the 48-72 Hour and Day 7 Visits in the ITT analysis set♦ patient-reported pain, by study visit ♦Safety ♦Population PK profile of TR-700
Study 113	
Design	Randomized, double blind, active controlled, multicenter,noninferioirty trial Sept. 2011- Jan. 2013

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Route/Dose/Duration	200mg tedizolid phosphate (IV to oral) daily x 6 days 600mg linezolid (IV to oral) bid x 10 days
Sites	95 sites in the US,, Europe South Africa, Australia/New Zealand, and Argentina
Study Populations	ITT: Tedizolid phosphate: 332 Linezolid: 334 Safety: Tedizolid phosphate:331 Linezolid: 327 mITT: Tedizolid phosphate: 197 Linezolid: 202
Pediatric Enrollment	Tedizolid phosphate : one 17 y/o subject Linezolid: one 15 y/o subject
Primary Endpoint	Noninferiority (NI) in the early clinical response rate at 48-72 hours in ITT population; responder 20% reduction in primary lesion
Secondary Endpoint	Similar to above

Notes: TR 701-112 title: A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral TR-701 Free Acid and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

TR 701-113 title: A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous to Oral 6-Day TR-701 Free Acid and Intravenous to Oral 10-Day Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infection

- Study 112 sites: North America (US, Canada), Europe (Germany, Latvia, Slovakia, Czech Republic, Hungary, Ukraine), Latin America (Argentina, Brazil, Peru)

-Study 113 sites: European countries included Germany, Poland, Russia, and Spain

For the safety evaluation, select Phase 1 trials as well as Phase 2 and 3 trials were examined. An overview of clinical studies in the tedizolid phosphate development program is provided in **Table** 5.1-2.

Table 5.1-2: Overview of Clinical Development Program for Tedizolid Phosphate

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 TR-701 Part B: oral 200, 300, or 400 mg once-daily TR-701,600 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 TR-701	Microdialysis in subcutaneous adipose and skeletal muscle tissues	12/12
TR701-103	Single oral 600 mg TR-701 either after a high-fat meal or in fasting conditions	Food effect	12/12
TR701-105	Multiple oral 200 mg TR-701 FA or placebo and tyramine HCl (25 mg then escalated in 50-mg increments until TYR_{30} reached)	Safety, tolerability, and blood pressure response of TR-701 FA in combination with tyramine	39/30
TR701-106	Single oral 204 mg [^{14}C]-TR-701 FA containing 100 µCi ^{14}C	Safety, tolerability, PK, route of TR-701 excretion, TR-700 metabolic profile	6/6
TR701-107	A. Single ascending IV dose, placebo or 50 to 400 mg TR-701 FA B. Multiple ascending IV dose, placebo or 200 or 300 mg TR-701 FA once daily for 7 days C. Open-label bioavailability, 200 mg TR-701 FA oral and IV D. Venous tolerability, placebo or 200 mg TR-701 FA 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 TR-701 FA 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 TR-701 FA	Safety, tolerability, PK in elderly	28/28
TR701-110	Multiple oral 200 mg TR-701 FA once daily for 10 days	Safety and ophthalmic and neurologic assessment	72/72
TR701-111	Single oral or IV 200 mg TR-701 FA	Safety, tolerability, PK in adolescents	20/20

Study No. and Phase	Dose and Regimen	Purpose	Subjects Enrolled/ Planned
TR701-114	Multiple oral 200 mg TR-701 FA or placebo once daily for 5 days and 60 mg PSE on Day 5	Safety and blood pressure response of TR-701 FA in combination with PSE	18/18
TR701-115	Single oral 200 mg or 1200 mg TR-701 FA, 400 mg moxifloxacin, or placebo	Potential QTcF effects	48/48
TR701-119	Oral 200 mg TR-701 FA once daily for 3 days	Safety, PK, and disposition of TR-700 into pulmonary epithelial lining fluid and alveolar macrophages	20/20
TR701-123	Single IV 200 mg TR-701 FA	Safety and PK in advanced renal impairment with or without hemodialysis	24/24
TR701-124	Single oral 200 mg TR-701 FA	Safety and PK in moderate or severe hepatic impairment	32/32
Phase 2 Studies			
TR701-104	Oral 200, 300, or 400 mg TR-701 once daily; for 5-7 days	Clinical and microbiological response, safety, popPK	192/180
TR701-126	Oral 200 mg TR-701 FA once daily for 6 days	Safety and exploratory skin lesion measurement	200/200
Phase 3 Studies			
TR701-112	Oral 200 mg TR-701 FA once daily for 6 days or 600 mg linezolid twice daily for 10 days	Efficacy, safety, popPK in the treatment of ABSSSI	667/658
TR701-113	IV to oral 200 mg TR-701 FA 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 TR-701 FA IV, I 200 mg TR-701 FA V/oral, or placebo	Safety, tolerability, PK, and absolute bioavailability	36/36
16102	IV or oral 200 mg TR-701 FA or placebo once daily for 7 days	Safety, tolerability, PK and intestinal flora evaluation	24/24

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; IV=intravenous; pk=pharmacokinetics; popPK=population pharmacokinetics; PSE=pseudoephedrine; QTcF=QT interval corrected for heart rate using Fridericia's formula
Note: TYR_{30}=the dose of tyramine required to raise systolic blood pressure by 30 mmHg.
[a]An optional treatment arm of 10 subjects was not conducted.

Source: Applicant's Clinical Overview 2.5 Table 1: Overview of Clinical Development Program

5.2 Review Strategy

Review of safety and efficacy for tedizolid phosphate were conducted separately by two clinical reviewers. Narratives of both reviews are integrated into a single document. The Safety Reviewer was Sheral Patel, M.D. and the Efficacy Reviewer was Shrimant Mishra, M.D., M.P.H. Sections requiring input from both safety and efficacy were completed jointly.

5.3 Discussion of Individual Studies/Clinical Trials

Study 112

Study 112 had an original protocol with 4 amendments. Subjects started enrollment under Amendment 1. Important protocol revisions included:

Amendment 1: DSMB was added; excluded subjects who were failing prior therapy from entering the trial; made pain component secondary endpoint more general (not just pain based on VAS)

Amendment 2: No major changes as regards efficacy were noted

Amendment 3: Clarified that for wounds and abscesses, erythema had to extend at least 5cm from the margin of the abscess/wound

Study 112 was a randomized, active controlled, double-blind, double dummy, multicenter noninferiority (NI) trial comparing 6 days of oral tedizolid phosphate 200 mg daily with 10 days of oral linezolid 600 mg twice daily for the treatment of ABSSSI. Eligible subjects were randomized 1:1 to either oral tedizolid phosphate 200 mg daily for 6 days or oral linezolid 600 mg twice daily for 10 days.

Subjects were stratified according to presence/absence of fever at baseline, geographic region, and one of three different clinical syndromes- cellulitis/erysipelas, major cutaneous abscesses, and wound infections. Major cutaneous abscesses were not to comprise more than 30% of the study population in order to limit the potential confounding effect of incision and drainage.

Study assessments were performed at screening (which could be the day before or Day 1 of study drug infusion), Day 1, Day 2, 48-72 hours after drug infusion, Day 7, Day 11 (end-of-treatment [EOT] visit), 7-14 days after the EOT visit (post-therapy efficacy [PTE] visit), and 18-25 days after the EOT visit (late follow-up [LFU] visit). Subjects were allowed to take study drug at home.

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Inclusion criteria were as follows:

1. Males or females ≥18 years old
2. ABSSSI meeting at least one of the clinical syndrome definitions listed below and requiring systemic oral antibacterial therapy. Local symptoms must have started within 7 days before the Screening Visit.

a. **Cellulitis/erysipelas** defined as a diffuse skin infection that is accompanied by all of the following within 24 hours:

i. Rapidly spreading areas of erythema of a minimum total lesion surface area of **75 cm2**

ii. No collection of pus apparent upon visual examination (diagnosis still consistent with cellulitis/erysipelas if pus is collected from the lesion)

iii. At least one of the following signs of infection:

1. Induration
2. Localized warmth
3. Pain or tenderness on palpation
4. Swelling

iv. At least one of the following regional or systemic signs of infection:

1. Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
2. 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)
3. WBC count ≥10,000 cells/mm3 or <4000 cells/mm3
4. >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:

i. Erythema 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 cm2**

ii. At least one of the following signs of infection:

1. Fluctuance
2. Incision and drainage (I&D) required
3. Purulent or seropurulent drainage
4. Localized warmth
5. Pain or tenderness on palpation

iii. At least one of the following regional or systemic signs of infection:

1. Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI

2. 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)

3. WBC count ≥10,000 cells/mm3 or <4000 cells/mm3

4. >10% immature neutrophils

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

i. Superficial incision surgical site infection (SSI) meeting all of the following criteria:

1. Follows clean surgery (elective, not emergency, nontraumatic, primarily closed, no acute inflammation; no break in technique; respiratory, gastrointestinal, biliary, and genitourinary tracts not entered)
2. Involves only the skin or subcutaneous tissue around the incision, does not involve fascia
3. Occurs within 30 days after procedure
4. Original surgical incision ≥3 cm
5. 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 cm2**
6. At least one of the following regional or systemic signs of infection:
   a. Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI
   b. 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)
   c. WBC count ≥10,000 cells/mm3 or <4000 cells/mm3
   d. >10% immature neutrophils

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

1. 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 cm2**
2. At least one of the following regional or systemic signs of infection:
   a. Lymph node tenderness and increase in volume or palpable proximal to the primary ABSSSI

b. 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)
c. WBC count ≥10,000 cells/mm3 or <4000 cells/mm3
d. >10% immature neutrophils

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

Important exclusion criteria (as relates to efficacy) included:

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 (e.g., 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:
    a. Suspected or documented Gram-negative pathogens in patients with cellulitis/erysipelas or major cutaneous abscess that require an antibacterial drug 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
    b. Diabetic foot infections, gangrene, or perianal abscess
    c. Concomitant infection at another site not including a secondary ABSSSI lesion (e.g., septic arthritis, endocarditis, osteomyelitis)
    d. Infected burns
    e. Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous)
    f. Any evolving necrotizing process (i.e., necrotizing fasciitis)
    g. Infected human or animal bites. However, arthropod (e.g., insects, spiders, “bugs”) bites are allowed; these are not considered animal bites in this study
    h. Infections at vascular catheter sites or involving thrombophlebitis
    i. Incision SSI with any of the following characteristics:

i. Follows clean-contaminated surgery (urgent or emergency case that is otherwise clean, elective opening of respiratory, gastrointestinal, biliary, or genitourinary tract with minimal spillage [e.g., appendectomy] not encountering infected urine or bile; minor technique break)
ii. 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)
iii. Follows dirty surgery (purulent inflammation [e.g., abscess]; preoperative perforation of respiratory, gastrointestinal, biliary, or genitourinary tract)
iv. Extends into the fascial or muscle layers, organs, or spaces

6. Use of antibacterial drugs as follows:
   a. Systemic antibacterial drug with Gram-positive cocci activity for the treatment of any infection within 96 hours before Dose 1 of study drug
   b. Patients who failed prior therapy for the primary infection site
   c. Topical antibacterial drug on the primary lesion except for antibacterial/antiseptic-coated dressing applied to the clean postsurgical wound
7. 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

8. ALT or AST (aspartate aminotransferase) ≥ 5 upper limit of normal **OR** moderate to severe hepatic disease with Child-Pugh score ≥7 defined by the following:
   a. Presence of ascites upon examination
   b. Evidence of encephalopathy upon examination
   c. Total bilirubin ≥ 2 mg/dL
   d. Serum albumin ≤ 3.5 g/dL
   e. Prothrombin time (PT) ≥ 4 seconds longer than control, or international normalized ratio (INR) ≥ 1.7
9. 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

10. Morbid obesity with body mass index (BMI) ≥ 40 kg/m2
11. 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)

Adjunctive systemic antibacterial therapy was not allowed in the case of subjects with cellulitis/erysipelas as well as major cutaneous abscess but adjunctive aztreonam and/or metronidazole for wound infections was allowed if a gram negative pathogen was suspected.

However, if only a gram negative pathogen ended up being isolated, the subject was to discontinue study drug. Prohibited antibiotics were prohibited from 96 hours prior to Dose 1 through LFU. Topical antibiotics on the primary ABSSSI lesion except associated with surgical dressing on a clean wound were prohibited 96 hours prior to Dose 1 through the LFU Visit.

For wounds and abscesses, incision and drainage of the ABSSSI site not planned before randomization and performed after Day 1 was discouraged, but could be performed if clearly indicated by the clinical condition. For cellulitis: incision and drainage of the ABSSSI site not planned before randomization and performed after the 48-72 Hour Visit was discouraged, but could be performed if clearly indicated by the clinical condition.

Topical antiseptics, disinfectants, and soaps for local care and body decontamination were allowed as was supportive measures for optimal medical care (such as debridement, wound packing, wound lavage, aspiration puncture, excision with or without grafting, etc).

Analgesic medications without antipyretic effects were recommended for use until after the 48-72 Hour Visit.

Discontinuation from study was recommended in situations including:

- ♦ Investigator-assessed treatment failure (treatment failure determined programmatically did not necessitate treatment discontinuation)
- ♦ Patients requesting discontinuation of the study drug or from the study
- ♦ Investigator considering a change of therapy would be in the best interest of the patient
- ♦ For patients with cellulitis/erysipelas or major cutaneous abscess, identification of Gram-negative pathogen(s) in the culture of the primary lesion that required antibiotic treatment for Gram-negative coverage
- ♦ For patients with wound infections, identification of Gram-negative pathogen(s) and no Gram-positive pathogen in the culture of the primary lesion
- ♦ Patient with staphylococcal bacteremia who did not meet the criteria for *low risk* staphylococcal bacteremia. Criteria for low risk included:
  - a If performed, transesophageal echocardiography excluded endocarditis
  - b The patient had no implanted prostheses (excluding dental implants)
  - c Follow-up cultures of blood specimens obtained 2 to 3 days after the initial blood cultures were negative for *S. aureus*
  - d The patient's temperature defervesced within 72 hours after initiation of therapy
  - e The patient had no signs or symptoms suggestive of metastatic staphylococcal infection

- ♦ A positive *S. aureus* bacteremia result at baseline and any time after at least 4 doses of therapy (unless low risk)
- ♦ If a patient with liver function test results that are within the normal range at baseline develops ALT or AST ≥ 3 × ULN, AND bilirubin ≥ 2 mg/dL, AND alkaline phosphatase < 2 × ULN during study treatment, discontinue study treatment and monitor the patient until medically stable
- ♦ Unacceptable toxicity

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♦ Patient becomes pregnant
♦ Patient requires treatment prohibited by the protocol that potentially affects the patient's safety

As noted earlier, subjects were randomized to take either tedizolid phosphate 200mg daily for 6 days followed by 4 days of placebo or 10 days of linezolid 600mg twice daily.

Study Visit Outline (can attach full list of procedures with each visit as an appendix if necessary).

The study visit schedule included:
Screening Visit (within 24 hours of Dose 1)
Day 1 Visit (which could be the same day as screening)- subjects received first dose here; if subject was to be treated as an outpatient, then drug doses and diary for recording drug administration time, pain/antipyretic medication usage, and vital signs were given
Day 2 Visit
48-72 Hour Visit (48-72 hours after 1st dose)- assessments made here for primary endpoint
Day 7 Visit (+ 2 days)

Day 11 EOT Visit (+2 days after the last dose) except in patients considered a clinical failure or who had early discontinuation of study drug, in which case the EOT assessments were to be completed within 2 days of last dose and before beginning rescue therapy, if feasible. Some secondary endpoints assessed here, including programmatic determination of sustained response at EOT

PTE Visit (7-14 days after EOT Visit)- some secondary endpoints assessed here, including investigator assessment of clinical response at PTE

LFU Visit (18-25 days after EOT visit): this could be a telephone interview; relapse assessed here

The Primary and Secondary Objectives were designated as follows:

Primary Objective: Noninferiority in the early clinical response rate of 6-day oral tedizolid phosphate compared with that of 10-day oral linezolid treatment at the 48-72 Hour Visit in the ITT analysis set in patients with ABSSSI.

Secondary Objectives
♦ To compare the clinical response of 6-day tedizolid phosphate and 10-day linezolid treatment at 48-72 hours that is sustained at the EOT Visit (Day 11) in the ITT and CE-EOT analysis sets

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♦ To compare the Investigator's assessment of clinical success at the PTE Visit (7-14 days after the EOT Visit) in the ITT and CE-PTE analysis sets
♦ To compare the Investigator's assessment of clinical response at the 48-72 Hour and Day 7 Visits in the ITT analysis set
♦ To compare patient-reported pain, by study visit
♦ To evaluate the safety profile of TR-701 FA in comparison with that of linezolid
♦ To assess the population pharmacokinetic profile of TR-700

Additional Objectives:
♦ To compare the per-patient favorable microbiological response rate at the PTE Visit in the microbiological ITT (MITT) and ME analysis sets
♦ To compare the per-pathogen favorable microbiological response rate at the PTE Visit in the MITT and ME analysis sets
♦ To compare the Investigator's assessment of clinical success at the PTE Visit in the MITT and ME analysis sets
♦ To compare the per-pathogen Investigator's assessment of clinical success at the PTE Visit in the MITT and ME analysis sets

For the primary outcome measure of early clinical response at the 48-72 hour visit, assessments were determined based on data recorded on the e-Case Report Forms (eCRF); an investigator's assessment was not a component of the primary outcome measure. At the 48-72 hour visit, the patient was determined programmatically as a responder or a nonresponder to therapy.
Patients were defined as **responders** if the following criteria were met:

- The patient has cessation of spread of the primary ABSSSI lesion, compared to baseline
- The temperature measurement (assessed by the investigator) is ≤ 37.6°C (oral) and the next measurement (investigator or patient assessed taken within 24 hours of the 48-72 hour visit) is also ≤ 37.6°C (oral)

Patients were defined as **nonresponders** if any of the following criteria were met:

- Spread of the primary ABSSSI lesion, compared to baseline
- Receipt of any systemic concomitant antibacterial therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
- Death (all-cause mortality)
- Either the temperature measurement at the 48-72 hour visit (assessed by the investigator) **OR** the next measurement (investigator or patient assessed taken within 24 hours of the 48-72 Hour Visit) is > 37.6°C (oral).

For the secondary outcome measure of sustained response at the EOT Visit in the ITT and CE-EOT analysis sets, patients assessed as a nonresponder at the 48-72 Hour Visit were

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considered a clinical failure at the EOT Visit (carried forward). Patients were also programmatically defined as a clinical failure as outlined below:

Clinical Failure:

• 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 the patient meets any of the following:

◊ Receipt of any systemic concomitant antibacterial 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 dose of study drug

Patients will 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

Patients who are not defined programmatically as a clinical failure or an indeterminate will be considered a **Clinical Success**.

For the secondary endpoint of Investigator assessments at multiple time points, the following criteria were used (taken from Applicant protocol):

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Figure 5.3-1: **Criteria for Assessment of Investigator Response, Study 112 and 113**

Table 8-1. Investigator's Assessment of Clinical Response Definitions at the 48-72 Hour Visit

Term	Definition
Improving	Improvement in overall clinical status of ABSSSI compatible with continuation of study drug therapy
Stable	Signs and symptoms stable, no apparent change in overall clinical status but compatible with continuation of study drug therapy

Table 8-2. Investigator's Assessment of Clinical Response Definitions at Day 7 Visit

Term	Definition
Improving	Improvement in overall clinical status of ABSSSI compatible with continuation of study drug therapy

Table 8-3. Investigator's Assessment of Clinical Response Definitions at End of Therapy and Post-Therapy Evaluation Visits

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

Table 8-4. Investigator's Assessment of Clinical Relapse Definitions at the LFU Visit

Term	Definition
Sustained Clinical Success	No new signs or symptoms of primary ABSSSI after PTE
Clinical Failure/Relapse	New or worsened signs or symptoms of primary ABSSSI after PTE
Indeterminate	Study data are not available for the evaluation of efficacy for any reason including the following: ♦ Patient lost to follow up ♦ Extenuating circumstances that preclude the classification of a clinical success or failure/relapse ♦ Patient withdraws consent

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; PTE=post-therapy evaluation

Source: Study 112 Protocol or Amendment, pg. 75

Study 113

The 3rd amendment for this protocol was submitted in August 2011 and the first patient was enrolled under this protocol. There were six total amendments and some important changes included:

Amendment 5: allowed for pediatric enrollment down to Age 12

Amendment 6: Changed the definition of responder for the primary efficacy outcome from a definition using lesion area and febrile status to lesion area only. The definition of responder was changed from cessation in spread or reduction in lesion size (length, width, and area) with afebrile status to a ≥20% reduction in lesion area and no fever component. A modified SPA reflecting this change granted in Dec. 2012

This was a randomized, double blind, double dummy, active controlled, multicenter, NI trial that compared a 6 day regimen of daily 200 mg IV to oral tedizolid phosphate with a 10 day regimen of twice daily 600 mg IV to oral linezolid in the treatment of ABSSSI. Randomization and stratification were overall similar to study112, however, there was no stratification based on fever. Subjects were required to receive at least two IV doses (the first dose would be Infusion A and the second dose would be Infusion B) and could then switch to oral medication provided certain prespecified criteria were met (afebrile, no spread of lesion, no worsening of signs and symptoms, and improvement in at least 1 sign or symptom). The visit schedule was similar to study 112.

Study 113 was similar to study 112 in many areas; however, there were a few key differences. In study 113:

- Allowed enrollment of 12 years and up
- measurement of a lesion (including distance from incision/wound) in order to assess eligibility did not have to be based on erythema alone but could be based on edema, erythema or induration.
- Cellulitis/erysipelas subjects had to have 2 rather than 1 local sign of infection

Also, as noted earlier, the primary endpoint in this trial differed from that of Study TR701-112. The primary outcome measure is described below:

At 48-72 hours after the first infusion of study drug, the subject was determined to be a responder or nonresponder.

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Patients were defined as **responders** if they had:

• ≥20% reduction in area of erythema, edema, and/or induration (length x width) of the primary ABSSSI lesion, compared to baseline.

Patients were defined as **nonresponders** if they met any of the following criteria:

• There was <20% reduction in the area of the primary ABSSSI lesion from baseline
• Through 72 hours after the first infusion of study drug, receipt of any systemic concomitant antibacterial therapy that was potentially effective against the baseline pathogen, with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
• Through 72 hours after the first infusion of study drug, death (all-cause mortality) occurs

Secondary endpoints were similar to those in study 112. However, there were again slight differences in how programmatic determinations of sustained clinical responses were made between the two trials. For the endpoint of sustained clinical response at EOT, these 2 changes were made in the assessment of clinical success:

- Criterion of no purulent drainage from a wound infection or the purulent drainage is of a lesser intensity than at Screening was added
- Criterion of patient-reported presence of pain was removed

No changes were made in the Investigator assessment of clinical success or failure between the two trials.

Study Populations:

In both studies, key populations were defined. Important analysis populations included:

ITT (Intent to Treat): All randomized patients

CE-EOT (Clinically Evaluable at End-Of-Treatment): All patients in the ITT analysis set who complied with the protocol with no major violations, as defined in the SAP, and who meet the following criteria:

◊ Completed the primary outcome assessment at the 48-72 Hour Visit and sustained outcome assessment at the EOT Visit (unless defined as a nonresponder at the 48-72 Hour Visit)
◊ No concomitant systemic antibiotic therapy from the first dose of study drug through the EOT Visit that is potentially effective against the baseline pathogen except adjunctive aztreonam and/or metronidazole in patients with wound infections.

MITT (Microbiological Intent-to-Treat): All ITT analysis set patients who have a baseline gram-positive bacterial pathogen known to cause ABSSSI. This includes bacterial pathogens known to cause ABSSSI identified in an appropriate specimen from the primary skin lesion or blood.

For the purposes of this review, most focus is placed on the ITT population, primarily because it is less subject to the effect of unmeasured subgroup biases post randomization. The CE-EOT population is less scrutinized given the above issues and the fact that in both studies it was somewhat loosely defined (many subjects with major protocol violations had violations that would not have necessarily affected efficacy assessments).

6 Review of Efficacy

Efficacy Summary

This summary discussion of efficacy will focus on evaluations/comparisons of the two Phase 3 trials individually rather than as a pooled analysis. There are multiple reasons for this, including the different formulations of tedizolid phosphate used in each study, differences in where the studies were conducted, slight differences in inclusion/exclusion criteria, as well as the moderate differences in primary and secondary endpoints between the studies.

Overall, tedizolid phosphate appears to be noninferior to linezolid for the treatment of ABSSSI. The basis for this arises from the fact that in both studies, tedizolid phosphate met the prespecified noninferiority margin for the primary endpoint. Though success rates appeared to be somewhat lower in Study 112, it was not to such a degree as to be of concern. Moreover, it appeared that most subjects experienced fairly large reductions in lesion size by 48-72 hrs. as opposed to just barely meeting the study 113 success criterion of ≤ 20% reduction in lesion size.

Tedizolid phosphate appeared to have sustained success overall as evidenced by the high rates of success at the EOT time point (programmatic determination of clinical response) as well as the fact that relatively few subjects designated as success/responder at the 48-72 hr. time point went on to become failures at the EOT time point. This appeared to be further strengthened by the high rates of clinical success at the PTE visit as assessed by the investigator.

There is concern that tedizolid phosphate may perform more poorly (either relative to linezolid or relative to the tedizolid phosphate population as a whole) in more vulnerable populations (such as the elderly, subjects with very large lesions, obese subjects, diabetics, particular minority groups), especially given its shortened dosing duration relative to linezolid. Indeed, poor performance of the tedizolid phosphate arm was noted in some of these subgroups at more than one time point. However, most of these findings could not be replicated from study to study or from earlier to later time points, and the subgroups themselves were generally small, thus limiting interpretation. Also, when looking at within tedizolid phosphate arm comparisons, it might be expected that some subgroups may do worse than for the overall

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population (cellulitis for example); such comparisons are even more difficult to interpret if there was similarly poor performance in the same subgroup in the comparator arm.

It should be noted that understanding response by clinical syndrome (major abscess, wound, cellulitis/erysipelas) was somewhat unclear given the difficulties in understanding how such classifications were made at baseline. However, given the inclusion/exclusion criteria, this concern should not spill over into the assessment of the adequacy of the study drug in ABSSSI as a whole. Also, it is reassuring to see that there are not marked discrepancies in response on the primary endpoint based on receipt of an I&D.

Though tedizolid phosphate appeared to have comparable activity to linezolid versus both MRSA and MSSA, its activity against other pathogens is difficult to assess given their relatively small study representation. In particular, it would be difficult to include pathogens such as *Staphylococcus haemolyticus* and *Staphylococcus lugdunensis* in labeling as an "indicated" pathogen given their very small sample size in the study. There also were fairly small sample sizes to evaluate *Enterococcus faecalis* and *Streptococcus agalactiae*, but per internal discussions appeared to have more supportive microbiological information warranting their inclusion in labeling.

Despite the moderately sized ITT population in both studies, there were some demographic peculiarities that may make the study findings somewhat less generalizable to the U.S. patient population at large. In particular, relatively few diabetic patients were enrolled while relatively many subjects with intravenous drug use were enrolled. Importantly, given the somewhat unique characteristic of tedizolid phosphate's pharmacodynamic reliance on neutrophil activity, only a few subjects with low neutrophil counts were enrolled into the study; thus, its efficacy in neutropenic subjects is unknown. Similar to the real world, however, many subjects received incision and drainage, and efficacy did not appear to change drastically relative to the receipt/nonreceipt of I&D. Importantly, concomitant antimicrobial use appeared to be low.

(b) (4)

Taken as a whole, the findings suggest general effectiveness of tedizolid phosphate in ABSSSI. The table below tries to compare the primary and secondary endpoint results of the two studies in a standardized fashion (sensitivity analyses are presented for Study 112 in order to facilitate comparison with Study 113).

Table 6 -1: **Comparison of Major Primary and Secondary Endpoint Results, ITT, Studies 112 and 113**

	Study 112[3]	Study 113[4]
Early Response 48-72 hr. visit[1]		
Tedizolid Phosphate	78.0%	85.2%
Linezolid	76.1%	82.6%
Difference	1.9%	2.6%
95% CI	(-4.5%; 8.3%)	(-3.0; 8.2%)
Programmatic Determination of Clinical Response at EOT[2]		
Tedizolid Phosphate	80.7%	87.0%
Linezolid	80.9%	88.0%
Investigator Assessment at PTE		
Tedizolid Phosphate	85.5%	88.0%
Linezolid	86.0%	87.7%

1- For both studies, the analysis for the 113 primary endpoint has been used here- ≤20% reduction in lesion size from baseline and no fever component

2- In study 112, the sensitivity analysis is used in which failures are not carried forward; note that even with this adjustment, the criteria are not exactly the same between the two studies.

3- ITT Population: tedizolid phosphate- 332 subjects, linezolid- 335 subjects

4- ITT population: tedizolid phosphate – 332 subjects; linezolid -334 subjects

6.1 Indication

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

6.1.1 Methods

Please refer to the discussion of trial design in section 5.3.

6.1.2 Demographics

Study 112

No notable imbalance was noted between the two arms in terms of gender, race, or age. Almost two thirds of each arm was male and most subjects were white. The mean age in both arms was 43-44 years old. The proportion of subjects ≥ 65 years old was 8.7% in the tedizolid phosphate arm and 7.8% in the linezolid arm. The proportion of subjects ≥ 75 years old was 3.0% in the tedizolid phosphate arm and 2.4% in the linezolid arm. The mean BMI in both arms was essentially equivalent as were the highest values in each arm (tedizolid mean 27.9 kg/m^2 and highest value 39.97 kg/m$^{2;}$ linezolid mean 28.0 kg/m^2 and highest value 39.99 kg/m^2). Generally, a third of subjects in both arms had a BMI ≥ 30 kg/m^2.

Over 80% of subjects in both arms were White; African Americans represented roughly 11% of the study population in both arms. Over 30% of subjects were Hispanic or Latino.

The majority of subjects were located in North America. In the tedizolid phosphate arm, 9 (2.7%) of tedizolid phosphate subjects were from Latin America, 53 (16%) were from Europe, and 270 (81.3 %) were from North America In the linezolid arm, 12 (3.6%) of subjects were from Latin America, 55 (16.4%) were from Europe, and 268 (80%) were from North America.

There was little difference between the two arms in important background medical history including HIV and previous ABSSSI. Interestingly, only a small proportion subjects were noted to have diabetes mellitus at baseline (7.8% of subjects in both arms). Moreover, over a third of subjects (35.2% of tedizolid phosphate subjects and 39.4% of linezolid subjects) had a history of current or recent IV drug use. Roughly 12% of subjects in both arms had a history of hepatitis C. There was a slightly increased proportion of individuals in the tedizolid phosphate arm with “poor living conditions” in their medical history and slightly more patients in the linezolid arm with a “history of current or recent IV drug use.” However, there were no real differences noted between arms in the reported medical and surgical history-associated body systems not directly relevant to the ABSSSI under study. Almost 20% of subjects in both arms reported fever in the 24 hours prior to screening.

Unsurprisingly, given the scheme for stratification at randomization, there was no difference between arms in infection type (cellulitis/erysipelas, major cutaneous abscess, and wound infection). Approximately 40% of subjects in both arms had a baseline infection classification of cellulitis/erysipelas and 30% of subjects had major cutaneous abscess or wound infection. It is likely that several misclassifications occurred, as noted by the Applicant as well as from this review. For example, a subject with an “ingrown toenail” was characterized as having a post-traumatic wound. Moreover, of the 135 tedizolid phosphate subjects classified as having cellulitis/erysipelas, 28 subjects (21%) had a procedure code of bedside or operative I&D (these could have occurred just prior to screening, at screening or post Day 1 study infusion), raising the concern that some of these cellulitis cases may have actually been abscesses. Also, in earlier protocol amendments, a hierarchical system of classification was laid out for infections that might have been classified into multiple infection types. Thus, it’s likely that misclassfications did occur though it’s unclear to what degree.

There were some slight imbalances in the location of primary infections. For example, 6.3% of tedizolid phosphate and 2.4% of linezolid subjects had abdominal infections, while 23.2% of tedizolid phosphate subjects and 27.5% of linezolid subjects had infections on the

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arm. The most common site of infection was the leg, with 40% of infections occurring on the leg in both treatment groups.

The median lesion surface area was essentially equivalent between both arms (tedizolid phosphate 188cm^2 vs. linezolid 190 cm^2). Cellulitis/erysipelas lesions were generally larger than lesions of the other two infection types. Interestingly, cellulitis/erysipelas lesions in North America were considerably smaller in general than those in Latin America and Europe; the significance and etiology of this is unclear. During this review, it was noted that though digital photographs were provided with case report forms to the Agency, it was difficult at times to corroborate recorded lesion measurements with photographic evidence. Thus, lesion measurement errors are possible (see further discussion in the efficacy section).
Subjects' prespecified local and regional signs and symptoms were recorded at baseline and these were evenly distributed between both arms. The vast majority of subjects had baseline moderate to severe erythema, swelling, warmth, and tenderness on palpation and this was evenly distributed between the two arms. Similarly, greater than 85% of subjects reported pain and were noted to have induration at baseline. Over half of the subjects had seropurulent and purulent drainage. Around 40% of subjects in both arms had leukocytosis or leukopenia at baseline.

The following table summarizes the demographic variables.

Table 6.1.2- 1: **Demographic Highlights, ITT, Study 112**

Demographic Variable	Tedizolid Phosphate N= 332	Linezolid N=335
Sex		
Female	128 (38.6%)	137 (40.9%)
Male	204 (61.4%)	198 (59.1%)
Age		
Mean (years)	43.6	43.1
≥ 65 years old	29 (8.7%)	26 (7.8%)
≥ 75 years old	10 (3.0%)	8 (2.4%)
Race		
White	280 (84.3%)	275 (82.0%)
African American	39 (11.7%)	38 (11.3%)
Ethnicity		
Hispanic or Latino	115 (34.6%)	108 (32.2%)
BMI		
Mean	27.9 kg/m^2	28.0 kg/m^2
≥ 30 kg/m^2	99 (29.8%)	114 (34%)
Site Location		
North America	270 (81.3%)	268 (80%)
Europe	53 (16%)	55 (16.4%)
Latin America	9 (2.7%)	12 (3.6%)

Medical History		
Diabetes Mellitus	26 (7.8%)	26 (7.8%)
Previous ABSSSI	75 (22.6%)	81 (24.2%)
Current or Recent IV drug use	117 (35.2%)	132 (39.4%)
Lesion Classification		
Cellulitis/Erysipelas	135 (40.7%)	139 (41.5%)
Major Abscess	100 (30.1%)	98 (29.3%)
Wound	97 (29.2%)	98 (29.3%)
Location of Primary Infection		
Leg	132 (39.8%)	137 (40.9%)
Arm	77 (23.2%)	92 (27.5%)
Buttock	36 (10.8%)	33 (9.9%)
Abdomen	21 (6.3%)	8 (2.4%)
Surface Area		
Median Overall	188cm^2	190 cm^2
Median Cellulitis	232 cm^2	238 cm^2
Median Abscess	168 cm^2	172 cm^2
Median Wound	162 cm^2	168 cm^2
Signs and Symptoms		
Moderate/Severe Erythema	311 (93.7%)	313 (93.4%)
Moderate/Severe Warmth	309 (93.1%)	312 (93.1%)
Moderate/Severe Swelling	280 (84.3%)	289 (86.3%)
Moderate/Severe Tenderness on Palpation	306 (92.2%)	313 (93.4%)
WBC ≥10,000 cells/mm3 or <4000 cells/mm3	140 (42.2%)	133 (39.7%)
Baseline ANC ≤ 1500 mm^3	1	3
Febrile at Baseline	56 (16.9%)	63 (18.8%)

In the MITT population, the majority of isolates were *Staph. aureus* and were evenly distributed between both arms and between MRSA and MSSA. Many fewer isolates were noted for other gram positive species, including species for which the Applicant is seeking an indication (i.e. *Staph haemolyticus* and *Staph. lugdunensis).* In fact, other than *Staph. aureus* and the *Strep. anginosus-milleri* group, no other bacterial species comprised more than 5% of the MITT population. Linezolid MICs for *Staph. aureus* were all in the susceptible range (≤ 4 ug/ml) and evenly distributed between both arms. Please note the following table highlighting the number of subjects with isolates for the Applicant's proposed indicated pathogens.

Table 6.1.2-2: Number of Subjects With Proposed Indicated Pathogens, MITT, Study 112

Pathogen	Tedizolid Phosphate N=209 n (%)	Linezolid N=209 n (%)
Staphylococcus aureus	171 (81.8%)	175 (83.7%)
MRSA	88 (42.1%)	90 (43.1%)
MSSA	83 (39.7%)	87 (41.6%)
Streptococcus anginosus-milleri group	15 (7.2%)	15 (7.2%)
Streptococcus agalactiae	9 (4.3%)	5 (2.4%)
Streptococcus pyogenes	8 (3.8%)	4 (1.9%)
Enterococcus faecalis	5 (2.4%)	0 (0%)
Staphylococcus haemolyticus	4 (1.9%)	3 (1.4%)
Staphylococcus lugdunensis	3 (1.4%)	2 (1%)

n= subjects;

Few subjects in both arms used antibacterial drugs in the 30 day period prior to start of study drug (tedizolid phosphate 3.6% vs. linezolid 4.5%). Concomitant systemic antibacterial usage through EOT in the ITT population occurred in 23 subjects (6.9%) in the tedizolid phosphate arm and 15 subjects (4.4%) in the linezolid arm. For antiseptics and disinfectants (such as povidone-iodine), usage through EOT occurred in 39 (11.7%) subjects in the tedizolid phosphate arm and 30 (9%) such subjects in the linezolid arm.

Usage of NSAIDs, oral steroids, and furosemide through EOT was fairly modest. Through the 48-72 hr. visit, 16 (4.8%) subjects in the tedizolid phosphate arm and 18 (5.4%) subjects in the linezolid arm used NSAIDs (as coded by the Applicant though this admittedly does not capture all usage). Through the EOT visit, NSAID usage occurred in 21 tedizolid phosphate subjects (6.3%) and 24 (7.2%) linezolid subjects. Only 2 (0.6%) subjects (both in the tedizolid phosphate arm) were noted to take oral steroids through the EOT visit. Only 4 (1.2%) subjects (all in the linezolid arm) used furosemide through EOT.

There was high usage of concomitant meds through the 48-72 hour visit that could have had an effect on fever assessment. Antipyretic use (as coded by the Applicant) occurred in 116 (34.9%) of tedizolid phosphate subjects and 111 (33.1%) linezolid (33.1%) subjects through the 48-72 hr. visit. Similar usage occurred through EOT.

Of considerable importance, 152 (45.7%) tedizolid phosphate and 160 (47.8%) linezolid subjects had “bedside incision and drainage” or “operative incision and drainage” occurring just prior to, on the day of, or post Day 1 of study drug infusion. The majority occurred on Day 1 and were considered to be standard-of-care; in the tedizolid phosphate arm only 20% of I&D’s occurred after day 1. It should be noted that incision and drainage (I&D) not planned before randomization and performed later than Day 1 were discouraged for wounds and abscesses. Similarly, for cellulitis/erysipelas, such procedures performed after the 48-72 hour visit were

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discouraged. As noted earlier, I&Ds performed on primary lesions at later time points were used in the assessment of clinical success or failure for sustained clinical response at EOT. Please note the following table.

Table 6.1.2-3: Selected Concomitant Medications and Procedures, ITT, Study 112

	Tedizolid Phosphate N=332	Linezolid N=335
Antibacterial usage in prior 30 days	12 (3.6%)	15 (4.5%)
Concomitant systemic antibacterial usage through EOT	23 (6.9%)	15 (4.4%)
Incision and drainage	152 (45.7%)	160 (47.8%)

"Incision and Drainage" means bedside incision and drainage" or "operative incision and drainage" occurring just prior to, on the day of, or post Day 1 of study drug infusion

Study 113

In this study, there was no difference between the two arms in terms of gender, age or race. Roughly two thirds of subjects in both arms were male and roughly 85% of subjects were white. The mean age in both groups was 45.6 years. There was a slightly increased proportion of subjects in the tedizolid phosphate arm who were ≥ 65 years old (tedizolid phosphate 13% vs. linezolid 10%). The mean BMI was similar in both arms (28.6 kg/m2 in the tedizolid phosphate arm and 28.7 kg/m2 in the linezolid arm). Roughly a third of subjects in both arms had a BMI categorized as at least obese.

Over 80% of subjects in both arms were White; African Americans represented roughly 11% of the study population in both arms. Around 20% of subjects were Hispanic or Latino.

Almost half of the subjects were from North America with the bulk of the rest of the subjects coming from Europe. In the tedizolid phosphate arm, 47% of subjects came from North America, 34% from Europe, 14% from South Africa, 4% from Argentina, and 1% from Australia/New Zealand. In the linezolid arm 47% of subjects came from North America, 33% from Europe, 14% from South Africa, 4% from Argentina, and 2% from Australia/New Zealand.

Similar to Study TR701-112, relatively few subjects had coexisting diabetes mellitus (10% of tedizolid phosphate subjects and 12% of linezolid subjects). Twenty percent of tedizolid phosphate subjects and 22% of linezolid subjects had a current or recent history of IV drug use (7.8% of tedizolid phosphate and 10.2% of linezolid subjects had a diagnosis of hepatitis C). Twenty-one percent of tedizolid phosphate subjects and 19% of linezolid subjects had a history of a previous ABSSSI. In general there were no real differences noted between arms in the reported medical and surgical history-associated body systems not directly relevant to the ABSSSI under study. However, more subjects in the linezolid arm had a medical condition

categorized under the body system "hepatobiliary" (82 subjects in linezolid arm and 56 in tedizolid arm). It should also be noted that subjects with ANC < 1000 cells/mm^3 were explicitly excluded.

There was no difference between arms in the proportion of subjects with cellulitis/erysipelas, major cutaneous abscess, and wound infection; half the subjects in both arms had cellulitis/erysipelas. Twenty percent of subjects had major cutaneous abscess and approximately 30% had wound infections. As discussed for Study TR701-112, there was some difficulty in assessing how and why individual subject infections were classified the way they were. For example, although 29% of subjects had wound infections, 45% of subjects reported "recent trauma that resulted in primary infection."

A slightly increased number of individuals in the tedizolid phosphate arm had an infection localized to the hand (tedizolid phosphate 9.3% vs. linezolid 6.0%); however similar to study 112, the most frequent anatomic location of the lesion was the leg (37% of tedizolid phosphate subjects and 39% of linezolid subjects).

The median lesion surface area of the primary lesion was similar between both arms (tedizolid phosphate 231cm^2 vs. linezolid 239 cm^2). Cellulitis/erysipelas lesions were generally larger than lesions of the other two infection types. There was a slightly increased proportion of individuals in the linezolid arm with moderate to severe erythema at baseline (tedizolid phosphate 91% vs. linezolid 95%). Slightly more subjects in the tedizolid phosphate arm had moderate to severe warmth (tedizolid phosphate 94% vs. linezolid 90%). No differences were noted in swelling, tenderness to palpation, pain (patient reported), fluctuance, induration, seropurulent/purulent drainage, lymphadenopathy, and fever at baseline. 103 (31%) of tedizolid and 97 (29%) of linezolid subjects had fever at baseline (T≥ 38.0 °C). More individuals in the tedizolid phosphate arm had leukocytosis/leukopenia at baseline (tedizolid phosphate 53% vs. linezolid 45%).

Table 6.1.2-4: Demographic Highlights, ITT, Study 113

Demographic Variable	**Tedizolid Phosphate N= 332**	**Linezolid N=334**
Sex		
Female	107 (32.2%)	120 (35.9%)
Male	225 (67.8%)	214 (64.1%)
Age		
Mean (years)	45.6	45.6
≥ 65 years old	43 (13.0%)	33 (9.9%)
≥ 75 years old	14 (4.2%)	17 (5.1%)
Race		
White	285 (85.8%)	282 (84.4%)
African American	38 (11.4%)	37 (11.1%)
Ethnicity		
Hispanic or Latino	67 (20.2%)	63 (18.9%)

BMI		
Mean	28.6 kg/m^2	28.7 kg/m^2
≥ 30 kg/m^2	101 (30.4%)	118 (35.3%)
Site Location		
North America	156 (47.0%)	158 (47.3%)
Europe	112 (33.7%)	111 (33.2%)
South Africa	48 (14.5%)	46 (13.8%)
Argentina	13 (3.9%)	13 (3.9%)
Australia/New Zealand	3 (0.9%)	6 (1.8%)
Medical History		
Diabetes Mellitus	32 (9.6%)	41 (12.3%)
Previous ABSSSI	71 (21.4%)	63 (18.9%)
Current or Recent IV drug use	66 (19.9%)	74 (22.2%)
Lesion Classification		
Cellulitis/Erysipelas	166 (50.0%)	168 (50.3%)
Major Abscess	68 (20.5%)	68 (20.4%)
Wound	98 (29.5%)	98 (29.3%)
Location of Primary Infection		
Leg	124 (37.3%)	131 (39.2%)
Arm	103 (31.0%)	105 (31.4%)
Hand	31 (9.3%)	20 (6.0%)
Buttock	22 (6.6%)	28 (8.4%)
Surface Area		
Median Overall	231cm^2	239 cm^2
Median Cellulitis	301 cm^2	314 cm^2
Median Abscess	155 cm^2	179 cm^2
Median Wound	265 cm^2	219 cm^2
Signs and Symptoms		
Moderate/Severe Erythema	302 (91.0%)	317 (94.9%)
Moderate/Severe Warmth	311 (93.7%)	302 (90.4%)
Moderate/Severe Swelling	290 (87.3%)	298 (89.2%)
Moderate/Severe Tenderness on Palpation	309 (93.1%)	310 (92.8%)
WBC ≥10,000 cells/mm3 or <4000 cells/mm3	176 (53.0%)	151 (45.2%)
Baseline ANC ≤ 1500 mm^3	4 (all responders)	3 (all responders)
Febrile at Baseline	103 (31.0%)	97 (29.0%)

In the MITT population, the vast majority of subjects had *Staph. aureus* isolates (80.2 % in the tedizolid phosphate arm and 82.7% in the linezolid arm), while a much smaller proportion of subjects had *Strep. pyogenes* and *Strep. anginosus-milleri* isolates. The proportion of subjects in each arm that had either MRSA or MSSA isolates was similar. Notably, the tedizolid phosphate arm had a higher proportion of subjects with *S. pyogenes* isolates (tedizolid phosphate 13% vs. linezolid 8%).

Table 6.1.2-5: Number of Subjects With Proposed Indicated Pathogens, MITT, Study 113

Pathogen	Tedizolid Phosphate N=197	Linezolid N=202
Staphylococcus aureus	158 (80.2%)	167 (82.7%)
MRSA	53 (26.9%)	56 (27.7%)
MSSA	105 (53.3%)	111 (55.0%)
Streptococcus anginosus-milleri group	15 (7.6%)	12 (5.9%)
Staphylococcus haemolyticus	1 (0.5%)	5 (2,5%)
Staphylococcus lugdunensis	1 (0.5%)	5 (2.5%)
Streptococcus pyogenes	25 (12.7%)	16 (7.9%)
Streptococcus agalactiae	0 (0%)	5 (2.5%)
Enterococcus faecalis	5 (2.5%)	4 (2.0%)

There was no difference in the proportion of subjects in each arm who used antibacterial drugs in the 30 day period prior to first dose of study drug (roughly 4% in both arms). In the ITT population, 24 (7%) of tedizolid phosphate subjects and 17 (5%) of linezolid subjects used concomitant systemic and topical antibacterial drugs through the 72 hour visit. The primary reason was adjunctive therapy for a Gram negative infection. Through the EOT visit, 35 (11%) tedizolid phosphate subjects and 28 (8%) linezolid subjects used such medications. Twenty-nine (9%) tedizolid phosphate and 25 (9%) linezolid subjects used concomitant antiseptics and disinfectants through EOT.

Usage of NSAIDs, oral steroids, and furosemide through EOT was fairly modest. Through the 48-72 hr. visit, 10 (3.0%) subjects in the tedizolid phosphate arm and 21 (6.3%) subjects in the linezolid arm used NSAIDs. Through the EOT visit, NSAID usage occurred in 18 tedizolid phosphate subjects (5.4%) and 22 (6.6%) linezolid subjects. Only 2 (0.6%) subjects (both in the tedizolid phosphate arm) were noted to take oral steroids through the EOT visit. Through EOT, 11 (3.3%) tedizolid phosphate and 13 (3.9%) linezolid subjects used furosemide.

Similar to Study 112, a large proportion of subjects in both arms had incision and drainage procedures. Fifty-five percent of subjects in both arms had “bedside incision and drainage” or “operative incision and drainage” occurring just prior to, on the day of, or post Day 1 of study drug infusion; the majority occurred on Day 1 and were considered to be standard-of-care. Incision and drainage not planned before randomization and performed later than Day 1

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was discouraged for wound and abscess lesions. Similarly, for cellulitis/erysipelas lesions, such procedures performed after the 48-72 hour visit were discouraged.

Table 6.1.2-6: Selected Concomitant Medications and Procedures, ITT, Study 113

	Tedizolid Phosphate N=332	Linezolid N=334
Antibacterial usage in prior 30 days	14 (4.2%)	15 (3.6%)
Concomitant systemic antibacterial usage through EOT	35 (10.5%)	28 (8.4%)
Incision and drainage	182 (54.8%)	183 (54.8%)

Both studies were similar in many demographic attributes. Study 112 had a different regional makeup (primarily North America) and had higher numbers of subjects with current or recent IV drug use. Study 113 appeared to have more cellulitis cases and the lesions, particularly for cellulitis and wound lesions, seemed to be larger than in Study 112; the anatomical distribution of lesions also differed somewhat between the two studies. Study 113 appeared to have less MRSA cases and more *Strep. pyogenes* cases comparatively than Study 112. In Study 113, concomitant usage of systemic antibacterials through EOT, incision and drainage, and use of steroids, NSAIDs, and diuretics (using crude search metrics) was slightly higher than in Study 112. In both studies, classification of a subject to an infection type may have been erroneous. As has been discussed in this section, within each study, both arms appeared to be fairly well matched

6.1.3 Subject Disposition

Study 112

Table 6.1.3 -1 Study 112; Analysis Populations

Study Population	Tedizolid Phosphate	Linezolid
ITT	332	335
CE-EOT	273	286
MITT	209	209

Three hundred thirty-two subjects were randomized (ITT) to tedizolid phosphate and 335 subjects were randomized to linezolid. Only one subject (in the tedizolid arm) was randomized but did not receive study drug. Similar to TR701-113, 91.6% of subjects in the tedizolid phosphate arm and 88.7% of linezolid subjects completed study drug treatment. 9.9% of

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tedizolid phosphate subjects and 8.4% of linezolid subjects discontinued from the study, the primary reason being patient loss to follow up. 6.6% of tedizolid phosphate subjects and 6.3% of linezolid subjects were lost to follow up.

In the ITT population, 27.7% of tedizolid subjects and 26.9% of linezolid subjects had major protocol violations, though this was vaguely defined as deviations that could have affected the safety and efficacy analysis; see the discussion below for study 113. Overall, 77.1% of tedizolid phosphate subjects and 72.5% of linezolid subjects had a protocol violation. 6.3% of tedizolid and 5.7% of linezolid subjects were randomized to the wrong infection type; this was likely not fully captured (note discussion of this in demographics).
4.8% of tedizolid phosphate and 3.3% of linezolid subjects did not have temperature measurements taken at a particular time, 3.0% of tedizolid phosphate and 1.8% of linezolid subjects did not have lesion measurements taken at a particular time, and 3.3% of tedizolid phosphate and 1.2% of linezolid subjects did not have their pain scale assessed at a particular time. These violations are relatively infrequent and equally distributed. For the 48-72 hour visit, 3.9% of tedizolid phosphate and 3.6% of linezolid subjects did not have their visit done during the prespecified window. For the EOT and PTE visits, the numbers were 4.5% and 3.6% for tedizolid phosphate and 2.4% and 3.0% for linezolid, respectively. Again, these violations are relatively infrequent, and similarly distributed between arms. Also, some of these violations (missing lesion and temperature measurements at 48-72 hours or measurements taken outside the 48-72 hour window) were counted as failures on the primary outcome. 31.9% of tedizolid phosphate and 26.6% of linezolid subjects had "at least 1 dose not taken 12 +/- 3 hours apart. Importantly, 8.4% of tedizolid phosphate and 6.9% of linezolid subjects had use of a prohibited medication or treatment.

In 112, very few individuals randomized (only 13 such subjects; 7 in the tedizolid phosphate arm and 6 in the linezolid arm) were found not to meet IC/EC. Most of these violations were safety related or related to recent topical antibiotic usage and it's doubtful such violations would have a significant effect on efficacy results.

Compliance in the study was high. Compliance was defined as the number of active doses actually received divided by the number of active doses expected (× 100) from the first to last dose date. Using this definition, the mean compliance for the ITT population was 99.1% in the tedizolid phosphate arm and 97.6% in the linezolid arm. For the CE-EOT population, mean compliance was 99.6% and 98.4%, respectively.

Study 113

The various study population sizes are noted in the following table. These populations were defined earlier.

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Table 6.1.3- 2 Study 113; Analysis Populations

Study Population	Tedizolid Phosphate	Linezolid
ITT	332	334
CE-EOT	304	299
MITT	197	202

At least 98% of randomized subjects (ITT population) received study drug. 92.5% of subjects in the tedizolid phosphate arm and 91% in the linezolid arm completed study drug treatment; study completion rates were 94.3% in the tedizolid phosphate arm and 91.6% in the linezolid arm. Conversely, 5.7% of subjects in the tedizolid phosphate arm and 8.4% of subjects in the linezolid arm discontinued from the study, primarily due to “patient loss to follow up. 3.3% of subjects in the tedizolid phosphate arm and 4.2% of subjects in the linezolid arm discontinued from the study due to a loss from follow-up.

A considerable number of subjects had major protocol violations in the ITT population of both arms - 31.9% of subjects in the tedizolid phosphate arm and 35.3% of subjects in the linezolid arm. However, major protocol violations were very generally defined as violations that affected the assessment of safety and efficacy in the study. Upon review, violations such as missed study visit or visits occurring out of window, missed study procedures (such as symptom assessment, labs, vital signs, lesion measurements), use of concomitant medications potentially affecting safety or efficacy, not meeting inclusion or exclusion criteria, and randomization to the wrong infection strata appeared to be the type of violations categorized as “major.” 6.9% of subjects in the tedizolid phosphate arm and 6% of subjects in the linezolid arm were not randomized to the right infection strata (this is the official assessment though as noted earlier, more such errors/confusion in randomization are likely).

Overall, 82.8% of tedizolid phosphate subjects and 82.6% of linezolid subjects in the ITT population had a protocol violation. For the purposes of efficacy outcomes, violations such as missing “signs and symptoms of infection – tedizolid phosphate 0.6% vs. linezolid 2.1%,” “lesion measurements- tedizolid phosphate 2.7% vs. linezolid 3.3%,” “pain scale-tedizolid phosphate 8.7% vs. linezolid 7.2%,” and “specimens for culture- both arms 6.3%” are important violations but appear to be infrequent and evenly distributed between both arms. For the primary outcome visit at 48-72 hours, 3.0% of tedizolid phosphate and 3.3% of linezolid subjects had their visits outside the window. For the EOT and PTE visits, the numbers were 3.6% and 3.3% for tedizolid phosphate and 3.3% and 4.2% for linezolid, respectively. Again, these numbers are infrequent and fairly evenly distributed between both arms. 28.9% of tedizolid phosphate and 26.0% of linezolid subjects had “dose 3 to 20 at least 1 dose not taken 12 +/- 3 hours apart.” Importantly, 8.4% of tedizolid and 10.2% of linezolid subjects had use of a prohibited medication or treatment.

In study 113, 25 subjects (10 subjects in the tedizolid phosphate arm and 15 in the linezolid arm) were randomized despite not meeting IC/EC. Though some of these errors could have affected efficacy outcomes (inclusion of individuals with smaller lesions, etc.), other

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violations were more related to safety violations and not likely to affect efficacy outcomes. Overall, the number of such individuals was low and represented <5% of the ITT population.

Compliance was defined as the number of active doses actually received divided by the number of active doses expected (×100). Mean treatment compliance was 100.0% in the tedizolid phosphate group and 96.4% in the linezolid group in the ITT population. It should be noted that 3 subjects in the tedizolid phosphate arm and 1 subject in the linezolid arm had more than the expected doses and thus had compliance > 100%. In the CE-EOT population, mean compliance was 100.4% and 99.2% respectively.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints agreed upon in the SPAs and used in both studies have several important considerations. First, lesions may be improperly measured leading to such issues as smaller lesions being included in the studies, improperly assessing reduction in lesion sizes, etc. Indeed, it should be noted that this reviewer found it difficult at times to corroborate lesion measurements with the digital photographs of lesions submitted for subjects. For example, in some cases, the photographs could not easily be interpreted while in other cases photographs did not appear to show as much improvement as was expected based on measurements alone. However, it is hoped that such errors in this blinded trial would be limited in scope and equally distributed between the two arms. Moreover, difficulties in measurement that hinder assessment at early time points, may not affect clinical assessment at later time points when a lesion should have more clearly improved or not responded to therapy. The efficacy reviews attempted to address some of these issues by looking at the response in different lesion sizes and also by looking at the degree of reduction in lesion size at the 48-72 hr. visit. Also, in the case of Study 112, there was concern that the fever component of the endpoint might be confounded by concomitant use of antipyretics. However, the role of fever in these infections is unclear and in such cases it is likely acceptable to rely on the measurement component of the primary endpoint alone. Indeed, in Study 113, fever was removed as a component of the primary endpoint. Lastly, one may not have full faith in the ability of early lesion measurements to predict treatment success and failure. As such, the primary endpoint results were compared and corroborated with clinical response assessments at later time points.

Study 112

As noted earlier, the primary outcome measure was early clinical response at the 48-72 hour visit. Assessments were determined based on data recorded on the e-Case Report Forms (eCRF); investigator's assessment was not a component of the primary outcome measure.
At the 48-72 hour visit, the patient was determined programmatically as a responder or a nonresponder to therapy. Patients were defined as **responders** if the following criteria were met:

• *The patient has cessation of spread of the primary ABSSSI lesion, compared to baseline*

• The temperature measurement (assessed by the investigator) is ≤ 37.6°C (oral) and the next measurement (investigator or patient assessed taken within 24 hours of the 48-72 hour visit) is also ≤ 37.6°C (oral)

*Patients were defined as **nonresponders** if any of the following criteria were met:*
• Spread of the primary ABSSSI lesion, compared to baseline
• Receipt of any systemic concomitant antibacterial therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
• Death (all-cause mortality)

*• Either the temperature measurement at the 48-72 hour visit (assessed by the investigator) **OR** the next measurement (investigator or patient assessed taken within 24 hours of the 48-72 Hour Visit) is > 37.6°C (oral).*

Based on this definition, tedizolid phosphate had a responder rate of 264 out of 332 subjects (79.5%) and linezolid had a responder rate of 266 out of 335 subjects (79.4%). The point estimate for the difference in response between the two arms was 0.1% with a 95% confidence interval of (-6.1, 6.2%). This result met the prespecified criteria of noninferiority (lower limit of 95% CI greater than -10%). Please note the Applicant table below.

Table 6.1.4-1 Primary Efficacy Analysis: Early Clinical Response at the 48-72 Hour Visit, ITT, Study 112

Response	Tedizolid Phosphate (N=332) n (%)	Linezolid (N=335) n (%)	Difference (%)	95% CI for Difference	p-value (Superiority)
Responder	264 (79.5)	266 (79.4)	0.1	(-6.1, 6.2)	0.9801
Nonresponder or indeterminate	68 (20.5)	69 (20.6)			
Nonresponder	27 (8.1)	35 (10.4)			
Indeterminate	41 (12.3)	34 (10.1)			

Abbreviations: CI=confidence interval; FA=free acid; ITT=intent-to-treat; N=number of patients in the analysis set; n=number of patients in the specific category. Notes: Percentages are calculated as 100 × (n/N). Difference (%)=responder rate for the TR-701 FA 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. p-value for superiority from a Mantel-Haenszel test adjusting for the presence or absence of fever at baseline
Source: Study 112 Study Report Body, pg. 293

The primary reasons subjects did not qualify as a responder were because of missing lesion or temperature assessments. Roughly 5% of subjects in both arms were not classified as responders because of the spread of the primary lesion. Please note the Applicant table below.

Table 6.1.4-2 Reasons for Early Clinical Nonresponse or Indeterminate Response at the 48-72 Hour Visit, ITT, Study 112

Reasons for Nonresponse or Indeterminate Response	**TR-701 FA (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; n=number of patients in the specific category; N=number of patients in the analysis set.
Notes: 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.
Source: Study 112 Study Report Body, pg. 293

Using the primary endpoint prespecified in Study 113 (≥20% reduction in primary lesion size at the 48-72 hr. visit; no fever component), the results were similar to the original primary endpoint. This is important given the high concomitant usage of antipyretics in both arms that could potentially confound response rates in the original analysis. Unsurprisingly, given the loss of the fever component, nonresponders make up a larger proportion of failures (as opposed to indeterminates) as compared to the primary analysis.

Table 6.1.4-3 Clinical Response at 48-72 Hrs., Using ≥ 20% Lesion Reduction Endpoint and No Fever Component, ITT, Study 112

Response	Tedizolid Phosphate N=332	Linezolid N=335	Difference (95% CI)
Responder	259 (78.0%)	255 (76.1%)	1.9% (-4.5%, 8.3%)
Nonresponder or Indeterminate	73 (22%)	80 (23.9%)	
Nonresponder	50 (15.1%)	56 (16.7%)	
Indeterminate	23 (6.9%)	24 (7.2%)	

As noted earlier in Section 3.2, the Applicant noted cGCP violations at 3 sites, involving a total of 18 subjects. If these subjects are removed, the primary analysis is virtually unchanged (see table below; taken from Dr. Gamalo's statistical review). Because of this, and also because OSI has yet to inspect these sites (and my own review was not definitive in establishing that the violations that took place would have affected efficacy), the analyses hereafter use the original ITT population. For study 112, analyses primarily focused on the ITT population minus the 18 subjects; please refer to Dr. Gamalo's review.

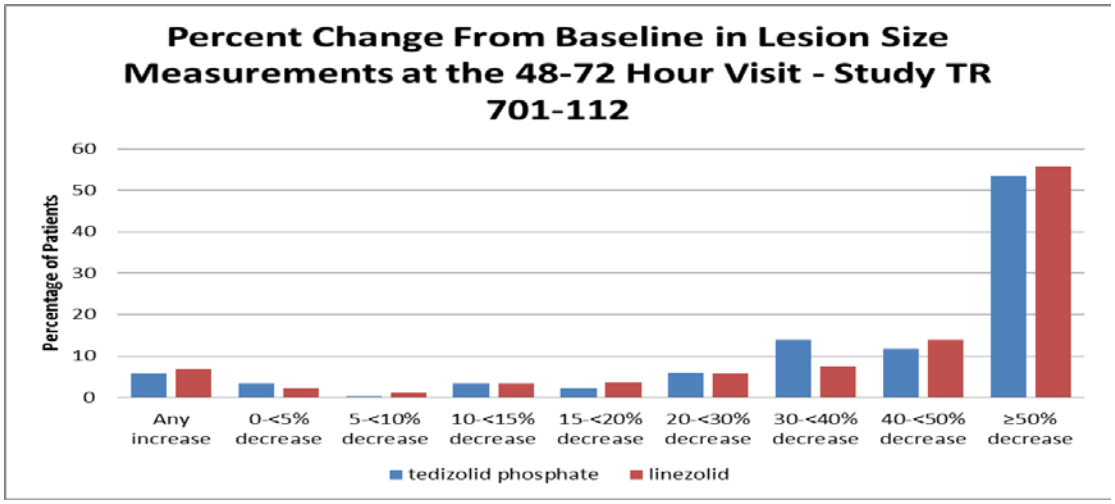
Table 6.1.4-4: ECE (Cessation and Afebrile) at 48-72 hours in Study TR 701-112 - ITT/ITT* populations

Response	ITT Tedizolid phosphate N = 332	Linezolid N = 335	ITT* Tedizolid phosphate N = 323	Linezolid N = 326
Responder	264 (79.5)	266 (79.4)	256 (79.3)	258 (79.1)
Difference (CI)	0.1 (-6.1, 6.2)[1]		0.2 (-6.2, 6.3)[1]	
Nonresponder or indeterminate	68 (20.5)	69 (20.6)	67 (20.7)	68 (20.9)
Nonresponder	27 (8.1)	35 (10.4)	27 (8.1)	35 (10.4)
Indeterminate	41 (12.3)	34 (10.1)	40 (12.4)	33 (10.1)

[1] 95% CI for the treatment difference in the primary endpoint and analysis, adjusted for fever at baseline using the method of Miettinen and Nurminen
*Represents ITT population with 18 subjects removed from analysis due to GCP violations.

*Source: Statistical Review, Pg.31*Importantly, most subjects in the tedizolid phosphate arm appeared to have a significantly greater reduction in the primary lesion than just 20%, thus hopefully limiting some the consequences of small lesion measurement errors. Please note Dr. Gamalo's figure below.

Figure 6.1.4-1: Percent Change from Baseline in Lesion Size Measurement at the 48-72 Hour Visit -Study TR 701-112



Source: Statistical Review, pg. 52

Several subgroups were evaluated in order to assess whether response rates (using the prespecified primary endpoint for Study 112) differed from the primary analysis as well as among the various subgroups themselves.

There were few subjects ≥ 65 years of age, however most of them were responders (24 [82.8%] of 29 tedizolid phosphate subjects and 24 [92.3%] of 26 such linezolid subjects). Though the response rate in both arms was higher than for the overall population, linezolid appeared to have a better response rate.

There were no gender disparities in response between treatment arms; within the tedizolid arm the responses of males and females was similar as well. Responses were also similar to the overall population. 161 of 204 (79%) males were responders in the tedizolid phosphate arm, and 158 of 198 (80%) males were responders in the linezolid arm. For females, 103 of 128 (80%) females were responders in the tedizolid phosphate arm, and 108 of 137 (79%) females in the linezolid arm were responders.

In terms of race or ethnicity, African Americans in the tedizolid phosphate arm appeared to respond more poorly. 27 (69.2%) of 39 tedizolid phosphate African American subjects were responders and 31 (81.6%) of 38 linezolid subjects were responders.

By region, tedizolid phosphate subjects in Europe responded at a rate of 45 (84.9%) of 53 subjects as compared to 41 (74.5%) of 55 such subjects in the linezolid arm. In North America, 213 (78.9%) of 270 subjects in the tedizolid phosphate arm were responders while for linezolid 216 (80.6%) of 268 subjects responded. Response rates were lower in Latin America (particularly in the tedizolid phosphate arm) but the sample size was too small to make any clear conclusions.

For subjects without fever at baseline, 221/276 (80.1%) of tedizolid phosphate subjects responded while 220 of 272 (80.9%) of linezolid subjects responded. For subjects with fever at baseline, 43 of 56 (76.8%) tedizolid phosphate subjects responded while 46 of 63 (73%) linezolid subjects responded.

For subjects classified as having cellulitis, both arms responded at a lower rate than that of the overall population though tedizolid phosphate subjects did slightly better than linezolid subjects. Subjects with wounds in both arms appeared to do better than the overall population. Subjects with abscesses appeared to do similar to (tedizolid phosphate arm) or slightly better (linezolid arm) than the overall population. Cellulitis subjects had a 74.8% (101 of 135) response rate in the tedizolid phosphate arm and a 71.9% (100 of 139) response rate for the linezolid arm. For abscess, response was 80% in the tedizolid phosphate arm (100 subjects) and 85.7% (84 of 98 subjects) in the linezolid arm. For wounds, the response rate was 85.6% (83 of 97) in the tedizolid phosphate arm and 83.7% (82 of 98) in the linezolid arm. As discussed earlier, classification of subjects into infection types was subject to error.

For tedizolid phosphate subjects with diabetes mellitus, 21 of 26 subjects were responders, 3 were nonresponders and 2 were indeterminate. For linezolid, 24 of 26 such

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subjects were responders, 1 was a nonresponder, and 1 was indeterminate. Though the response rate is considerably lower in the tedizolid phosphate arm compared to the linezolid arm, given the small sample size, it is unclear what conclusions can be drawn from this subgroup.

For obese individuals (BMI of 30 or greater), there were 99 such subjects in the tedizolid arm of which 77 (78%) were responders, 10 nonresponders, and 12 indeterminates. In the linezolid arm, there were 114 such subjects of which 94 (82%) were responders, 10 nonresponders, and 10 indeterminate. Though tedizolid phosphate subjects appear to do slightly poorer relative to linezolid subjects, the difference is less striking when evaluating subjects ≥ 35 kg/m^2 (see table below).

To the extent that lesions may be overestimated in size, it's useful to look at lesions with a baseline area slightly greater than 75cm^2 in order to exclude subjects with smaller lesions that were measured inappropriately and allowed into the trial. For lesions ≥130 cm^2 , the tedizolid phosphate arm performed comparably to the overall population though slightly poorer than the linezolid arm. Similar findings were noted for lesions ≥ 500cm^2. However, it should be noted that the linezolid subjects appeared to have more failures categorized as nonresponders rather than indeterminates relative to the tedizolid phosphate arm. For lesions greater than or equal to 1000cm^2, 13 of 14 such linezolid subjects responded, while for tedizolid phosphate, 15 of 21 such subjects responded.

Table 6.1.4-5: Subgroup Analysis of Primary Endpoint, ITT, Study 112

	Tedizolid Phosphate N=332			Totals	**Linezolid N=335**			Totals
	R	N	I		R	N	I	
Overall Response	264 (79.5%)	27 (8.1%)	41 (12.3%)	332	266 (79.4%)	35 (10.4%)	34 (10.1%)	335
Sex								
Male	161 (78.9%)	17 (8.3%)	26 (12.7%)	204	158 (79.8%)	23 (11.6%)	17 (8.6%)	198
Female	103 (80.5%)	10 (7.8%)	15 (11.7%)	128	108 (78.8%)	12 (8.8%)	17 (12.4%)	137
Age								
≥65 years old	24 (82.8%)	4 (13.8%)	1 (3.4%)	29	24 (92.3%)	1 (3.8%)	1 (3.8%)	26
Race								
White	229 (81.7%)	24 (8.6%)	27 (9.6%)	280	217 (78.9%)	28 (10.2%)	30 (10.9%)	275
African American	27 (69.2%)	2 (5.1%)	10 (25.6%)	39	31 (81.6%)	4 (10.5%)	3 (7.9%)	38
Ethnicity								

Hispanic or Latino	99 (86.1%)	7 (6.1%)	9 (7.8%)	115	92 (85.2%)	9 (8.3%)	7 (6.5%)	108
Medical History								
Diabetes Mellitus	21 (80.7%)	3 (11.5%)	2 (7.7%)	26	24 (92.3%)	1 (3.8%)	1 (3.8%)	26
IV drug use	95 (81.2%)	3 (2.6%)	19 (16.2%)	117	111 (84.1%)	4 (3.0%)	17 (12.9%)	132
BMI								
≥ 30 kg/m^2	77 (77.8%)	10 (10.1%)	12 (12.1%)	99	94 (82.4%)	10 (8.8%)	10 (8.8%)	114
≥ 35 kg/m^2	35 (81.4%)	5 (11.6%)	3 (7.0%)	43	33 (82.5%)	3 (7.5%)	4 (10.0%)	40
Lesion Size								
≥ 130 cm^2	191 (77.3%)	22 (8.9%)	34 (13.8%)	247	193 (78.8%)	28 (11.4%)	24 (9.8%)	245
≥ 500 cm^2	38 (77.6%)	6 (12.2%)	5 (10.2%)	49	35 (81.4%)	7 (16.3%)	1 (2.3%)	43
≥ 1000 cm^2	15 (71.4%)	3 (14.3%)	3 (14.3%)	21	13 (92.9%)	1 (7.1%)	0	14
Region								
North America	213 (78.9%)	20 (7.4%)	37 (13.7%)	270	216 (80.6%)	22 (8.2%)	30 (11.2%)	268
Europe	45 (84.9%)	6 (11.3%)	2 (3.8%)	53	41 (74.5%)	11 (20.0%)	3 (5.5%)	55
Latin America	6 (66.7%)	1 (11.1%)	2 (22.2%)	9	9 (75.0%)	2 (16.7%)	1 (8.3%)	12
Infection Type								
Cellulitis/Erysipelas	101 (74.5%)	24 (17.8%)	10 (7.4%)	135	100 (71.9%)	28 (20.1%)	11 (7.9%)	139
Abscess	80 (80.0%)	2 (2.0%)	18 (18.0%)	100	84 (85.7%)	1 (1.0%)	13 (13.3%)	98
Wound	83 (85.6%)	1 (1.0%)	13 (13.4%)	97	82 (83.7%)	6 (6.1%)	10 (10.2%)	98
Bacteremia	4 (100%)	0	0	4	2 (50%)	2 (50%)	0	4

R= Responder, N= Nonresponder, I= Indeterminate; percentages are percentages of row totals

As noted earlier, there were high levels of incision and drainages done in the study (though some may not have been performed on the primary lesion). However, response rates in the tedizolid phosphate arm did not change dramatically as a function of I&D status. Please note the following table from Dr. Gamalo's review.

Reference ID: 3521547

Table 6.1.4-6: Primary Endpoint as a Function of I&D Status, Study 112 and Study 113, ITT[2]

	Study 112		Study 113	
	Tedizolid Phosphate N=323	Linezolid N=326	Tedizolid Phosphate N=332	Linezolid N=334
I&D[1] performed prior to Study Day 1 through the 48-72 Hour Visit, N1	148	153	175	177
Responder, n (n/N1%)	118 (79.7)	125 (81.7)	157 (89.7)	151 (85.3)
No I&D[1] performed prior to Study Day 1 through the 48-72 Hour Visit, N1	175	173	157	157
Responder, n (n/N1%)	138 (78.9)	133 (76.7)	126 (80.3)	125 (79.6)

[1]Bedside and operative incision and drainage
[2] The statistical reviewer chose to not include 18 subjects from 3 sites with GCP violations in Study 112 analyses
Source: Statistical Review, pg. 36

Overall, the tedizolid phosphate arm was not inferior to the linezolid arm whether using the prespecified study 112 primary endpoint or using the prespecified study 113 endpoint. Importantly lesion reduction appeared to occur at a greater degree than just 20% in most subjects. Subgroup analyses were difficult to interpret given the differing and small size of many groups. Relative to linezolid, tedizolid phosphate appeared to do worse in the elderly, African Americans, diabetics, subjects in Latin American sites, abscesses, and subjects with lesion size ≥ 1000 cm^2 (using a threshold of a 5% difference in successful response between arms to make comparisons). Within the tedizolid phosphate arm, African Americans, subjects with lesion size ≥ 1000 cm^2, subjects in Latin American sites, and subjects with cellulitis did worse relative to the overall population (using a threshold of a 3% difference between the overall tedizolid phosphate population and the subgroup plus a success rate < 75% in the subgroup). Whether such disparities represent a true phenomenon (ie—perhaps 6 day dosing was not long enough for such subjects in the tedizolid phosphate arm) or not is difficult to ascertain given the small sample sizes for these subgroups.

Reference ID: 3521547

Study 113

For this trial, the primary endpoint was programmatically recorded from the e- CRF for the ITT population at the 48-72 hr. visit. In contrast to study 112, responder/nonresponder status was based on lesion measurements alone. Specifically responder and nonresponder were programmatically defined as:

Responder:

At the 48-72 Hour Visit, ≥20% reduction in area of erythema, edema, and/or induration (length × width) of the primary ABSSSI lesion compared with baseline

Nonresponder:
- At the 48-72 Hour Visit, <20% reduction in the area of the primary ABSSSI lesion compared with baseline
- Through 72 hours after the first infusion of study drug, 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
- Through 72 hours after the first infusion of study drug, death (all-cause mortality)

Tedizolid phosphate was noninferior to linezolid on the primary endpoint. 85.2% of tedizolid phosphate and 82.6% of linezolid subjects were designated as responders at the 48-72 hour visit. The point estimate of the difference in response between the two arms was 2.6% (95% CI; -3.0, 8.2%), and noninferiority was met because the lower margin of the 95% confidence interval was greater than -10%. Failures were categorized as nonresponders or indeterminate with the majority being nonresponders. Please note the Applicant table below.

Reference ID: 3521547

Table 6.1.4-7 Primary Efficacy Analysis: Early Clinical Response at the 48-72 Hour Visit (ITT Analysis Set)

Response	TR-701 FA (N=332) n (%)	Linezolid (N=334) n (%)	Difference (%)	95% CI for Difference	p-value (Superiority)
Responder	283 (85.2)	276 (82.6)	2.6	(-3.0, 8.2)	0.3989
Nonresponder or indeterminate	49 (14.8)	58 (17.4)			
Nonresponder	44 (13.3)	44 (13.2)			
Indeterminate	5 (1.5)	14 (4.2)			

Source: Post-text Table 14.2.1
Abbreviations: CI=confidence interval; FA=free acid; ITT=intent-to-treat; N=number of patients in the analysis set; n=number of patients in the specific category
Notes: Percentages are calculated as 100 × (n/N). Difference (%)=responder rate for the TR-701 FA treatment group minus linezolid treatment group. 95% CI is unadjusted and calculated using the method of Miettinen and Nurminen. p-value for superiority from a Fisher's exact test.

Source: Study 113 Study Report Body; pg. 112

The majority of subjects who failed in both arms did so because there was a < 20% reduction in the size of the primary lesion. Please note the following Applicant table.

Table 6.1.4-8 Reasons for Early Clinical Nonresponse or Indeterminate Response at the 48-72 Hour Visit (ITT Analysis Set)

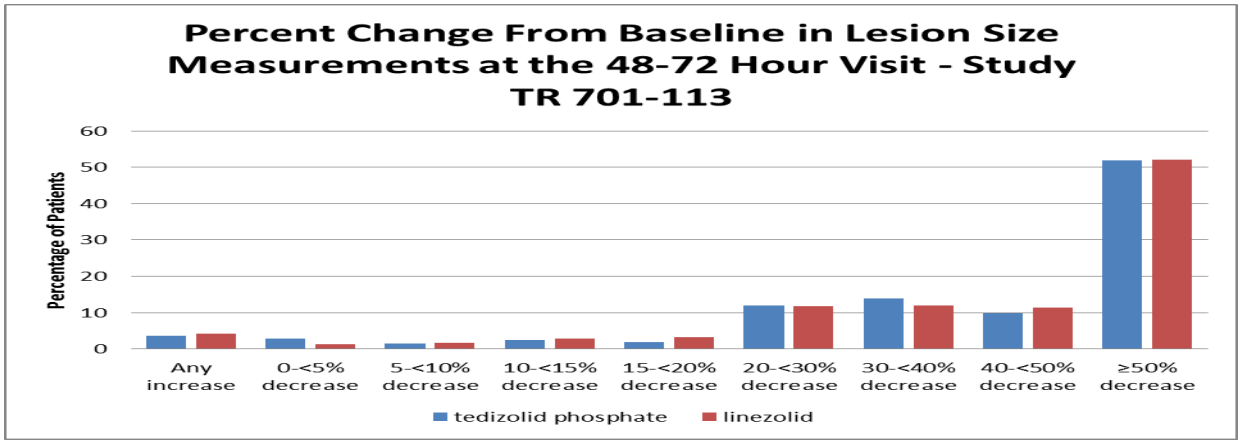
Reasons for Nonresponse or Indeterminate Response	TR-701 FA (N=332) n (%)	Linezolid (N=334) n (%)
Number of nonresponder or indeterminates	49 (14.8)	58 (17.4)
<20% reduction in primary ABSSSI lesion area	40 (12.0)	41 (12.3)
Missing lesion measurement data	5 (1.5)	14 (4.2)
Systemic concomitant antibiotics potentially effective against baseline pathogen	7 (2.1)	6 (1.8)

Source: Post-text Table 14.2.3
Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; FA=free acid; ITT=intent-to-treat; n=number of patients in the specific category; N=number of patients in the analysis set
Notes: A patient may have more than one reason for nonresponse. Strata are as randomized.

Source: Study 113 Study Report Body, pg. 112

As in Study 112, the vast majority of subjects had a significantly greater decrease than 20% at the 48-72 hr. visit. Please note the following figure from Dr. Gamalo's review.

Figure 6.1.4-2 Percent Change from Baseline in Lesion Size Measurement at the 48-72 Hour Visit -Study TR 701-113



Source: Statistical review, Pg. 52

Several subgroups were evaluated in order to assess whether response rates differed from the primary analysis as well as among the various subgroups themselves.
In both arms, males appeared to perform slightly better than females. In the tedizolid phosphate arm, there were 225 males of which 196 (87%) were responders, while the linezolid arm had 214 males of which 181 (85%) were responders. However, in the tedizolid phosphate arm, there were 107 females of which 87 (81%) responded, while in the linezolid arm, there were 120 females, of which 95 responded (79%).

There were similar rates of response in both arms for subjects ≥ 65 years of age. In the tedizolid phosphate arm, 35 (81%) of 43 such subjects were responders, while in the linezolid arm 27 (81%) of 33 such subjects were responders. Compared to the overall population, both arms performed slightly worse in the population (though more so in the tedizolid phosphate arm).

African American subjects performed worse in the linezolid arm. In these subjects, the response rate was 86.8% in tedizolid phosphate arm and 67.6% in the linezolid arm. In Hispanics, the tedizolid phosphate arm performed slightly worse than the overall population (80.6% vs. 85.2%, respectively).

Subjects from Europe in both arms had an improved response relative to the overall population; South African subjects taking tedizolid phosphate did much better (81.3% response) than their linezolid counterparts (67.4% response).

For subjects with fever at baseline, 96 (93.2%) of 103 tedizolid phosphate and 89 (91.8%) of 97 linezolid subjects responded. For subjects without fever at baseline, 187 (81.7%) of 229 tedizolid phosphate subjects and 187 (78.9%) of 237 linezolid subjects responded

Subjects with DM appeared to respond better in the linezolid arm. In the tedizolid phosphate arm, 25 (78%) of 32 such subjects were responders, while in the linezolid arm, 34 (83%) of 41 such subjects were responders.

Tedizolid phosphate performed slightly worse in subjects with BMI ≥ 30 kg/m^2 compared to the overall population. In this arm, there were 101 such subjects, of which 80 (79%) were responders. The difference between the two arms in such subjects was minimal. However, tedizolid phosphate performed much more poorly compared to the overall population and compared to linezolid in subjects with baseline BMI ≥ 35 kg/m^2 and ≥ 40 kg/m^2. In subjects with BMI ≥ 40 kg/m^2, the response rate was 59.3% in the tedizolid phosphate arm and 80.8% in such linezolid subjects.

Tedizolid phosphate performed slightly worse in cellulitis subjects and slightly better in wound subjects relative to the overall population. Linezolid subjects with abscess seemed to perform better than their wound and cellulitis counterparts and better than the overall population. Wound subjects in the tedizolid phosphate arm performed better than their similar linezolid counterparts.

For the reasons already outlined, clinical response in lesions of different sizes was analyzed. For lesions greater than or equal to 130 cm^2, response in both arms was similar to the overall population. For lesions 500 cm^2 and greater, response in the tedizolid phosphate arm was similar to the overall population; in the linezolid arm, it was slightly improved relative to the overall population. For lesions greater than or equal to 1000 cm^2, both arms performed worse compared to the overall population but the tedizolid phosphate arm (27 such subjects; 21 (77.8%) responders) performed better than the linezolid arm (21 such linezolid subjects;14 (66.7%) responders).

Whether subjects took only IV medication or had an IV to oral switch, the response was similar to the overall population.

Table: 6.1.4-9 Subgroup Analysis of Primary Endpoint, ITT, Study 113

	Tedizolid Phosphate N=332			Total	Linezolid N=334			Total
	R	N	I		R	N	I	
Overall Response	283 (85.2%)	44 (13.2%)	5 (1.5%)	332	276 (82.6%)	44 (13.2%)	14 (4.2%)	334
Sex								
Male	196 (87.1%)	27 (12%)	2 (1%)	225	181 (84.6%)	25 (11.7%)	8 (3.7%)	214
Female	87 (81.3%)	17 (15.9%)	3 (2.8%)	107	95 (79.2%)	19 (15.8%)	6 (5%)	120
Age								
≥65 years old	35 (81.4%)	7 (16.3%)	1 (2.3%)	43	27 (81.8%)	6 (18.2%)	0	33
Race								
White	243 (85.3%)	38 (13.3%)	4 (1.4%)	285	239 (84.8%)	35 (12.4%)	8 (2.8%)	282
African	33	5	0	38	25	7	5	37

American	(86.8%)	(13.2%)			(67.6%)	(18.9%)	(13.5 %)	
Ethnicity								
Hispanic or Latino	54 (80.6%)	12 (17.9%)	1 (1.6%)	67	52 (82.5%)	7 (11.1%)	4 (6.3%)	63
Medical History								
Diabetes Mellitus	25 (78.1%)	6 (18.8%)	1 (3.1%)	32	34 (82.9%)	6 (14.6%)	1 (2.4%)	41
IV drug use	54 (81.8%)	8 (12.1%)	4 (6.0%)	66	60 (81.1%)	8 (10.8%)	6 (8.1%)	74
BMI								
≥ 30 kg/m^2	80 (79.2%)	20 (19.8%)	1 (1%)	101	96 (81.4%)	17 (14.4%)	5 (4.2%)	118
≥35 kg/m^2	37 (71.1%)	14 (26.9%)	1 (1.9%)	52	38 (82.6%)	7 (15.2%)	1 (2.2%)	46
≥40 kg/m^2	16 (59.3%)	11 (40.7%)	0	27	21 (80.8%)	4 (15.4%)	1 (3.8%)	26
Lesion Size								
≥ 130 cm^2	202 (85.2%)	31 (13%)	4 (1.7%)	237	209 (81.3%)	36 (14%)	12 (4.7%)	257
≥ 500 cm^2	61 (85.9%)	10 (14.1%)	0	71	69 (86.3%)	10 (12.5%)	1 (1.3%)	80
≥ 1000 cm^2	21 (77.8%)	6 (22.2%)	0	27	14 (66.7%)	7 (33.3%)	0	21
Route								
Only IV Therapy	54 (84.4%)	8 (12.5%)	2 (3.1%)	64	48 (82.8%)	8 (13.8%)	2 (3.4%)	58
Region								
North America	128 (82%)	23 (14.7%)	5 (3.2%)	156	131 (82.9%)	16 (10.1%)	11 (7.0%)	158
Europe	104 (92.9%)	8 (7.1%)	0	112	99 (89.1%)	11 (9.9%)	1 (1%)	111
South Africa	39 (81.3%)	9 (18.8%)	0	48	31 (67.4%)	13 (28.3%)	2 (4.3%)	46
Latin America	11 (84.6%)	2 (15.4%)	0	13	12 (92.3%)	1 (7.7%)	0	13
Infection Type								
Cellulitis/Erysipelas	134 (80.7%)	30 (18.1%)	2 (1.2%)	166	135 (80.3%)	29 (17.3%)	4 (2.4%)	168
Abscess	59 (86.8%)	7 (10.3%)	2 (2.9%)	68	61 (89.7%)	3 (4.4%)	4 (5.9%)	68
Wound	90	7	1	98	80	12	6	98

	(91.8%)	(7.1%)	(1%)		(81.6%)	(12.2%)	(6.1%)	
Bacteremia	7 (100%)	0	0	7	9 (75%)	2 (16.7%)	1 (8.3%)	12

R= Responder, N= Nonresponder, I= Indeterminate
Percentages are percentages of row totals

As noted before, there were a significant number of individuals who had incision and drainage (I&D) procedures performed either just prior to or on the day of study drug infusion. The statistical reviewer evaluated subjects who did and did not have I&D procedures performed prior to Study Day 1 through the 48-72 hr. visit. Notably, subjects in both arms who had an I&D did appear to do somewhat better relative to their non I&D counterparts. Please note Table xxx shown earlier from Dr. Gamalo's review.

Overall, the tedizolid phosphate arm was not inferior to the linezolid arm using the prespecified primary endpoint. Importantly, lesion reduction appeared to occur at a greater degree than just 20% in most subjects at the 48-72 hour time point. For subjects with baseline BMI ≥ 35 kg/m^2, tedizolid phosphate appeared to perform worse than linezolid (a threshold of a 5% difference between arms was chosen to make comparisons). Within the tedizolid phosphate arm, there appeared to be more notably worse performance in diabetics, obese (by BMI) subjects, and subjects with lesions ≥ 1000 cm^2 relative to the overall tedizolid phosphate population (using a threshold of a 3% difference between the overall population and the subgroup plus a success rate < 80% in the subgroup). However, similar to Study 112, given the small sample size of these subgroups, it is difficult to know whether this response represents a true area of concern.

6.1.5 Analysis of Secondary Endpoints(s)

Study 112

A main secondary outcome measure in Study 112 was sustained response at the EOT Visit in the ITT and CE-EOT analysis sets. Patients assessed as a nonresponder at the 48-72 hour Visit were considered a clinical failure at the EOT Visit (carried forward). Patients were also programmatically defined as a **clinical failure** at EOT 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*

Reference ID: 3521547

• At any time from the first dose of study drug through the EOT Visit 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 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 dose of study drug

*Patients will 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

*Patients who are not defined programmatically as a clinical failure or an indeterminate will be considered a **clinical success**.*

Both the tedizolid phosphate and linezolid arms had similar clinical success rates at EOT, though the response was slightly better in the linezolid arm. The response rate in the tedizolid phosphate arm was 69.3% and in the linezolid arm it was 71.9%, with a treatment difference of -2.6%. No prespecified noninferiority margin was set for this endpoint. Though the sustained response is decreased in both arms in the ITT population compared to the primary endpoint, this is partly due to the fact that patients assessed as a nonresponder at the 48-72 Hour Visit were considered a clinical failure at the EOT Visit (carried forward). The tedizolid phosphate arm also performed slightly worse on this endpoint relative to linezolid compared to their respective primary endpoints. The CE-EOT had higher response rates in both arms for this endpoint compared to the ITT, which is unsurprising given the parameters by which this population is defined. Please note the following Applicant table (in the following Applicant table, the CE-EOT results incorporate the errata sent by the Applicant with the original

study report. This errata allowed for the inclusion of six more subjects in this population, the effect of which was quite minimal).

Table 6.1.5-1: Sustained Clinical Response at the EOT Visit, ITT and CE-EOT, Study 112

Outcome	Analysis Set	Response	Tedizolid Phosphate n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
Sustained Clinical Response -EOT	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)		
Sustained Clinical Response-EOT	CE-EOT, N		276	289		
		Clinical success	219 (79.3)	232 (80.3)	-1.0	(-7.9, 5.4)
		Clinical failure	57 (20.7)	57 (19.7)		

Abbreviations: CE-EOT=clinically evaluable at EOT; 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
Source: Study 112 Study Report Body, pg. 183

The following Applicant table highlights the reasons for failure on this secondary endpoint. Nonresponders carried forward and Investigator assessment of pain were the two primary reasons for failure in both arms. Any notable differences between the arms in terms of reasons for failure generally favored the tedizolid phosphate arm.

Table 6.1.5-2: Reasons for Clinical Failure at the EOT Visit (ITT Analysis Set), Study 112

Reasons for Nonresponse or Indeterminate Response	TR-701 FA (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.
Source: Study 112, Study Report Body, pg. 302

A sensitivity analysis was conducted where failures were not carried forward. In this analysis, the findings appear more consistent with the primary endpoint findings. Please note the Applicant table below.

Table 6.1.5-3 Programmatic Determination of Sustained Clinical Response at the EOT Visit (Failures Not Carried Forward), ITT and CE-EOT, Study 112

Analysis Analysis Set	Response	TR-701 FA n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
Failures at 48-72 hour visit not carried forward					
ITT, N		332	335		
	Clinical success	268 (80.7)	271 (80.9)	-0.2	(-6.2, 5.8)
	Clinical failure or indeterminate	64 (19.3)	64 (19.1)		
	Clinical failure	40 (12.0)	43 (12.8)		
	Indeterminate	24 (7.2)	21 (6.3)		
CE-EOT, N		273	286		
	Clinical success	239 (87.5)	249 (87.1)	0.4	(-5.2, 6.0)
	Clinical failure or indeterminate	34 (12.5)	37 (12.9)		
	Clinical failure	34 (12.5)	36 (12.6)		
	Indeterminate	0	1 (0.3)		

Source: Study 112 Study report Body, pg. 306

Subgroup analyses were performed on variables for which worse responses (relative to linezolid or relative to the overall tedizolid phosphate population) were noted in the primary analysis (see section 6.1.4). This analysis was done was using the dataset where failures were not carried forward in order to have a better (independent of prior response) assessment of what was happening at EOT with regard to these subgroups.

Table 6.1.5-4 Subgroup Analysis of Sustained Response at EOT, Failures Not Carried Forward, ITT, Study 112

	Tedizolid Phosphate N=332			Total	**Linezolid N=335**			Total
	Success	Failure	I		Success	Failure	I	
Overall Response	268 (80.7%)	40 (12%)	24 (7.2%)	332	271 (80.9%)	43 (12.8%)	21 (6.3%)	335
Age								
≥65 years old	21 (72.4%)	8 (27.6%)	0	29	20 (76.9%)	6 (23.1%)	0	26
Race								
African American	31 (79.5%)	4 (10.3%)	4 (10.2%)	39	31 (81.6%)	3 (7.9%)	4 (10.5%)	38
Medical History								
Diabetes Mellitus	14 (53.8%)	10 (38.5%)	2 (7.7%)	26	21 (80.8%)	5 (19.2%)	0	26
Lesion Size								
≥ 1000 cm^2	14 (66.7%)	6 (28.6%)	1 (4.8%)	21	7 (50%)	7 (50%)	0	14
Region								
Latin America	6 (66.7%)	2 (22.2%)	1 (11.1%)	9	10 (83.3%)	2 (16.7%)	0	12
Infection Type								
Cellulitis/Erysipelas	108 (80%)	20 (14.8%)	7 (5.2%)	135	106 (76.3%)	28 (20.1%)	5 (3.6%)	139
Abscess	83 (83%)	10 (10%)	7 (7%)	100	84 (85.7%)	3 (3.1%)	11 (11.2%)	98

I= Indeterminate; Percentages are percentages of row totals

The subgroups that appeared to perform poorly in the primary analysis were reanalyzed at this time point. Compared to the assessment at the primary endpoint, only diabetics and subjects at Latin American sites in the tedizolid phosphate arm continued to have a poor response relative to linezolid (using a 5% difference as a threshold). Also, in the tedizolid phosphate arm, diabetics, subjects with lesion size ≥ 1000 cm^2 subjects at Latin American sites, and subjects ≥ 65 years old performed poorly relative to the overall tedizolid phosphate population. Again it remains unclear whether these findings represent artifact given the size of these subgroups or represent potential shortcomings of the drug (ie, does the drug perform worse/require longer dosing in vulnerable subgroups?).

The Investigator Assessment of clinical success and failure at PTE and LFU is noted in the table below. The results displayed for the PTE time point is from the derived dataset in which assessments at earlier time points were taken into account in deciding the assessment at

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PTE. For example, if a subject was assessed as a failure at EOT then the investigator assessment would be carried forward in the derived PTE dataset

Table 6.1.5-5 Investigator Assessment of Clinical Response at PTE and LFU Visits, ITT, Study 112

	PTE Success	Failure	Indeterminate	**LFU** Sustained	Relapse	Indeterminate	Missing*	ITT
Linezolid	288 (86.0%)	14 (4.2%)	33 (9.9%)	283 (84.5%)	0 (0%)	1 (0.3%)	51 (15.2%)	335
Tedizolid Phosphate	284 (85.5%)	15 (4.5%)	33 (9.9%)	275 (82.8%)	3 (0.9%)	0	54 (16.3%)	332

*Missing data present in LFU analysis generally include subjects already counted as failures in prior analyses so wouldn't be considered for this assessment

At the PTE endpoint, there is some improvement in response compared to the primary endpoint and this is similar between the two arms. In the CE-PTE population, the success rate was 94.6% (264/279 subjects) in the tedizolid phosphate arm and 95.4% (267/280) in the linezolid arm. This is not surprising, given the timing of the PTE visit, when some natural resolution of disease is expected. Sustained clinical success at LFU was high and similar in both arms.

Assessment of pain was a secondary outcome. The following methods of measurement were prespecified in the protocol:

Figure 6.1.5-1: Methods of Pain Assessment, Study 112

1. *VISUAL ANALOG SCALE FOR PAIN ASSESSMENT (PATIENT USE)*

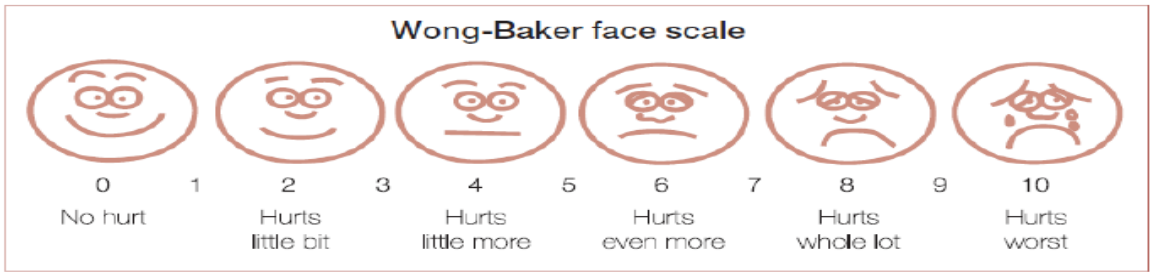
Using a 10 cm VAS (similar to that shown below), instruct the patient to indicate the point along the line that represents the pain they are feeling now. Once the patient indicates how much pain they are feeling, measure the distance (cm, mm) from no pain and enter the value on the e-CRF.

Visual analogue scale (VAS)

2. WONG-BAKER FACE SCALE FOR PAIN ASSESSMENT (PATIENT USE)

Ask the patient to rate their pain: 'How would you rate your pain at present out of 10, with 0 being no pain at all and 10 being the worst pain you could imagine?' The patient can answer verbally or by pointing to where they would rate their pain. Enter the numerical value on the e-CRF.

Faces rating scale (FRS)



Source: Study 112 Protocol or Amendment, pgs. 105-106

Per the Applicant's study report, at Day 10-13, both arms had similar reductions in pain measurements on both scales (data not shown). However, over 50 subjects in both arms did not have pain assessments at baseline. Moreover, given the uncertainty as to the interpretation of these scales as well as pain's incorporation into secondary endpoints, this will not be further discussed or assessed.

Study 113

Secondary endpoints in this study were similar to those in Study TR701-112. As noted earlier, there were slight differences in how the programmatic determination of sustained clinical response at EOT was defined in this study compared to study 112. Important changes were:

- the criterion of "no purulent drainage from a wound infection or the purulent drainage is of a lesser intensity than at Screening" was added to the definition
- the criterion involving patient-reported presence of pain was removed
- failures/nonresponders were not carried forward from the 48-72 hour visit.

Both arms had similar rates of success for the programmatic determination of clinical success at EOT in the ITT arm. The clinical success rate in the tedizolid phosphate arm was 87.0%, and it was 88.0% in the linezolid arm. The difference between the two arms was -1.0%; a noninferiority margin was not prespecified. Response rates for the ITT population were slightly improved when compared to the primary endpoint in both arms. The clinical success rates in the CE-EOT population were also high though the tedizolid phosphate arm did slightly worse than the linezolid arm. Please note the following Applicant table.

Table: 6.1.5-6 Programmatic Determination of Clinical Response at the EOT Visit (ITT and CE-EOT Analysis Sets) , Study 113

Analysis Set	Response	Tedizolid n (%)	Linezolid n (%)	Difference (%)	95% CI for Difference
ITT, N		**332**	**334**	-1.0	(-6.1, 4.1)
	Clinical success	289 (87.0)	294 (88.0)		
	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**	-4.1	(-8.8, 0.3)
	Clinical success	272 (89.5)	280 (93.6)		
	Clinical failure	32 (10.5)	19 (6.4)		

Abbreviations: CE=clinically evaluable; CI=confidence interval; EOT=end of therapy; FA=free acid; 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 TR-701 FA treatment group minus linezolid treatment group.
Source: Study 113, Study Report Body, pg. 121

Subgroup analyses for this secondary endpoint were performed for variables noted to have within arm or between arm imbalances (favoring linezolid) in the primary analysis (please see section 6.1.4).

Table 6.1.5 -7 Subgroup Analysis of Sustained Response at EOT, ITT, Study 113

	Tedizolid Phosphate N=332			Totals	**Linezolid** N=334			Totals
	R	N	I		R	N	I	
Overall Response	283 (85.2%)	44 (13.2%)	5 (1.5%	332	276 (82.6%)	44 (13.2%)	14 (4.2%)	334
Medical History								
Diabetes Mellitus	25 (78.1%)	6 (18.8%)	1 (3.1%)	32	38 (92.7%)	3 (7.3%)	0	41
BMI								
≥ 30 kg/m^2	86 (85.1%)	13 (12.9%)	2 (2.0%)	101	104 (88.1%)	9 (7.6%)	5 (4.2%)	118
≥35 kg/m^2	42 (80.8%)	8 (15.4%)	2 (3.8%)	52	40 (86.9%)	5 (10.9%)	1 (2.2%)	46
≥40 kg/m^2	22 (81.5%)	5 (18.5%)	0	27	24 (92.3%)	2 (7.7%)		26
Lesion Size								
≥ 1000 cm^2	19 (70.4%)	8 (29.6%)	0	27	15 (71.4%)	5 (23.8%)	1 (4.8%)	21

R- Responder, N – Nonresponder, I- Indeterminate; Percentages are of row totals

Using a 5% difference as a threshold, the tedizolid phosphate arm performed more poorly than linezolid in diabetics and subjects with a BMI ≥35 kg/m^2. Relative to the overall tedizolid phosphate population, the diabetic and ≥ 1000 cm^2 lesion subgroups performed more poorly. As with study 112, the small size of these subgroups (as well as the variability that may occur with multiple assessments) makes it difficult to interpret these results.

Table 6.1.5–8 Investigator Assessment of Clinical Response at the PTE and LFU Visits, ITT, Study 113

	PTE Success	Failure	Indeterminate	**LFU** Sustained success	Relapse	Indeterminate	Missing*	ITT
Linezolid	293 (87.7%)	11 (3.8%)	30 (9.0%)	289 (86.5%)	2 (0.6%)	3 (1.0%)	40 (12.0%)	334
Tedizolid Phosphate	292 (88.0%)	22 (6.6%)	18 (5.4%)	284 (85.5%)	5 (1.5%)	2 (1.0%)	41 (12.3%)	332

*Missing data present in LFU analysis generally include subjects already counted as failures in prior analyses so wouldn't be considered for this assessment

Investigator assessment of success at the PTE was relatively high and similar in both arms in both studies. In the CE-PTE population, the success rate was 92.4% (268/290) in the tedizolid phosphate arm and 96.1% (269/280 subjects) in the linezolid arm. At LFU, sustained success rates were similar in both arms in both studies, with a very slight preponderance of relapses occurring in the tedizolid phosphate arms of both studies.

For both Study 112 and 113, the success rates for the programmatic determination of clinical response at EOT (with failures not carried forward) were similar/slightly improved from that of the primary endpoint. Also, the success rate in both studies was similar in both arms. Importantly, relatively few subjects counted as successes at the early time point went on to become failures at EOT though this occurred more often in the tedizolid phosphate arm. Please note the following table from Dr. Gamalo's review.

Table 6.1.5-9: Concordance between ECE at 48-72 hours and Clinical Response at EOT – ITT/ITT* population

		STUDY TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
Early Clinical Response at 48-72 Hours	**Programmatic Determination of Sustained Clinical response at EOT**	**Tedizolid phosphate N=323**	**Linezolid N=326**	**Tedizolid phosphate N=332**	**Linezolid N=334**
		n (%)	**n (%)**	**n (%)**	**n (%)**
Responder	Clinical Success	224 (87.5)	236 (91.5)	258 (91.2)	260 (94.2)
	Clinical failure	**24 (9.4)**	**16 (6.2)**	**18 (6.4)**	**10 (3.6)**
	Indeterminate	8 (3.1)	6 (2.3)	7 (2.5)	6 (2.2)
Nonresponder	Clinical Success	20 (74.1)	16 (45.7)	30 (68.2)	32 (72.7)
	Clinical failure	7 (25.9)	17 (48.6)	14 (31.8)	12 (27.3)
	Indeterminate	0	2 (5.7)	0	0
Indeterminate	Clinical Success	18 (43.9)	13 (39.4)	1 (20.0)	2 (14.3)
	Clinical failure	6 (14.6)	7 (21.2)	1 (20.0)	2 (14.3)
	Indeterminate	16 (39.0)	13 (39.4)	3 (60.0)	10 (71.4)

*Does not include 18 subjects from 3 sites with GCP violations

Source: Statistical Review; pg. 42

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6.1.6 Other Endpoints

For study 112, the clinical response in the MITT population is displayed in the following table:

Table 6.1.6-1 Clinical Response at Multiple Time Points, MITT, Study 112

	48-72 Hr. Responder	**EOT** Success	**PTE** Success	**MITT**
Linezolid	166 (79.4%)	154 (73.7%)	181 (86.6%)	209
Tedizolid Phosphate	164 (78.5%)	149 (71.3%)	177 (84.7%)	209

-48-72 hr. column displays clinical response on primary endpoint, EOT column displays programmatically determined sustained clinical response at EOT and PTE column displays Investigator assessment of clinical response at PTE

At all three time points, using the various methods of assessment of response, the response/success rate does not differ between the two arms. However, it should be noted that while the response/success rates are similar to the ITT population for the 48-72 hr. and PTE assessments, it is decreased in both arms in the EOT assessment.

In Study 113, tedizolid phosphate appeared to have a slightly better response/success rate than linezolid at the 48-72 hr. assessment, though in general the results did not differ greatly from the ITT population at all three time points. Please note the table below.

Table 6.1.6-2 Clinical Response at Multiple Time Points, MITT, Study 113

	48-72 Hr. Responder	**EOT** Success	**PTE** Success	**MITT**
Linezolid	166 (82.2%)	181 (89.6%)	178 (88.1%)	202
Tedizolid Phosphate	174 (88.3%)	171 (86.8%)	173 (87.8%)	197

-48-72 hr. column displays clinical response on primary endpoint, EOT column displays programmatically determined sustained clinical response at EOT and PTE column displays Investigator assessment of clinical response at

The per pathogen clinical response is highlighted in the following tables taken from Dr. Gamalo's review. These tables only analyze the pathogens for which the Applicant is seeking an indication.

Table 6.1.6-3: : Per patient Clinical Response at 48-72 Hours to Common Pathogenic Organisms from Baseline Primary ABSSSI Site or Blood Culture by Genus and Species – mITT Population (ECE definitions for Study TR 701-112 and Study TR 701-113)

	Study TR 701-112 (MITT*)		**Study TR 701-113 (MITT)**	
	Tedizolid phosphate N = 203 n(%)	**Linezolid N = 206 n(%)**	**Tedizolid phosphate N = 202 n(%)**	**Linezolid N = 197 n(%)**
Gram-positive organisms (aerobes)				
Staphylococcus aureus	134/167 (80.2)	139/173 (80.3)	152/170 (89.4)	151/181 (83.4)
MRSA	68/86 (79.1)	68/87 (78.2)	54/64 (84.4)	56/69 (81.2)
MSSA	66/81 (81.5)	71/86 (82.6)	**98/106 (92.5)**	**95/112 (84.8)**
Streptococcus pyogenes	6/8 (75.0)	3/4 (75.0)	20/25 (80.0)	13/16 (81.3)
Streptococcus anginosus-milleri group	10/15 (66.7)	13/15 (86.7)	14/17 (82.4)	12/13 (92.3)
Enterococcus faecalis	3/4 (75.0)		4/5 (80.0)	2/5 (40.0)
Enterococcus faecium	0/1 (0)	0/1 (0)		
Staphylococcus haemolyticus	3/4 (75.0)	3/3 (100.0)	1/1 (100.0)	4/5 (80.0)
Staphylococcus lugdunensis	2/3 (66.7)	1/2 (50.0)	1/1 (100.0)	4/5 (80.0)
Streptococcus agalactiae	5/7 (71.4)	3/5 (60.0)		4/4 (100.0)

-MITT* population excludes subjects from 3 sites with cGCP violations
Source: Statistical review; pg. 55

At the 48-72 hr. assessment, tedizolid phosphate appeared to have similar response/success rate for MRSA as linezolid but had a better response/success rate for MSSA (in Study 113 only). Tedizolid phosphate appeared to have less success compared to linezolid for the *Streptococcus anginosus* group though the sample size was small in both arms. For all other pathogens, assessing and comparing responses is limited by the very small sample sizes.

Table 6.1.6-4: : Per patient Clinical Response at the PTE Visit to Common Pathogenic Organisms from Baseline Primary ABSSSI Site or Blood Culture by Genus and Species – mITT

	Study TR 701-112 (MITT*)		Study TR 701-113 (MITT)	
	Tedizolid phosphate N = 203 n(%)	Linezolid N = 206 n(%)	Tedizolid phosphate N = 202 n(%)	Linezolid N = 197 n(%)
Gram-positive organisms (aerobes)				
Staphylococcus aureus	145/167 (86.8)	155/173 (89.6)	154/170 (90.6)	159/181 (87.8)
MRSA	74/86 (86.0)	74/87 (85.1)	53/64 (82.8)	55/69 (79.7)
MSSA	**71/81 (87.7)**	**81/86 (94.2)**	101/106 (95.3)	104/112 (92.9)
Streptococcus pyogenes	7/8 (87.5)	4/4 (100.0)	23/25 (92.0)	15/16 (93.8)
Streptococcus anginosus-milleri group	11/15 (73.3)	12/15 (80.0)	12/17 (70.6)	12/13 (92.3)
Enterococcus faecalis	3/4 (75.0)		4/5 (80.0)	5/5 (100.0)
Enterococcus faecium	0/1 (0)	1/1 (100.0)		
Enterococcus gallinarum	0/1 (0)			
Staphylococcus haemolyticus	4/4 (100.0)	3/3 (100.0)	1/1 (100.0)	4/5 (80.0)
Staphylococcus lugdunensis	3/3 (100.0)	½ (50.0)	1/1 (100.0)	5/5 (100.0)
Streptococcus agalactiae	7/7 (100.0)	3/5 (60.0)		4/4 (100.0)

-MITT* population excludes subjects from 3 sites with cGCP violations
Source: Statistical Review; pg. 56

In contrast to the 48-72 hr. assessment, at the PTE assessment, tedizolid phosphate appeared to have similar response/success rate for MRSA as linezolid but had a worse response/success rate for MSSA (in Study 112 only). Similar success/response rates in both arms were noted for *Streptococcus pyogenes*. Tedizolid phosphate appeared to have less success compared to linezolid for the *Streptococcus anginosus* group though the sample size was small in both arms. For all other pathogens, assessing and comparing responses was limited by the very small sample sizes.

In study 112, there were 4 subjects in both arms considered to have bacteremia at baseline (blood culture positive with pathogenic organisms). In study 113, there were 7 subjects

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in the tedizolid phosphate arm and 12 in the linezolid arm considered to have bacteremia at baseline. The following table highlights the microbiologic response of all the isolates taken from these subjects. Given the small numbers, it is difficult to interpret, though tedizolid phosphate appears to perform similarly, or slightly better, than linezolid as regards *Staph. aureus* bacteremia

Table 6.1.6-5: Microbiological Response at the PTE Visit by Baseline Pathogen from Blood Culture, Study 112 and 113[1]

	Tedizolid phosphate			**Linezolid**		
	Eradication*	Persistence**	Indeterminate	Eradication	Persistence	Indeterminate
Staph. Aureus	5	1		5		4
MRSA	2			3		3
MSSA	3	1		2		1
Strep. anginosus group	1					
Strep. agalactiae	1			1		
Strep. viridans						1
Strep pyogenes	1	1				
Staph. capitis				1		
Staph. hominis	1			3		
Strep. Group C				1		
Gemella morbillorum					1	
Peptosteptococcus anaerobius					1	

[1]numbers represent number of isolates
*includes eradication and presumed eradication
** includes persistence and presumed persistence

6.1.7 Subpopulations

Most subgroup analyses have been incorporated into earlier discussions. However, during the course of the review, it was noted that there were several adverse events coded under the preferred terms abscess and cellulitis. Upon further investigation, it was noted that such adverse events could be the result of several scenarios, including occurrence of a secondary lesion in an area different from the primary lesion during the study, occurrence of a secondary lesion in an area close to the primary lesion, secondary lesions at baseline that worsened, etc. In all scenarios these secondary lesions might have needed some sort of intervention such as I&D or antimicrobial treatment. After internal discussions, it was decided that a sensitivity analysis should be conducted where all such cases in both arms were counted as a failure according to the time period when the event occurred. For example, if such an event occurred prior to the 48-72 hr. visit, the subject would be counted as a failure from the 48-

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72 hr. visit (primary analysis onward). Similarly, if such a case occurred between the 48-72 hr. visit and EOT visit, then that subject would be counted as a failure from the EOT visit onward. An information request was sent to the Applicant to conduct these analyses.

There were 67 patients (37 in study 112 and 30 in study 701-113) with an adverse event of abscess or cellulitis from first dose through the PTE Visit. There were an additional 22 patients (13 in study 112 and 9 in study 113) with an adverse event of abscess or cellulitis from the PTE to the LFU Visit. The results of the sensitivity analyses are noted below

Table: 6.1.7-1 Sensitivity Analyses: Abscess and Cellulitis Adverse Events Counted as Failures, ITT, Study 112

	Tedizolid Phosphate N=332 Responders/Success	Linezolid N=335 Responders/Success	Point estimate for difference; 95% CI	Original point estimate; 95% CI
Primary analysis; using ≥ 20% reduction criterion; no fever	256 (77.1%)	253 (75.5%)	1.6%	1.9%
Sustained response at EOT; failures not carried forward; pain component included	256 (77.1%)	266 (79.4%)	-2.3%	-0.2%;
Investigator Assessment at PTE	264 (79.5%)	279 (83.3%)	-3.8%	-0.5%;

Table 6.1.7-2 Sensitivity Analyses: Abscess and Cellulitis Adverse Events Counted as Failures, ITT, Study 113

	Tedizolid Phosphate N=332 Responders/Success	**Linezolid** N=334 Responders/Success	Point estimate for difference;	Original point estimate;
Primary analysis; using ≥ 20% reduction criterion; no fever	281 (84.6%)	272 (81.4%)	3.2%	2.6%
Sustained response at EOT;	283 (85.2%)	289 (86.5%)	-1.3%	-1.0%
Investigator Assessment at PTE	277 (83.4%)	282 (84.4%)	-1.0%	0.3%

As can be seen, though there were some slight changes in the point estimates assessing the difference in response between the two arms (particularly for the later time points in Study 112), overall the changes were relatively modest. Though there is concern that such subjects might represent a patient population for which longer tedizolid phosphate therapy is needed, it is notable that the number of people to be reclassified was fairly evenly matched between both arms in Study 113 and only slightly more prevalent in the tedizolid arm in study 112. Please note the table below.

Table 6.1.7-3 Number of Subjects with AE of Abscess or Cellulitis Reclassified as Failures, Studies 112 and 113

	48-72 Hr. visit	EOT	PTE	
Study 112				
Tedizolid	3	12	20	
Linezolid	2	5	9	
Study 113				
Tedizolid	2	6	15	
Linezolid	4	5	11	

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please refer to the Clinical Pharmacology and Clinical Safety review for further discussion of the safety of 6 day dosing of 200mg tedizolid phosphate as well as the relevance of the 200mg dose to the pharmacodynamic parameter of interest (AUC/MIC). Please also refer to Clinical Pharmacology review for discussion of the bioavailability of the oral drug relative to the IV form. Importantly, a Phase 2 study (Study TR701-104) comparing 5 to 7 day courses of 200mg, 300mg, and 400mg of tedizolid phosphate, (non-free acid form) in the treatment of complicated skin and skin structure infections was conducted in part to assess efficacy dose response. The primary variable was investigator-assessed clinical response at the TOC visit. 192 subjects were randomized and 188 received study drug. There was no difference among the three groups (in the clinical modified intent to treat population) on the primary endpoint (56/63 [88.9%], 56/63 [88.9%], and 53/62 [85.5%] clinical cure for the 300, 300, and 400 mg groups, respectively at TOC). Similar results were noted at the EOT visit. Given these findings, and the prospects for improved safety with a lower dose, the 200mg dose was pursued for further development in the Phase 3 trials. Please see the Applicant CSR for study TR701-104.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

In the Phase 2 study, Study TR701-126, 200 subjects were enrolled in an uncontrolled, open label study to evaluate the safety and efficacy of 6 days of oral daily 200mg tedizolid phosphate (free acid form) in the treatment of cellulitis/erysipelas, and major cutaneous abscess. However, this study also had several exploratory objectives, focusing on interobserver reproducibility of lesion measurements, differences in lesion measures depending on the method chosen, etc. The results of this study noted that measurements from two separate observers did not markedly differ whether using a head to toe measurement for lesion length or the longest length measurement or whether measuring the lesion using erythema alone or erythema, induration, and edema. Lesion measurements for a particular observer did differ somewhat when comparing lesion sizes at a particular visit measured using erythema alone vs. erythema, induration, and edema (regardless of the type of measurement used); however when looking at percent changes from baseline to the 48-72 hr. visit, lesion measurements using the two methods did not appear to differ markedly. Please note the Applicant tables below

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Table 6.1.10-1 Comparison of Lesion Surface Area between Observations by Measurement Type (Per-protocol Analysis Set)

	TR-701 FA N=188			
	Surface Area of Erythema/ Induration/Edema (cm^2)		Surface Area of Erythema (cm^2)	
Visit	Longest Head-to-Toe Length × Width	Longest Length × Width	Longest Head-to-Toe Length × Width	Longest Length × Width
Baseline				
Observation 1				
n	185	185	185	185
Median	182.0	185.9	168.0	166.1
Min, Max	76.5, 1748	76.5, 1748	15.75, 1748	15.75, 1748
Observation 2				
n	183	183	183	183
Median	182.0	182.0	169.0	168.0
Min, Max	60, 1748	60, 1748	15.51, 1748	15.51, 1748
ICC (95% CI)[a]	0.992 (0.989, 0.994)	0.991 (0.987, 0.993)	0.982 (0.976, 0.987)	0.982 (0.976, 0.987)
48-72 Hour Visit				
Observation 1				
n	188	188	188	188
Median	63.0	63.0	49.3	49.3
Min, Max	0, 2592	0, 2592	0, 1040	0, 1040
Observation 2				
n	188	188	188	188
Median	63.0	63.0	49.8	49.8
Min, Max	0, 2806	0, 2806	0, 1548	0, 1548
ICC (95% CI)[a]	0.989 (0.985, 0.992)	0.989 (0.986, 0.992)	0.960 (0.947, 0.970)	0.960 (0.947, 0.970)

Source: Post-text Table 14.2.5.3
Abbreviations: CI=confidence interval; ICC=intraclass correlation coefficient; Max=maximum; Min=minimum.
Notes: N=number of patients in the Per-protocol Analysis Set; n=number of patients with the specified lesion surface area at the indicated visit.
[a]ICC comparing observations 1 and 2 for the specified lesion surface area and visit.

Source: Study 126, Study Report Body; pg. 72

Table 6.1.10-2 Percent Change from Baseline in Infection Measurements at the 48-72 Hour Visit by Observation (Per-protocol Analysis Set)

	Tedizolid Phosphate (N=188) n (%)			
	Surface Area of Erythema/ Induration/Edema (cm^2)		Surface Area of Erythema (cm^2)	
	Longest Head-to-Toe Length × Width	Longest Length × Width	Longest Head-to-Toe Length × Width	Longest Length × Width
Observation 1				
N1	185	185	185	185
Any increase	14 (7.6)	15 (8.1)	13 (7.0)	14 (7.6)
0 to <5% decrease	1 (0.5)	2 (1.1)	3 (1.6)	3 (1.6)
5 to <10% decrease	5 (2.7)	4 (2.2)	2 (1.1)	3 (1.6)
10 to <15% decrease	4 (2.2)	3 (1.6)	4 (2.2)	3 (1.6)
15 to <20% decrease	2 (1.1)	3 (1.6)	0	1 (0.5)
20 to <30% decrease	9 (4.9)	10 (5.4)	8 (4.3)	6 (3.2)
30 to <40% decrease	18 (9.7)	15 (8.1)	14 (7.6)	11 (5.9)
40 to <50% decrease	18 (9.7)	16 (8.6)	16 (8.6)	18 (9.7)
≥50% decrease	114 (61.6)	117 (63.2)	125 (67.6)	126 (68.1)
Observation 2				
N1	183	183	183	183
Any increase	11 (6.0)	11 (6.0)	14 (7.7)	15 (8.2)
0 to <5% decrease	4 (2.2)	4 (2.2)	3 (1.6)	3 (1.6)
5 to <10% decrease	4 (2.2)	3 (1.6)	3 (1.6)	2 (1.1)
10 to <15% decrease	2 (1.1)	1 (0.5)	2 (1.1)	2 (1.1)
15 to <20% decrease	3 (1.6)	3 (1.6)	0	1 (0.5)
20 to <30% decrease	11 (6.0)	13 (7.1)	9 (4.9)	9 (4.9)
30 to <40% decrease	12 (6.6)	13 (7.1)	15 (8.2)	12 (6.6)
40 to <50% decrease	23 (12.6)	18 (9.8)	15 (8.2)	16 (8.7)
≥50% decrease	113 (61.7)	117 (63.9)	122 (66.7)	123 (67.2)

Notes: N=Number of patients in the Per-protocol Analysis Set.; N1=Number of patients in the Per-protocol Analysis Set with the specified lesion surface area at Baseline and the 48-72 hour visit; n=number of patients in the specific category; percentages are calculated as 100×(n/N1).

Source: Study 126, Study Report Body, pg. 62

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7 Review of Safety

Safety Summary

A review of the submitted data support the safety of tedizolid phosphate when used at a dose of 200 mg orally or intravenously once daily for 6 days to treat acute bacterial skin and skin structure infections caused by susceptible organisms in adults.

Pooled safety analyses were conducted on data from the Phase 2 and 3 trials. Data from relevant Phase 1 studies were also reviewed.

In the Phase 1 clinical studies, there were 438 subjects (437 unique subjects) enrolled, including both oral and IV administration routes. In the clinical development program, healthy volunteers or patients received TR-701 or TR-701 FA 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.

In the Phase 2 and 3 trials, there were 1050 subjects (1048 unique individuals) who received tedizolid phosphate ≥200 mg for treatment of cSSSI or ABSSSI. The majority of the patients in the Phase 2 and Phase 3 trials were white males. Limited data was available in patient subpopulations such as < 18 years old, the elderly as well as neutropenic, renally impaired and diabetic individuals.

Data from the two Phase 2 trials, TR701-104 and TR701-126, and the two Phase 3 trials, TR701-112 and TR701-113, were pooled into two groups for Phase 2 and 3 safety analyses, respectively. In the Phase 2 studies, there were 388 patients in the safety population who received ≥200 mg tedizolid phosphate as either a disodium salt capsule (Study TR701-104) or as a free acid tablet (Study TR 701-126) once daily for 5 to 7 days. In the Phase 3 trials, patients received tedizolid phosphate 200 mg (intravenous or orally) once daily for 6 days or linezolid 600 mg twice daily (intravenous or orally) for 10 days. In the Phase 3 safety population, there were 662 patients in both the tedizolid phosphate and linezolid arms.

In the Phase 2 and Phase 3 trials, the most common treatment emergent adverse events occurring at ≥2% incidence for both tedizolid phosphate and linezolid, were diarrhea, nausea, vomiting, abscess, cellulitis, dizziness and headache. In the Phase 3 trials, treatment emergent adverse events occurring at ≥2% incidence in the gastrointestinal disorders body system or organ class were numerically lower in the tedizolid phosphate arm versus the comparator (16.0% versus 23.0%, respectively). Specific treatment emergent adverse events numerically lower in the tedizolid phosphate arm versus the linezolid arm included diarrhea (3.9% versus 5.3%, respectively), nausea (8.2% versus 12.2%, respectively), and vomiting (2.9% versus 5.6%).

Based on the known safety concerns with linezolid, the Applicant's overall safety evaluation plan included studies of volunteers (subjects) and patients with cSSSI or ABSSSI to detect specific adverse events that could potentially occur with the use of tedizolid phosphate. Thus, this safety review focused on general areas such as QT prolongation, hepatotoxicity and renal toxicity, as well as linezolid (oxazolidinone drug class) specific concerns such as peripheral and ophthalmic neuropathy, myelosuppression, MAO-related drug interactions, serotonergic syndrome, lactic acidosis, hypoglycemia, and convulsions. Further details can be found in Section 7.3.5 Submission Specific Safety Concerns, Section 7.4.2 Laboratory Findings, Section 7.5.4 Drug-Disease Interactions, and Section 7.5.5 Drug-Drug interactions. Highlights of the safety review pertaining to the aforementioned issues follow.

General: At the proposed dose and duration of tedizolid phosphate (200 mg oral/intravenous once daily for 6 days), tedizolid phosphate does not appear to influence QT prolongation, hepatotoxicity, or renal toxicity. Highlights from relevant studies follow.

1. *QT prolongation:* Findings from a thorough Phase 1 QT study (TR701-115) showed that a single therapeutic or supratherapeutic dose of tedizolid phosphate did not prolong the QT interval in healthy individuals. Safety analyses of ECG results from Phase 2 and Phase 3 trials suggest that clinically relevant QTc interval prolongation is low in patients receiving tedizolid phosphate. In addition, potentially clinically significant changes in QTc were low and similar for tedizolid phosphate and the comparator.
2. *Hepatotoxicity:* A Phase 1 (TR701-124) safety and pharmacokinetic study in subjects with hepatic impairment suggested that no dosage adjustments are required. No patients met Hy's Law criteria in the tedizolid phosphate arm of the Phase 3 trials. In addition, potentially clinically significant changes in transaminases, bilirubin and alkaline phosphatase were similar and low for tedizolid phosphate and linezolid in the Phase 3 trials.
3. *Renal toxicity:* Results from a Phase1 (TR701-123) safety and pharmacokinetic study in subjects with advanced renal impairment who did and did not require dialysis suggested that no dosage adjustments are required. Furthermore, potentially clinically significant changes in blood urea nitrogen and creatinine were similarly low for tedizolid phosphate and linezolid in the Phase 3 trials.

Oxazolidinone drug class (linezolid) specific: The Applicant's nonclinical and clinical drug development program actively addressed known safety concerns with the only approved drug in the oxazilidinone class, linezolid. Review of the available clinical data suggest that tedizolid phosphate, at the proposed dose (200 mg po/IV once daily) and duration (6 days), was similar to the comparator, linezolid, with respect to potential class specific toxicities such as, peripheral and ophthalmic neuropathy, myelosuppression, lactic acidosis, convulsions and hypoglycemia. Nonclinical and Phase 1 studies suggest that the risk of MAO-related drug interactions and serotonergic syndrome may be less in

tedizolid phosphate versus linezolid in healthy adults; however further study will be required to understand these interactions better in a clinically relevant population. Patients taking concomitant medications which would increase the risk of MAO-related drug interaction and serotonergic syndrome were excluded from the Phase 2 and Phase 3 studies.

1. *Peripheral and ophthalmic neuropathy:* Peripheral and optic neuropathies have been reported in patients treated with linezolid, particularly when treatment exceeds the maximum recommended duration of 28 days. Some patients report visual blurring when treated with linezolid for less than 28 days. A 9-month placebo-controlled rat neurotoxicology study suggested no evidence of functional or histopathologic optic or peripheral neuropathic lesions. Specialized safety assessments incorporated into select studies with tedizolid phosphate suggest that treatment emergent adverse events potentially related to ophthalmic or peripheral neuropathy were similar to the comparator, linezolid. A Phase 1 (TR701-110), open-label, ophthalmology and neurology safety study of oral 200 mg TR-701 FA once daily for 10 days suggested no clinically meaningful changes occur in healthy adults during the course of treatment. Similar results were obtained in a Phase 1 (TR701-101) randomized, placebo or active controlled double blind study where subjects received TR701 capsules, qd, at 200, 300, or 400 mg doses for 21 days. It should be noted that patients were not exposed to tedizolid phosphate for longer than 28 days, the time period when peripheral and ophthalmic neuropathy tends to be reported for linezolid. Standard MedRA Queries for Peripheral Neuropathy and Optic Nerve Disorders revealed the incidence of Treatment Emergent Adverse Events to be similar and low in both the tedizolid phosphate and linezolid arms of the Phase 3 trials. Further study is required to determine if tedizolid phosphate contributes to peripheral and ophthalmic neuropathy at different treatment doses and durations.
2. *Myelosuppression:* Myelosuppression, including anemia, leukopenia, pancytopenia, and thrombocytopenia, is known to occur in patients receiving linezolid, particularly when treatment is given for longer than 2 weeks. Nonclinical studies showed that TR-701 was immunotoxic in animals at high doses. The Applicant conducted a randomized, placebo or active controlled double blind Phase 1 study (TR701-101), where subjects received TR701 capsules, once daily, at 200, 300, or 400 mg doses for 21 days. Results suggest that the risk of myelosuppression is comparable to placebo when tedizolid phosphate is dosed at 200 mg for 6 days. However, there was a decreasing trend in platelets, white blood cell counts, neutrophils and red blood cell counts at higher doses and longer durations of treatment. In addition, the Applicant collected data on hematology parameters during the drug development program including the Phase 2 and Phase 3 trials.

Potentially clinically significant changes in platelets, white blood cell counts, neutrophils, and red blood cell counts were similar for tedizolid phosphate and linezolid in the Phase 3 trials. Further study is required to determine if tedizolid phosphate contributes to myelosuppression at different treatment doses and durations.

3. *MAO-related drug interactions*: There are potential interactions with linezolid which may elevate blood pressure. Current prescribing information indicates that linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine). Nonclinical and Phase 1 studies in healthy individuals suggest that potential MAO related drug-drug interactions with tedizolid phosphate may be less than that observed with linezolid. In nonclinical studies, a tyramine challenge in rats had no significant effect on mean arterial pressure. Results from Phase 1 studies, conducted to evaluate whether TR-701 FA potentiates sensitivity to tyramine (TR701-105) and the MAO-mediated pressor response to pseudoephedrine HCl (TR701-114), suggest that there is minimal drug-drug interaction in healthy individuals. MAO-related drug interactions were not assessed in Phase 2 and Phase 3 trials due to study design and patient exclusion criteria. Further data will be required to determine possible MAO related drug interactions in a clinically relevant population. .
4. *Serotonergic syndrome:* Current prescribing information for linezolid indicates that patients taking drugs with serotonergic potential should take the drug only if no other therapies are available, and to discontinue serotonergic drugs and monitor for serotonergic syndrome. Data from a study examining serotonergic brain activity in a murine behavioral model suggest no increase in head twitch rates at TR701 exposures equivalent to 30 times the human therapeutic dose. In the Phase 2 and Phase 3 trials, patients taking concomitant serotonergic agents were excluded. In the few individuals taking concomitant $5HT_3$ antagonists in the Phase 3 trials, the incidence of treatment emergent adverse events were similar for tedizolid phosphate and linezolid, and were not characteristic of serotonin syndrome. Preliminary studies suggest that interactions with serotonergic potentiating drugs may be less than linezolid in healthy adults; however additional data is needed.
5. *Lactic acidosis:* Lactic acidosis has been reported in patients treated with linezolid. In a Phase 1 (TR701-101) randomized, placebo or active controlled double blind study where healthy subjects received TR701 capsules, qd, at 200, 300, or 400 mg doses for 21 days, plasma L-lactate

levels did not exceed the upper limit of normal. In the Phase 2 and 3 trials, lactic acid levels were not reported and no patients were identified with substantially abnormal postbaseline bicarbonate levels. There were no patients with a treatment emergent adverse event of lactic acidosis or serum bicarbonate decreased. Further study is required to determine if tedizolid phosphate contributes to lactic acidosis at different treatment doses and durations in a clinically relevant population.

6. *Convulsions:* There have been reports of convulsions in patients treated with linezolid. No patients receiving tedizolid phosphate or linezolid In the Phase 2 and Phase 3 trials had a treatment emergent adverse event of seizure or convulsion.
7. *Hypoglycemia:* Symptomatic hypoglycemia has been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid. In the Phase 2 and 3 trials, no patients were identified with a treatment emergent adverse event of hypoglycemia or blood glucose decreased in patients receiving tedizolid phosphate or linezolid.

In conclusion, based on the data submitted, tedizolid phosphate has a favorable safety profile for approval for the treatment of acute bacterial skin and skin structure infections caused by susceptible organisms in adults at a dosage of 200 mg orally or intravenously once daily for six days. The most common treatment emergent adverse events occurring at ≥2% incidence for both tedizolid phosphate and linezolid, were diarrhea, nausea, vomiting, abscess, cellulitis, dizziness and headache. In the Phase 3 trials, the incidence of diarrhea, nausea and vomiting were numerically lower in the tedizolid phosphate versus linezolid arm. Tedizolid phosphate is similar to linezolid with respect to oxazolidinone drug class (linezolid) specific safety concerns at the proposed dose and duration of tedizolid phosphate. Tedizolid phosphate will require further study if used at higher doses and longer durations. Preliminary studies suggest a dose- and time-dependent relationship of tedizolid phosphate and myelosuppression. tedizolid phosphate was not studied for longer than 28 days in humans, the time frame when peripheral and ophthalmic neuropathy is typically noted in patients treated with linezolid. Definitive conclusions regarding safety in patient subpopulations such as patients < 18 years old, the elderly as well as neutropenic, renally impaired and diabetic individuals cannot be made because of limited data available. Furthermore, additional studies are required in patients using tedizolid phosphate at different doses and durations of treatment for other indications such as osteomyelitis or septic arthritis. Given the comparable safety profile with linezolid, post-market risk evaluation and mitigation strategies are not required for tedizolid phosphate.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant completed nineteen clinical studies to evaluate tedizolid phosphate. Nonclinical and initial clinical studies were performed with a disodium salt of the prodrug (TR-701). Subsequently, a free acid form (TR-701 FA) of the prodrug was formulated for oral and intravenous (IV) administration and was used for later clinical studies, including the two Phase 3 trials. The disodium salt and free acid form of the prodrug were evaluated and shown to be bioequivalent. Tedizolid phosphate is formulated for once daily intravenous (IV) or oral administration – the oral dosage form is 91% bioavailable.

The tedizolid phosphate drug development program consisted of 15 Phase 1 studies, two Phase 2 studies (TR701-104 and TR701-126) in patients with complicated skin and skin structure infections (cSSSI) or ABSSSI (only cellulitis or abscess), and two Phase 3 studies (TR701-112 and TR701-113) in patients with ABSSSI. In addition, the Applicant completed 2 Phase 1 studies performed by their partner, Bayer. TR701-104 used the TR-701 capsule formulation in the study while TR701-126, TR701-112, and TR701-113 used the TR-701 FA tablet formulation.

There were 438 subjects who received tedizolid phosphate in a variety of Phase 1 studies (elderly subjects, healthy subjects, subjects with renal and hepatic impairment, etc.), at multiple dose levels and durations including 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

Data from the two Phase 2 trials, TR701-104 and TR701-126, and the two Phase 3 trials, TR701-112 and TR701-113, were pooled into two groups for Phase 2 and 3 analyses, respectively. As noted earlier, in the Phase 2 studies, patients received ≥200 mg tedizolid phosphate as either a disodium salt capsule (Study TR701-104) or as a free acid tablet (Study TR 701-126) once daily for 5 to 7 days. In the Phase 3 trials, patients received tedizolid phosphate 200 mg once daily for 6 days or linezolid 600 mg twice daily for 10 days.

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A tabular overview of the studies and clinical trials used to evaluate safety is provided in Table 7.1.1-1. Additional details can be found in Section 5.1 Tables of Studies/ Clinical Trials.

Table 7.1.1-1: Overview of studies and data pools used in the Safety Review.

Phase	Study ID	n		Description
		Tedizolid phosphate	Linezolid	
1	15 studies	438	-	Healthy, adolescent, elderly, renally, and hepatically impaired subjects Multiple dose levels and durations
2	TR701-104	388	-	Adults with cSSSI, 200, 300, or 400 mg oral tedizolid phosphate for 5 to 7 days
	TR701-126			Adults with major cutaneous abscess or cellulitis/erysipelas, 200 mg oral tedizolid phosphate for 6 days
3	TR701-112	662	662	Adults with ABSSSI, 200 mg oral tedizolid phosphate for 6 days or 1200 mg linezolid for 10 days
	TR701-113			Adults and adolescents with ABSSSI, IV with optional oral switch 200 mg tedizolid phosphate for 6 days or 1200 mg linezolid for 10 days

7.1.2 Categorization of Adverse Events

The applicant's categorization of adverse events was assessed by comparing the verbatim terms to the preferred terms used by investigators and subjects, focusing on the events leading to dropouts or other changes in treatment. All adverse events in the Applicant's clinical development program were recorded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 13.1.

As discussed at the Pre-NDA Meeting on 10 May 2013, there are slight differences in the preferred terms between the Phase 3 CSRs and the ISS which the Applicant lists in Table 4 of the Reviewer's Guide (1.2). These differences are minor and are unlikely to lead to a change in interpretation of the safety analyses.

The Safety Reviewer utilized the Computational Science Center JumpStart Service to augment the evaluation of the Applicant's data management and coding quality for the two

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pivotal trials (TR701-112 and TR701-113). The JumpStart team used the FDA Investigators Rapid Review System (FIRRS) to perform coding assessments by term matching algorithms and provided information on data composition, unit matching and domain consistency. For both Phase 3 pivotal trials, TR701-112 and TR701-113, all AEDECOD values matched a MedDRA Preferred Term, indicating that the data was consistently coded to a MedDRA dictionary. Hence, the Applicant's categorization of adverse events was adequate for the safety analyses.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In order to improve the precision of determining estimated adverse event incidence rates, data were pooled based on Phase of study, subject/patient population and study drug regimen. Pooling of data would provide a larger database to detect lower frequency events and permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population.

The Applicant submitted Data from 19 individual studies in Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format. CDISC SDTM domain data from the individual studies were pooled. The Applicant's ISS analysis datasets were primarily used for evaluation of safety of tedizolid phosphate.

The safety database for tedizolid phosphate consists of data from 1050 patients (1048 unique 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. The safety database includes healthy volunteers and patients who received TR-701 or TR-701 FA 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.

Data from studies of similar design were combined for the safety analyses. Therefore, data from the two Phase 2 studies, TR701-104 and TR701-126, and the two Phase 3 studies, TR701-112 and TR701-113, were pooled into two groups for Phase 2 and 3 analyses, respectively. No weighting method was used.

In the Phase 2 studies, patients with complicated skin and skin structure infection (cSSSI) or ABSSSI received ≥200 mg tedizolid phosphate once daily for an intended 5 to 7 days. In the Phase 3 studies, patients received tedizolid phosphate 200 mg once daily for an intended 6 days or linezolid 600 mg twice daily for an intended 10 days. For subjects participating in more than one study, data were treated as if they were derived from different subjects/patients in each study for the safety analyses.

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After the NDA filing letter was issued, the Applicant reported three sites with GCP violations for study TR701-112 (sites 120, 121, and 122). There were 18 patients total from these sites. While the Applicant submitted a revised Clinical Study Report excluding patients from these study sites, the Safety Reviewer has included data from these 18 patients in the safety analyses. All 18 patients received study drug (tedizolid phosphate, *n*=9; linezolid *n*=9) and data from these patients would augment data for the safety analyses.

Table 7.1.1-1 in Section 7.1.1 Studies/Clinical Trials Used to Evaluate Safety provides an overview of studies and data pools used in the Safety Review.

7.2 Adequacy of Safety Assessments

The Applicant has adequately studied drug exposure and safety as part of the drug development program. The Applicant reported safety variables and evaluations such as adverse events, clinical laboratory assessments, vital signs, electrocardiograms, and physical examinations, including extensive neurological examinations (with cranial nerves) and visual acuity (with Snellen assessments). Clinical and nonclinical testing was conducted to evaluate for potential oxazolidinone class specific toxicities such as monoamine oxidase (MAO)-related drug-drug interactions, tyramine effects, serotonin syndrome, myelosuppression and lactic acidosis. In addition to the Phase 2 and 3 trials, concentrating on the patients with ABSSSI, the Applicant provided supportive safety data from 15 Phase 1 clinical pharmacology studies, including studies in healthy subjects, adolescents receiving antibiotics for treatment or prophylaxis of an infection, and subjects with renal or hepatic impairment.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Demographic data and baseline characteristics for patients enrolled in the Phase 2 studies are summarized in Table 7.2.1-1. In Phase 2 studies, the mean age of the patients was 38.0 years, with 64.7% male, 75.8% White, 26.3% Hispanic or Latino, and 2.3% ≥65 years of age. In the Phase 2 studies, 29.4% of the patients were obese (BMI ≥30 kg/m^2), 34.3% of the patients had cellulitis/erysipelas and 62.9% had a major cutaneous abscess in the Phase 2 studies. Similar to the Phase 3 studies, IV drug use was reported in 30.2% of patients); 28.1% of patients had hepatic disease with 0.8% having hepatic impairment. The incidence of moderate to severe renal dysfunction (1.0%) and diabetes (7.7%) was low in the Phase 2 studies.

Demographic data and baseline characteristics for patients enrolled in the Phase 3 studies are summarized in Table 7.2.1-1. For the safety analyses of the Phase 3 studies, the tedizolid phosphate and linezolid arms were comprised of a similar patient population. The randomization schedule was stratified by geographic region, so the number of enrollees from each region were similar. The majority of the patients were enrolled from the United States (64.1% for tedizolid

phosphate and 63.6% for linezolid). In the Phase 3 studies, enrollees from Russia accounted for 104 (15.7%) patients in each arm, tedizolid phosphate and linezolid (n=208 total).

In the Phase 3 studies, the mean age in the tedizolid phosphate arm was 44.6 years and 44.4 years in the linezolid arm. In addition, there were 72 (10.9%) patients in the tedizolid phosphate arm and 59 patients (8.9%) patients in the linezolid arm ≥ 65 years of age. The mean BMI in the tedizolid phosphate arm was 28.2 kg/m^2 and in the linezolid arm was 28.4 kg/m^2, with 200 (30.2%) and 229 (34.6%), respectively, considered obese (BMI ≥ 30 kg/m^2).

In the Phase 3 studies, the majority of patients in the study were white (85.1 % for tedizolid phosphate and 83.8% for linezolid), male (64.8% and 61.6% respectively), and non-Hispanic (72.5% and 74.3% respectively). Cellulitis and erysipelas accounted for the majority of the patients in the Phase 3 studies (311 [47.0%] for tedizolid phosphate and 315 [47.6%] for linezolid). The protocols for the Phase 3 studies capped enrollment of patients with abscess at 30%. This is consistent with the analyses where there were 173 (26.1%) patients for the tedizolid phosphate arm and 174 (26.3%) patients for the linezolid arm with major cutaneous abscesses.

The number of patients with self-reported recent or concurrent IV drug use was high in both groups (182 [27.5%] for tedizolid phosphate and 203 [30.7%] for linezolid). In addition, a large number of patients had hepatic disease (175 [26.4%] for tedizolid phosphate and 209 [31.6%] for linezolid); however only a small number had hepatic impairment (14 [2.1%] and 12 [1.8%], respectively). Similarly few patients had moderate or severe renal dysfunction (20 [3.0%] for tedizolid phosphate and 29 [4.4%] for linezolid). The number of patients with diabetes enrolled in the Phase 3 studies was similar (58 [8.7%] for tedizolid phosphate and 67 [10.1%] for linezolid).

Table 7.2.1-1: Demographic Data and Baseline Characteristics

	Phase 2 Studies	Phase 3 Studies	
	Tedizolid phosphate (≥ 200 mg) n=388	Tedizolid phosphate (200mg) n=662	Linezolid (1200mg) n=662
Age (years)			
n	388	662	662
Mean (SD)	38 (12.7)	44.6 (15.4)	44.4 (15.4)
Median	37.5	45	44
Min, Max	18, 73	17, 86	15, 100
Age Groups			
< 18 years	0 (0%)	1 (0.2%)	1 (0.2%)
18 - 65 years	382 (98.5%)	597 (90.2%)	606 (91.5%)
< 65 years	379 (97.7%)	590 (89.1%)	603 (91.1%)

≥ 65 years	9 (2.3%)	72 (10.9%)	59 (8.9%)
≥ 75 years	0 (0%)	24 (3.6%)	25 (3.8%)
Sex			
F	137 (35.3%)	233 (35.2%)	254 (38.4%)
M	251 (64.7%)	429 (64.8%)	408 (61.6%)
Weight (kg)			
n	388	662	662
Mean (SD)	83.9 (18.2)	83.3 (21.6)	83.5 (19.9)
Median	81.7	80	81
Min, Max	43.4, 166.8	37.8, 226.4	37.9, 204.1
BMI (kg/m2)			
n	388	662	662
Mean (SD)	28.2 (6.0)	28.2 (6.7)	28.4 (6.2)
Median	27.3	27.2	27.3
Min, Max	17.7, 53.5	14.2, 69.9	14.8, 56.2
BMI Subgroup, *n (%)*			
< 18.5 (Underweight)	4 (1.0%)	12 (1.8%)	7 (1.1%)
18.5 -< 30 (Normal/overweight)	270 (69.6%)	450 (68.0%)	426 (64.4%)
≥ 30 (Obese)	114 (29.4%)	200 (30.2%)	229 (34.6%)
Race, *n (%)*			
White	294 (75.8%)	563 (85.1%)	555 (83.8%)
Black or African American	79 (20.4%)	77 (11.6%)	71 (10.7%)
Other	11 (2.8%)	16 (2.4%)	22 (3.3%)
Asian	4 (1.0%)	6 (0.9%)	14 (2.1%)
Race, *n (%)*			
American Indian or Alsaka Native	7 (1.8%)	7 (1.1%)	9 (1.4%)
Asian	4 (1.0%)	6 (0.9%)	14 (2.1%)
Black or African American	79 (20.4%)	77 (11.6%)	71 (10.7%)
Native Hawaiian or Native Pacific Islander	2 (0.5%)	2 (0.3%)	3 (0.5%)
Other	2 (0.5%)	7 (1.1%)	10 (1.5%)
White	294 (75.8%)	563 (85.1%)	555 (83.8%)
Ethnicity, *n (%)*			
Hispanic or Latino	102 (26.3%)	182 (27.5%)	170 (25.7%)
Not Hispanic or Latino	286 (73.7%)	480 (72.5%)	492 (74.3%)
Type of Infection, *n (%)*			
Cellulitis/Erysipelas	133 (34.3%)	311 (47.0%)	315 (47.6%)
Major Cutaneous Abscess	244 (62.9%)	173 (26.1%)	174 (26.3%)

Wound Infection	11 (2.8%)	178 (26.9%)	173 (26.1%)
Renal Function Status, *n (%)*			
Moderate/Severe	4 (1.0%)	20 (3.0%)	29 (4.4%)
Normal/Mild	376 (96.9%)	633 (95.6%)	612 (92.5%)
Hepatic Function Status or Disease, *n (%)*			
Normal	276 (71.1%)	474 (71.6%)	443 (66.9%)
Hepatic Disease	106 (27.3%)	175 (26.4%)	209 (31.6%)
Hepatic Impairment	3 (0.8%)	14 (2.1%)	12 (1.8%)
IV Drug Use, *n (%)*			
Yes	117 (30.2%)	182 (27.5%)	203 (30.7%)
No	271 (69.8%)	480 (72.5%)	459 (69.3%)
Diabetes, *n (%)*			
Yes	30 (7.7%)	58 (8.7%)	67 (10.1%)
No	358 (92.3%)	604 (91.2%)	595 (89.9%)
Country, *n (%)*			
US/Canada	388 (100%)	424 (64.1%)	421 (63.6%)
Europe	0 (0%)	165 (24.9%)	166 (25.1%)
Russia (included in Europe)	0 (0%)	104 (15.7%)	104 (15.7%)
Other*	0 (0%)	73 (11.0%)	75 (11.3%)

*Other countries include Argentina, Australia, Brazil, New Zealand, Peru and South Africa.

7.2.2 Explorations for Dose Response

The extent of exposure is summarized in Table 7.2.2-2. In the Phase 2 studies, various doses were used. In Study TR701-104, tedizolid phosphate was dosed at 200 mg, 300 mg, or 400 mg per day for 5 to 7 days while in Study TR701-126, patients received 200 mg tedizolid phosphate once daily for 6 days. The median number of doses of tedizolid phosphate administered was 6 (range 1,7). Fifty nine percent of the patients in the Phase 2 trials received 5-6 doses of tedizolid phosphate.

In the Phase 3 studies, the oral or IV dosage of tedizolid phosphate was 200 mg once daily for 6 days and of linezolid was 600 mg twice daily (1200-mg daily dose) for 10 days. In the Phase 3 trials, the median number of doses of active drug was 6 for tedizolid phosphate and 20 for linezolid. In the tedizolid phosphate arm, 93.5% of the patients received 5-6 doses while in the linezolid arm, 89.1% of the patients received 17-20 doses.

There was one patient (TR701-112-129-459) randomized to the linezolid group who received 1 day of tedizolid phosphate, followed by 4 days of placebo, followed by 5 days of linezolid. Per

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the Applicant, this patient's data is captured in both the tedizolid phosphate and linezolid groups for exposure and in the linezolid group for safety analyses (see TR701-112 CSR).

Table 7.2.2-2: Extent of Exposure in Phase 2 and Phase 3 Studies.

		Phase 2 Studies	Phase 3 Studies	
Parameter	**Analysis Category**	**Tedizolid phosphate (≥200 mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Number of patients exposed		388	663*	662
Exposure of tedizolid phosphate (mg)	200 mg	263 (67.8%)	663 (100.2%)	NA
	>200 mg	125 (32.2%)	0 (0.0%)	NA
Number of Doses of Active Drug (Tedizolid phosphate ≥200mg)	1-2 doses	12 (3.1%)	20 (3.0%)	NA
	3-4 doses	9 (2.3%)	20 (3.0%)	NA
	5-6 doses	228 (58.8%)	619 (93.5%)	NA
	>6 doses	139 (35.8%)	3 (0.5%)	NA
Number of Doses of Active Drug (Linezolid 1200mg)	1-4 doses	NA	NA	19 (2.9%)
	5- 8 doses	NA	NA	26 (3.9%)
	9-12 doses	NA	NA	12 (1.8%)
	13-16 doses	NA	NA	14 (2.1%)
	17-20 doses	NA	NA	590 (89.1%)
	>20 doses	NA	NA	1 (0.2%)
Number of Days of Active Drug (Tedizolid phosphate ≥200mg)	0-3 days	20 (5.2%)	31 (4.7%)	NA
	4-6 days	229 (59.0%)	627 (94.7%)	NA
	7-10 days	138 (35.6%)	3 (0.5%)	NA
	>10 days	1 (0.3%)	1 (0.15%)	NA
Number of Days of Active Drug (Linezolid 1200mg)	0-3 days	NA	NA	35 (5.3%)
	4-6 days	NA	NA	21 (3.2%)
	7-10 days	NA	NA	508 (76.7%)
	>10 days	NA	NA	98 (14.8%)**

*One patient in study TR701-112 received both TR-701 FA and linezolid and is counted in both treatment columns in the Phase 3 studies.

**Some patients received linezolid only on Day 1 or the 20th administration on Day 11.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant conducted adequate non-clinical and clinical studies in pharmacology, pharmacokinetics and toxicology. These studies include an examination of the effect of tedizolid phosphate and/or its metabolites on the renal, cardiac, gastrointestinal and nervous system as well as drug interactions. Additional details can be found in Section 4.3 Preclinical/ Toxicology, 7.3.5 Specific Safety concerns and the individual discipline review.

7.2.4 Routine Clinical Testing

The Applicant conducted adequate routine clinical testing during the Phase 2 and 3 trials. There was consistency in the reporting of adverse events between verbatim and preferred terms. Data for routine and relevant laboratory parameters, vital signs, ECGs, drug interactions, neurologic exams and tests for visual acuity were collected.

The Applicant conducted special studies in the drug development program to evaluate for potential adverse events related to QT prolongation, hepatotoxicity, and renal toxicity. Details are described below.

1. *QT prolongation:* The Applicant conducted a Phase 1 blinded, placebo-controlled crossover study to evaluate the effects of oral tedizolid phosphate on the electrocardiogram (TR701-115) in healthy volunteers receiving a single administration of 200 mg tedizolid phosphate (therapeutic dose) or 1200 mg tedizolid phosphate (5 times the therapeutic dose). In addition, the Applicant includes ECG measurements in Phase 2 and 3 studies.

2. *Hepatotoxicity:* TR701-124 was a Phase 1 open-label study with oral tedizolid phosphate to assess pharmacokinetics and safety in subjects with moderate or severe hepatic impairment. In addition, the Applicant collected data on relevant demographic and laboratory parameters during Phase 2 and 3 clinical studies.

3. *Renal toxicity:* The Applicant conducted a Phase 1 open-label study with 200 mg intravenous tedizolid phosphate to assess safety and pharmacokinetics in subjects with advanced renal impairment (TR701-123). In addition, the Applicant collected data on relevant demographic and laboratory parameters during Phase 2 and 3 clinical studies.

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7.2.5 Metabolic, Clearance, and Interaction Workup

Tedizolid phosphate is an oral and intravenous forms is a prodrug that is converted by phosphatases to tedizolid, the microbiologically-active moiety. There are no other significant circulating metabolites in humans, other than tedizolid, which accounts for approximately 95% of the total radiocarbon AUC in plasma. Furthermore, per the Applicant, there was no degradation of tedizolid in human liver microsomes indicating that the drug is unlikely to be a substrate for hepatic CYP450 enzymes.

Tedizolid is eliminated in excreta as a non-circulating and microbiologically inactive sulfate conjugate. In a study following single oral administration of ^{14}C-labeled tedizolid phosphate under fasted conditions, the majority of elimination occurred via the liver, with 82% of the radioactive dose recovered in feces and 18% in urine. Most of the elimination (>85%) occurred within 96 hours. Less than 3% of tedizolid phosphate dose is excreted as active tedizolid.

Additional details of the metabolic, clearance and interaction workup can be found in the separate Clinical Pharmacology review with a brief summary provided in Section 4.4 of this review.

The major potential safety concerns of drug-drug interactions are described in Sections 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Class, 7.3.5 Submission Specific Primary Safety Concerns and 7.5.5 Drug-Drug Interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant's overall safety evaluation plan included studies of volunteers (subjects) and patients with cSSSI or ABSSSI to detect class specific adverse events that could potentially occur with the use of tedizolid phosphate. These included linezolid (oxazolidinone drug class) specific concerns such as peripheral and ophthalmic neuropathy, myelosuppression, MAO-related drug interactions, serotonergic syndrome, and lactic acidosis. In addition, Phase 2 and Phase 3 data were reviewed to examine treatment emergent adverse events of hypoglycemia or convulsions in patients exposed to tedizolid phosphate.

Oxazolidinone drug class (linezolid) specific:

1. *Peripheral and ophthalmic neuropathy:* The Applicant incorporated specialized safety assessments into selected Phase 1, 2, and 3 studies to detect evidence of ophthalmic or peripheral neuropathy in comparison to linezolid or placebo. This included Snellen visual acuity assessments as well as neurologic examinations comprising of general neurologic, peripheral, sensory, cranial nerve and peripheral

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motor examinations. In addition, the Applicant conducted TR701-110, a Phase 1, open-label, ophthalmology and neurology safety study of oral 200 mg tedizolid phosphate once daily for 10 days in healthy adults.

2. *Myelosuppression:* The Applicant collected data on hematology parameters during the drug development program. In addition, the Applicant conducted a Phase 1 study (TR701-101), which was a randomized, placebo or active controlled double blind study where subjects received mg tedizolid phosphate, qd, at 200, 300, or 400 mg doses for 21 days.
3. *MAO-related drug interactions:* Clinical and nonclinical testing were conducted to evaluate the potential for monoamine oxidase (MAO)-related drug-drug interactions. Because of the potential to produce an uncontrolled hypertensive response, patients receiving linezolid, the only marketed oxazolidinone antimicrobial agent, are advised to avoid consuming large amounts of tyramine and avoid use of over-the-counter preparations containing pseudoephedrine HCl or phenylpropanolamine HCl. Studies TR701-114 and TR701-105 were conducted to evaluate whether mg tedizolid phosphate potentiates the MAO-mediated pressor response to pseudoephedrine HCl and sensitivity to tyramine, respectively. In addition, blood pressure measurements during Phase 2 and Phase 3 studies were taken.
4. *Serotonergic syndrome:* Current prescribing information for linezolid indicates that patients taking drugs with serotonergic potential are advised to take the drug only if no other therapies are available, and to discontinue serotonergic drugs and monitor for serotonergic syndrome. The Applicant used an animal model of serotonergic brain activity to investigate the potential for serotonin syndrome. In the Phase 2 and Phase 3 trials, patients taking concomitant medications with sympathomimetic, vasopressive, dopaminergic, or serotonergic activity were to be excluded. This encompassed serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and serotonin 5-hydroxytryptamine (5-HT_1) receptor agonists (triptans), meperidine, or buspirone. There were a small number of patients taking concomitant serotonin (5-HT_3) antagonists in the Phase 3 and 3 trials.
5. *Lactic acidosis:* The Applicant collected data on relevant laboratory parameters during the drug development program. In addition, the Applicant conducted a Phase 1 study (TR701-101), which was a randomized, placebo or active controlled double blind study where subjects received mg tedizolid phosphate capsules, qd, at 200, 300, or 400 mg doses for 21 days and also had lactate levels sequentially collected. Lactic acid levels were not reported/collected during the Phase 2 and Phase 3 trials.
6. *Convulsions:* The Applicant reported treatment emergent adverse events during the drug development program. No other special safety assessment was done.
7. *Hypoglycemia:* The Applicant collected data on glucose measurements during the drug development program and identified diabetic patients in the integrated safety analysis datasets.

Additional details can be found in Section 7.3.5 Submission Specific Safety Concerns. The Applicant's evaluation for potential adverse events associated with the only approved drug, linezolid, in the same drug class was adequate.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant reports three deaths in the drug development program. All three deaths occurred during the Phase 3 trials. Two deaths occurred in patients receiving tedizolid phosphate tedizolid phosphate and 1 death occurred in a patient receiving the comparator drug, linezolid. All three deaths appear unrelated to the study drug or active comparator from the information provided. The two patients receiving mg tedizolid phosphate were elderly and had multiple comorbidities. The third death occurred in the linezolid group where the patient was HIV positive with a low CD4.

Results are summarized in Table 7.3.1-1 and brief narratives follow.

Table 7.3.1-1: Deaths Listing

Analysis Unique Subject ID	Age	Sex	Country	Body System or Organ Class	Dictionary-Derived Term	Actual Treatment	Onset Date (Relative study day)	Date (Relative study day)
TR701-112-342-605	86	M	Peru	Infections and infestations	Septic shock	TR-701 FA 200mg	2011-09-24 (55)	2011-09-25 (56)
TR701-113-451-258	84	M	South Africa	Cardiac disorders	Myocardial infarction	TR-701 FA 200mg	2012-07-15 (11)	2012-07-19 (15)
TR701-113-444-230	33	F	South Africa	Infections and infestations	Meningitis tuberculous	Linezolid 1200mg	2012-07-03 (14)	2012-07-09 (20)

TR701-112-342-605: In study TR701-112, an 86-year-old Hispanic white male was hospitalized with pneumonia. Medical history was significant for current/recent IV drug use, pneumonia, 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. The patient received several concomitant medications including digoxin, omeprazole, salmeterol/fluticasone, ipratropium bromide, enoxaparin, furosemide, fenoterol, and spironolactone. The patient received tedizolid phosphate for six days to treat a left arm cellulitis. The patient was readmitted for pneumonia 21 days after completing 6 days of treatment with tedizolid phosphate. Subsequently, the patient

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experienced a myocardial infarction (MI) and septic shock with multiorgan system failure ensued. The Applicant reports that respiratory tract cultures revealed growth of *Pseudomonas aeruginosa*. The patient died on Study Day 56.

TR701-113-451-258: In study TR701-113, an 84-year-old white male received tedizolid phosphate for treatment of right leg cellulitis/erysipelas. Medical history was significant for myocardial infarction, heart failure, hypertension, dyslipidemia, chronic obstructive pulmonary disease, coronary artery bypass, and pulmonary hypertension. The patient received several concomitant medications including furosemide, ramipril, bisoprolol, atorvastatin, amlodipine, and tamsulosin. The patient experienced a new MI 4 days after receiving 6 days of treatment with tedizolid phosphate. Supportive measures were discontinued and the patient died on Study Day 15.

TR701-113-444-230: In study TR701-113, a 33-year-old black female was started on linezolid treatment for right lower leg cellulitis/erysipelas. Medical history was significant for human immunodeficiency virus (HIV) infection diagnosed during hospitalization. Concomitant medications for the patient included acetaminophen/codeine for pain associated with the ABSSSI. The patient completed 10 days of linezolid treatment . Five days later, the patient developed CNS signs and symptoms including progressive headache, nausea, and weakness. The patient was readmitted to hospital, subsequently diagnosed with tuberculous meningitis, and started on rifampicin, pyrazinamide, ethambutol and isoniazid. The patient's CD4 count was 49 cells/mm^3. The patient received therapy for tuberculosis meningitis diagnosis based on the clinical presentation and CSF results. Six days after readmission, the patient developed a convulsion and received diazepam IV. The patient was found dead in the hospital bed later that day (Study Day 20).

7.3.2 Nonfatal Serious Adverse Events

The incidence of serious adverse events occurring in patients receiving tedizolid phosphate and linezolid was similar. The majority of the serious adverse events reported were unrelated to tedizolid phosphate or linezolid.

In the Phase 2 and Phase 3 studies, serious adverse events occurred in 19 (1.8%) patients receiving tedizolid phosphate; with 16 (1.5%) patients receiving mg tedizolid phosphate at 200 mg, the proposed dose. Thirteen (1.96%) of the patients receiving linezolid experienced serious adverse events (Table 7.3.2-1).

Table 7.3.2-1: Serious Adverse Events by Drug and Dosage

Serious Event	Tedizolid phosphate Dose			
	200mg	300mg	400mg	1200mg
Number (%)	16 (1.7%)	1 (1.6%)	2 (3.2%)	13 (2.0%)
Subject Totals	925	63	62	662

In Phase 1 studies, the Applicant reports that SAEs were reported for 2 subjects (mild appendicitis and extradural abscess). In TR701-107, the SAE occurred on Day 22 after the subject received 7 infusions of 200 mg tedizolid phosphate. In TR701-124, a severe extradural abscess occurred on Day 14 after a subject had received a single oral administration of 200 mg tedizolid phosphate.

In the Phase 2 studies, 7 patients receiving tedizolid phosphate experienced 1 or more SAE.

In Phase 3 studies, SAEs occurred in 12 patients (1.8%) in the tedizolid phosphate group and in 13 patients (2.0%) in the linezolid group. Infections and infestations was the most commonly reported SOC with SAE (6 patients [0.9%] with tedizolid phosphate and 4 [0.6%] with linezolid). One event was reported in both groups (urinary tract infection in 1 patient each).

The majority of the SAEs in the 19 patients receiving tedizolid phosphate in Phase 2 and 3 studies were singular events. There were 2 patients each with pneumonia, septic shock, and staphylococcal infection. Three patients had abscesses. Both cases of staphylococcal infection were bacteremia and one occurred prior to study drug infusion.

Table 7.3.2-2 listing serious adverse events, categorized by system organ class and dictionary derived term, for the Phase 2 and 3 studies follows.

Table 7.3.2-2: Serious Adverse Events during Phase 2 and Phase 3 studies*

		Phase 2 Studies	Phase 3 Studies	
Body System or Organ Class	**Dictionary-Derived Term**	**Tedizolid phosphate (≥200 mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Number (%) patients with at least 1 SAE		7 (1.8%)	12 (1.8%)	13 (2.0%)
Cardiac disorders			2 (0.3%)	2 (0.3%)
	Acute coronary syndrome	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Acute myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Cardiac arrest	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Myocardial infarction	0 (0.0%)	1 (0.2%)	0 (0.0%)
Gastrointestinal disorders		0 (0.0%)	2 (0.3%)	0 (0.0%)
	Upper gastrointestinal haemorrhage	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Vomiting	0 (0.0%)	1 (0.2%)	0 (0.0%)
Hepatobiliary disorders		1 (0.3%)	0 (0.0%)	0 (0.0%)
	Cholecystitis acute	1 (0.3%)	0 (0.0%)	0 (0.0%)
Immune system disorders		0 (0.0%)	0 (0.0%)	1 (0.2%)
	Anaphylactic reaction	0 (0.0%)	0 (0.0%)	1 (0.2%)
Infections and infestations		4 (1.0%)	6 (0.9%)	4 (0.6%)
	Abscess	2 (0.5%)	1 (0.2%)	0 (0.0%)
	Cellulitis	1 (0.3%)	0 (0.0%)	2 (0.3%)
	Endophthalmitis	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Meningitis tuberculous	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Pneumonia	0 (0.0%)	2 (0.3%)	0 (0.0%)
	Septic shock	0 (0.0%)	2 (0.3%)	0 (0.0%)
	Staphylococcal infection	1 (0.3%)	1 (0.2%)	0 (0.0%)
	Thrombophlebitis septic	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Urinary tract infection	0 (0.0%)	1 (0.2%)	1 (0.2%)
Investigations		0 (0.0%)	1 (0.2%)	1 (0.2%)
	Blood glucose increased	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Weight decreased	0 (0.0%)	1 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders		0 (0.0%)	2 (0.3%)	1 (0.2%)
	Dehydration	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Diabetes mellitus	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Diabetic ketoacidosis	0 (0.0%)	0 (0.0%)	1 (0.2%)
Nervous system disorders		0 (0.0%)	1 (0.2%)	0 (0.0%)
	VIIth nerve paralysis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Pregnancy, puerperium and perinatal conditions		0 (0.0%)	0 (0.0%)	1 (0.2%)
	Abortion spontaneous	0 (0.0%)	0 (0.0%)	1 (0.2%)
Psychiatric disorders		1 (0.3%)	0 (0.0%)	2 (0.3%)
	Alcoholic psychosis	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Major depression	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Suicidal ideation	1 (0.3%)	0 (0.0%)	1 (0.2%)
Renal and urinary disorders		0 (0.0%)	1 (0.2%)	0 (0.0%)

	Nephrolithiasis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Respiratory disorders		1 (0.3%)	0 (0.0%)	0 (0.0%)
	Haemoptysis	1 (0.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders		0 (0.0%)	1 (0.2%)	1 (0.2%)
	Hypertension	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Thrombophlebitis superficial	0 (0.0%)	0 (0.0%)	1 (0.2%)

*Includes 3 patients with SAE outcome of death.

CRFs and the Applicant's narrative summaries were used to review details of selected serious adverse events. A tabular summary of nonfatal serious adverse events in the Phase 2 and Phase 3 studies are listed in **Table 7.3.2-3**.

Table 7.3.2-3: Serious Adverse Event Listing

Analysis Unique Subject ID	Age	Sex	Country	Pooled Actual Treatment	Study Day of Start of Adverse Event	Body System or Organ Class	Dictionary-Derived Term	Reported Term for the Adverse Event	Causality by Investigator
TR701-104-001-043	57	F	USA	TR-701 > 200mg	9	Hepatobiliary disorders	Cholecystitis acute	ACUTE CHOLECYSTITIS	POSSIBLE
TR701-104-002-006	49	M	USA	TR-701 > 200mg	28	Psychiatric disorders	Suicidal ideation	SUICIDAL IDEATION	NOT RELATED
TR701-104-004-056	41	F	USA	TR-701 200mg	22	Infections and infestations	Abscess	SECONDARY ABSCESS RIGHT ARM	NOT RELATED
TR701-104-006-001	45	M	USA	TR-701 200mg	3	Infections and infestations	Cellulitis	WORSENING CELLULITIS	NOT RELATED
TR701-104-007-002	43	F	USA	TR-701 > 200mg	2	Infections and infestations	Abscess	ABSCESS, RIGHT LEG WITH CELLULITIS	NOT RELATED
TR701-112-104-192	21	F	USA	Linezolid 1200mg	12	Metabolism and nutrition disorders	Diabetic ketoacidosis	DIABETIC KETOACIDOSIS	NOT RELATED
TR701-112-104-496	26	M	USA	Linezolid 1200mg	15	Psychiatric disorders	Suicidal ideation	SUICIDAL IDEATION	NOT RELATED
				Linezolid 1200mg	15	Psychiatric disorders	Major depression	MAJOR DEPRESSIVE DISORDER	NOT RELATED
TR701-112-105-042	24	F	USA	TR-701 200mg	35	Infections and infestations	Endophthalmitis	ENDOPHTHALMITIS RIGHT EYE	NOT RELATED
TR701-112-105-405	36	M	USA	TR-701 200mg	27	Infections and infestations	Abscess	WORSENING OF NEW ABSCESS RIGHT DELTOID	NOT RELATED
TR701-112-128-665	27	F	USA	TR-701 200mg	33	Metabolism and nutrition disorders	Dehydration	DEHYDRATION	NOT RELATED

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				TR-701 200mg	10	Nervous system disorders	VIIth nerve paralysis	SEVENTH CRANIAL NERVE PALSY	NOT RELATED
				TR-701 200mg	33	Gastrointestinal disorders	Vomiting	INTRACTABLE VOMITING	NOT RELATED
				TR-701 200mg	33	Investigations	Weight decreased	WEIGHT LOSS	NOT RELATED
TR701-112-173-402	74	F	CAN	TR-701 200mg	21	Gastrointestinal disorders	Upper gastrointestinal haemorrhage	UPPER GASTRO INTESTINAL BLEEDING	NOT RELATED
TR701-112-242-408	69	M	HUN	Linezolid 1200mg	14	Psychiatric disorders	Alcoholic psychosis	PSYCHOSIS ALCOHOLICA	NOT RELATED
TR701-112-262-467	28	F	UKR	Linezolid 1200mg	23	Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	SPONTANEOUS ABORTION	PROBABLE
TR701-112-342-605	86	M	PER	TR-701 200mg	37	Cardiac disorders	Cardiac arrest	CARDIAC ARREST	NOT RELATED
				TR-701 200mg	31	Infections and infestations	Pneumonia	PNEUMONIA	NOT RELATED
TR701-113-105-073	65	F	USA	TR-701 200mg	18	Infections and infestations	Septic shock	SEPTIC SHOCK SECONDARY TO NECROTIZING INFECTION LEFT SHOULDER	NOT RELATED
TR701-113-105-075	50	M	USA	Linezolid 1200mg	2	Immune system disorders	Anaphylactic reaction	ANAPHYLACTIC REACTION	DEFINITE
TR701-113-105-126	23	M	USA	Linezolid 1200mg	27	Infections and infestations	Cellulitis	CELLULITIS RIGHT ARM (ANTECUBITAL)	NOT RELATED
TR701-113-141-111	58	M	USA	Linezolid 1200mg	30	Infections and infestations	Cellulitis	NEW RLE CELLULITIS	NOT RELATED
TR701-113-143-546	61	M	USA	Linezolid 1200mg	8	Cardiac disorders	Acute coronary syndrome	ACUTE CORONARY SYNDROME	NOT RELATED
TR701-113-143-647	38	F	USA	TR-701 200mg	14	Renal and urinary disorders	Nephrolithiasis	WORSENING OF KIDNEY STONES	NOT RELATED
TR701-113-147-354	82	M	USA	TR-701 200mg	5	Infections and infestations	Urinary tract infection	URINARY TRACT INFECTION (E.COLI)	NOT RELATED

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TR701-113-147-639	82	M	USA	TR-701 200mg	2	Vascular disorders	Hypertension	AGGRAVATED HYPERTENSION	NOT RELATED
TR701-113-160-453	53	F	USA	Linezolid 1200mg	25	Infections and infestations	Urinary tract infection	CITROBACTER KOSERI UTI	NOT RELATED
TR701-113-165-478	61	F	USA	Linezolid 1200mg	7	Investigations	Blood glucose increased	ELEVATED GLUCOSE	NOT RELATED
TR701-113-286-148	59	F	RUS	TR-701 200mg	16	Metabolism and nutrition disorders	Diabetes mellitus	DIABETIS MELLITUS TYPE 2 EXACERBATED	NOT RELATED
TR701-113-290-195	40	M	RUS	Linezolid 1200mg	3	Cardiac disorders	Acute myocardial infarction	ACUTE NON-Q MYOCARDIAL INFARCTION OF THE LEFT VENTRICLE	NOT RELATED
TR701-113-358-326	63	F	ARG	TR-701 200mg	37	Infections and infestations	Pneumonia	HOSPITAL ACQUIRED PNEUMONIA	NOT RELATED
				TR-701 200mg	19	Infections and infestations	Staphylococcal infection	METHICILLIN SENSITIVE STAPHYLOCOCCUS AUREUS BACTEREMIA	NOT RELATED
TR701-113-449-602	49	F	ZAF	Linezolid 1200mg	4	Vascular disorders	Thrombophlebitis superficial	SUPERFICIAL THROMBOPHEBITIS OF THE SAPHENOUS VEINS(LOWER EXTREMITIES0	NOT RELATED
TR701-126-105-064	59	M	USA	TR-701 200mg	8	Respiratory, thoracic and mediastinal disorders	Haemoptysis	HEMOPTYSIS	NOT RELATED
TR701-126-115-185	49	M	USA	TR-701 200mg	1	Infections and infestations	Staphylococcal infection	MRSA BACTEREMIA	NOT RELATED
				TR-701 200mg	2	Infections and infestations	Thrombophlebitis septic	SEPTIC THROMBOPHLEBITIS OF THE GREATER SAPHENOUS VEIN	NOT RELATED

Brief patient narratives are included where investigator causality for an SAE was possible, probable or definite for tedizolid phosphate or linezolid. Additional narratives are included for a patient with pneumonia, septic shock, and septic thrombophlebitis. Two of the narratives suggest linezolid related serious adverse event (anaphylaxis and spontaneous abortion). The additional narratives selected suggest that it is unlikely that tedizolid phosphate directly contributed to the serious adverse event. Narratives for the patients with an outcome of death have been reported previously.

Cholecystitis (TR701-104-001-043): A 57 year old 70 kg Hispanic female completed 7 days of TR701 therapy. Significant medical history included fibromyalgia, hypertension, gastrointestinal reflux disease, back pain, back surgery, and hysterectomy. Concomitant medications include pregabalin, estrogens, acetaminophen/hydrocodone, and metoclopramide. On Study Day 8, one day after treatment completion, the patient presented to the ER with a 2 hour history of severe right upper quadrant pain and nausea. The patient had mild right upper quadrant tenderness without other abdominal signs. Pertinent laboratory results were within normal ranges. The patient received 1 liter normal saline, morphine, ondansetron, and promethazine and the pain resolved. The patient was discharged with acetaminophen/ hydrocodone and metoclopramide. The patient was hospitalized the following day for cholecystitis and underwent cholecystectomy. Pathologic examination of the excised gallbladder revealed subacute and chronic cholecystitis with cholelithiasis. The patient recovered and was discharged five days after the last dose of the study drug.

Pregnancy/Spontaneous Abortion (TR701-112-262-467): A 28 year old white female was initiated on linezolid for treatment of cellulitis of the left buttock. Concomitant medication included paracetamol. Urine hCG was negative and serum hCG was positive at study initiation. On Study Day 9, serum hCG results were reported and the patient was instructed to discontinue the study drug. On Study Day 10, a repeat serum hCG was positive. Thirteen days after last study drug administration, the patient experienced vaginal bleeding and lower abdominal pain. The patient was hospitalized due to a spontaneous abortion and underwent dilation and curettage. The patient recovered and was discharged on Study Day 25.

Septic shock (TR701-113-105-073): A 66 year old black female was started on tedizolid phosphate for treatment of a left leg wound infection. Significant medical history included IV drug use, hepatitis C, hypertension, nicotine use, asthma, and anemia. The patient's concomitant medications included albuterol, fluticasone/salmeterol, and valsartan. Baseline culture showed no growth. Eight days after final study drug administration, the patient became confused, hypotensive and had a large erythematous left scapular abscess. The patient received IV normal saline and vancomycin in the Emergency Room. CT scan of the chest revealed gas in the

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edematous tissue of the posterior left shoulder and upper back suspicious for gas-forming organisms. Anaerobic tissue and fluid cultures grew moderate *Prevotella melaninogenica*; aerobic cultures showed light growth of *Staphylococcus lugdunensis*, *Streptococcus constellatus*, and beta-hemolytic streptococci. The wound was debrided, a split thickness skin graft was performed and the patient was treated with IV aztreonam, clindamycin, vancomycin, cefazolin, and ampicillin/sulbactam. The patient required mechanical ventilation during the course of her hospitalization. The patient was discharged 14 days after admission.

Anaphylactic Reaction (TR701-113-105-075): A 50 year old white male was started on linezolid treatment for cellulitis/erysipelas of the left buttock. The patient received three doses of study drug (linezolid). Significant medical history includes IV drug use, hepatitis C, prior cellulitis/erysipelas of the left buttock, occasional migraine and nonmigraine headaches, anxiety, depression, and alcohol and tobacco use. Concomitant medication included oxycodone. Two minutes after receiving the third dose of the study drug, the patient developed headaches and burning at the IV site. Signs and symptoms progressed and included worsening headache, difficulty breathing, and stridor. The infusion was stopped 8 minutes after initiation and the patient was treated with diphenhydramine 50 mg IV. Emergency medical services (EMS) transported the patient to an ER. No medications were administered by EMS or the ER. After 6 hours of observation in the ER, the patient was discharged and received trimethoprim/sulfamethoxazole 1 tablet twice daily for 10 days for cellulitis.

Pneumonia (TR701-113-358-326)*:* A 63-year-old white Hispanic female, was initiated on TR-701 FA for treatment of right forearm cellulitis/erysipelas while hospitalized for a myocardial infarction. Significant medical history included type 2 diabetes mellitus, hypertension, hypertensive and diabetic retinopathy, acute heart failure, and acute myocardial infarction. The patient received concomitant medications including insulin, cetirizine, atorvastatin, amlodipine, clopidogrel, heparin, omeprazole, acetylsalicylic acid, enalapril, nitroglycerine, potassium gluconate, and furosemide. Blood cultures before initiation of study drug grew methicillin sensitive *Staphylococcus aureus* (MSSA). Repeat blood cultures were negative. The patient completed the treatment course for tedizolid phosphate and cellulitis was assessed as clinical success on Study Day 10. On Study Day 19, a new right upper arm and elbow cellulitis were noted. The patient was treated with oral ciprofloxacin and clindamycin which resulted in resolution of the cellulitis in 3 days. Blood cultures grew MSSA and the patient was readmitted to hospital and treated with IV cephalothin. Echocardiogram was negative for endocarditis. On Study Day 31, the patient developed right paracardiac infiltrates. The patient was diagnosed with hospital-acquired pneumonia with no pathogen identified. Antibiotic therapy was changed to piperacillin/tazobactam. The patient was discharged home on oral ciprofloxacin and amoxicillin clavulanate until the pneumonia was resolved.

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Septic thrombophlebitis (TR701-126-115-185): , A 49-year-old white male with BMI of 42.4 kg/m^2, started TR-701 FA treatment for cellulitis on the right leg. After administration of a single dose, the patient was discontinued from the study drug due to septic thrombophlebitis of the right greater saphenous vein noted on Day 2 prior to study drug administration. Significant medical history included diabetes mellitus, hypertension, deep vein thrombosis (DVT), cholecystectomy, and irregular heartbeat. Concomitant medications included lisinopril, warfarin, metoprolol, and insulin. Doppler ultrasound on the day of study drug initiation was negative for DVT but positive for a thrombus in the right greater saphenous vein. A blood culture obtained at the screening visit became positive for methicillin resistant *Staphylococcus aureus* (MRSA). The patient was admitted for treatment of septic thrombophlebitis of the greater saphenous vein and bacteremia. The patient was noted to have severe cellulitis with an abscess on his right thigh and was treated with IV nafcillin, vancomycin, and heparin. On the following day, the patient underwent removal of his right saphenous vein, and incision and drainage of multiple abscesses, with purulent drainage noted. Hospital admission blood cultures and surgical drainage cultures grew MRSA. Post-operative blood cultures were negative. The patient was discharged 5 days after admission with IV vancomycin via a peripherally inserted central catheter line. The patient had extensive swelling of the leg, a large open wound with wound vacuum assisted closure (VAC) in place, and 2 smaller closed wounds. The patient received approximately six weeks of IV vancomycin therapy and both the septic thrombophlebitis and MRSA bacteremia were considered resolved.

Serious adverse events were examined by various patient subgroups and are described in Table 7.3.2-4. With the exception of SAEs in patients ≥75 years as well as ≥65 and renal impairment, results were similar for tedizolid phosphate and linezolid. Small numbers in the patient subpopulations preclude the ability to draw conclusions on these findings.

Table 7.3.2-4: Serious Adverse Events in Various Patient Subgroups

		Phase 2 Studies	**Phase 3 studies**	
		Tedizolid phosphate (≥200mg) n=388	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
	Total SAE	7 (1.8%)	12 (1.8%)	13 (2.0%)
Age Groups	< 65 years	7 (1.8%)	6 (0.9%)	12 (1.8%)
	>= 65 years	0 (0.0%)	6 (0.9%)	1 (0.2%)
	>= 75 years	0 (0.0%)	4 (0.6%)	0 (0.0%)
Sex	Female	3 (0.8%)	7 (1.1%)	6 (0.9%)
	Male	4 (1.0%)	5 (0.8%)	7 (1.1%)
Race	Black or African American	3 (0.8%)	1 (0.2%)	3 (0.5%)
	White	4 (1.0%)	11 (1.7%)	10 (1.5%)
Infection Type	Cellulitis/Erysipelas	2 (0.5%)	9 (1.4%)	8 (1.2%)
	Major Cutaneous Abscess	5 (1.3%)	0 (0.0%)	2 (0.3%)
	Wound Infection	0 (0.0%)	3 (0.5%)	3 (0.5%)
IV Drug Use		1 (0.3%)	5 (0.8%)	4 (0.6%)
Diabetic Patient		1 (0.3%)	2 (0.3%)	2 (0.3%)
Hepatic	Hepatic Impairment	0 (0.0%)	1 (0.2%)	2 (0.3%)
	Hepatic Disease	2 (0.5%)	2 (0.3%)	4 (0.6%)
Renal Function Status	Moderate/Severe	0 (0.0%)	5 (0.8%)	0 (0.0%)

7.3.3 Dropouts and/or Discontinuations

The percentage of dropouts and discontinuations was similar in patients receiving tedizolid phosphate and linezolid in the Phase 3 studies. In the Phase 3 studies, 92.3% in the tedizolid phosphate arm and 90.8% in the linezolid arm completed the study drug. In the Phase 2 studies, 94.1% of the patients completed the study drug. Most of the patients completed the Phase 3 studies (92.5% tedizolid phosphate and 92.6% linezolid). In Phase 2 studies, 92.0% of

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the patients completed the study. Reasons for discontinuation from study drug and study are described in the following Table 7.3.3-1.

The most common reason for study drug discontinuation in Phase 3 and Phase 2 studies was lost to follow-up. In the Phase 3 study, 17 (2.6%) patients in the tedizolid phosphate arm and 22 (3.3%) in the linezolid arm were lost to follow-up. In the Phase 2 study, 11 (2.8%) were lost to follow-up. In Phase 3 studies, adverse events led to study drug discontinuation for 2 (0.3%) patients in the tedizolid phosphate arm and 6 (0.9%) in the linezolid arm. Two (0.5%) patients in the Phase 2 studies discontinued study drug due to an adverse event. Finally, in the Phase 3 studies, 11 (1.7%) of the patients in the tedizolid phosphate arm and 9 (1.4%) patients in the linezolid arm discontinued study drug due to lack of efficacy. Three (0.7%) patients withdrew study drug due to lack of efficacy in the Phase 2 studies.

The most common reason for study discontinuation in Phase 3 and Phase 2 studies was lost to follow-up. In the Phase 3 study, 33 (5.0%) patients in the tedizolid phosphate arm and 35 (5.3%) in the linezolid arm were lost to follow-up. In the Phase 2 study, 25 (6.4%) were lost to follow-up.

Table 7.3.3-1: Reasons for Discontinuation from Study Drug and Study

	Phase 2 Studies	**Phase 3 Studies**	
Reason for Discontinuation from Study Drug	**Tedizolid phosphate (≥200 mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Total	23 (5.9%)	51 (7.7%)	61 (9.2%)
Lost to Follow-up	11 (2.8%)	17 (2.6%)	22 (3.3%)
Adverse Event	2 (0.5%)	3* (0.5%)	6 (0.9%)
Lack of Efficacy	3 (0.8%)	11 (1.7%)	9 (1.4%)
Withdrawal by Subject	3 (0.8%)	11 (1.7%)	10 (1.5%)
Physician Decision	1 (0.3%)	4 (0.6%)	5 (0.8%)
Patient Requires Prohibited Medication	0 (0.0%)	0 (0.0%)	3 (0.5%)
Gram-negative Infection	1 (0.3%)	2 (0.3%)	5 (0.8%)
Staphylococcus aureus	1 (0.3%)	0 (0.0%)	0 (0.0%)
Other	1 (0.3%)	4 (0.6%)	1 (0.2%)
Reason for Discontinuation from Study			
Total	31 (8.0%)	50 (7.6%)	49 (7.4%)
Lost to Follow-Up	25 (6.4%)	33 (5.0%)	35 (5.3%)
Withdrawal by Subject	4 (1.0%)	15 (2.3%)	12 (1.8%)
Physician Decision	1 (0.3%)	0 (0.0%)	1 (0.2%)
Other	1 (0.3%)	2 (0.3%)	1 (0.2%)

*One patient had multiple reasons including an adverse event.

7.3.4 Significant Adverse Events

Discontinuation of study drug due to treatment emergent adverse events (TEAE) are described in the following Table 7.3.4-1. Overall, the incidence was low. In Phase 3 studies, 3 (0.5%) patients in the tedizolid phosphate arm and 6 (0.9%) patients in the linezolid arm discontinued study drug due to TEAE. These TEAEs occurred most frequently in the Gastrointestinal Disorders SOC.

Table 7.3.4-1: Discontinuation of study drug due to Treatment Emergent Adverse Events

		Phase 2 Studies	Phase 3 Studies	
Body System or Organ Class	**Dictionary-Derived Term**	**Tedizolid phosphate (≥200 mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
	Number of subjects	2 (0.5%)	3 (0.5%)	6 (0.9%)
Eye disorders		0 (0.0%)	0 (0.0%)	1 (0.2%)
	Visual acuity reduced	0 (0.0%)	0 (0.0%)	1 (0.2%)
Gastrointestinal disorders		0 (0.0%)	2 (0.3%)	3 (0.5%)
	Abdominal discomfort	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Diarrhoea	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Nausea	0 (0.0%)	0 (0.0%)	3 (0.5%)
	Vomiting	0 (0.0%)	1 (0.2%)	3 (0.5%)
General disorders and administration site conditions		0 (0.0%)	0 (0.0%)	1 (0.2%)
	Pain	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Pyrexia	0 (0.0%)	0 (0.0%)	1 (0.2%)
Immune system disorders		1 (0.5%)	0 (0.0%)	1 (0.2%)
	Anaphylactic reaction	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Drug hypersensitivity	1 (0.3%)	0 (0.0%)	0 (0.0%)
Infections and infestations		1 (0.5%)	1 (0.2%)	0 (0.0%)
	Osteomyelitis	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Thrombophlebitis septic	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nervous system disorders		0 (0.0%)	0 (0.0%)	2 (0.3%)
	Headache	0 (0.0%)	0 (0.0%)	2 (0.3%)
Psychiatric disorders		0 (0.0%)	0 (0.0%)	1 (0.2%)
	Restlessness	0 (0.0%)	0 (0.0%)	1 (0.2%)

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A listing of patients discontinuing study drug due to treatment emergent adverse events is provided in **Table 7.3.4-2.**

Table 7.3.4-2: Listing of patients discontinuing study drug due to Treatment Emergent Adverse Events

Analysis Unique Subject ID	Age	Sex	Country	Race	Actual Treatment	Study Day of Start of Adverse Event	Body System or Organ Class	Dictionary-Derived Term	Reported Term for the Adverse Event	Outcome of Adverse Event	Causality
TR701-112-103-351	31	M	USA	WHITE	Linezolid 1200mg	3	Gastrointestinal disorders	Vomiting	INTERMITTENT VOMITING	RECOVERED/ RESOLVED	POSSIBLE
					Linezolid 1200mg	2	Gastrointestinal disorders	Nausea	NAUSEA	RECOVERED/ RESOLVED	POSSIBLE
TR701-112-103-565	37	M	USA	WHITE	Linezolid 1200mg	1	Gastrointestinal disorders	Vomiting	VOMITING	NOT RECOVERED/ NOT RESOLVED	PROBABLE
					Linezolid 1200mg	1	Gastrointestinal disorders	Nausea	NAUSEA	NOT RECOVERED/ NOT RESOLVED	PROBABLE
TR701-112-112-487	56	F	USA	WHITE	TR-701 200mg	3	Infections and infestations	Osteomyelitis	OSTEOMYELITIS THIRD TOE ON RIGHT FOOT	RECOVERED/ RESOLVED	NOT RELATED
TR701-112-130-086	35	M	USA	AMERICAN INDIAN OR ALASKA NATIVE	TR-701 200mg	2	Gastrointestinal disorders	Vomiting	VOMITTING	RECOVERED/ RESOLVED	POSSIBLE
					TR-701 200mg	2	Gastrointestinal disorders	Diarrhoea	DIARRHEA	RECOVERED/ RESOLVED	POSSIBLE
TR701-113-103-046	21	F	USA	WHITE	Linezolid 1200mg	2	General disorders and administration site conditions	Pyrexia	FEVER	RECOVERED/ RESOLVED	POSSIBLE
					Linezolid 1200mg	33	Reproductive system and breast disorders	Dysmenorrhoea	MENSTRUAL CRAMPS	RECOVERED/ RESOLVED	NOT RELATED

					Linezolid 1200mg	2	General disorders and administration site conditions	Pain	BODYACHES	RECOVERED/ RESOLVED	POSSIBLE
					Linezolid 1200mg	2	Nervous system disorders	Headache	HEADACHE	RECOVERED/ RESOLVED	POSSIBLE
TR701-113-105-075	50	M	USA	WHITE	Linezolid 1200mg	2	Psychiatric disorders	Restlessness	RESTLESSNESS	RECOVERED/ RESOLVED	DEFINITE
					Linezolid 1200mg	2	General disorders and administration site conditions	Infusion site pain	IV SITE PAIN	RECOVERED/ RESOLVED	DEFINITE
					Linezolid 1200mg	2	Nervous system disorders	Headache	WORSENING OF HEADACHE	RECOVERED/ RESOLVED	DEFINITE
					Linezolid 1200mg	2	Immune system disorders	Anaphylactic reaction	ANAPHYLACTIC REACTION	RECOVERED/ RESOLVED	DEFINITE
TR701-113-105-180	51	F	USA	WHITE	TR-701 200mg	1	Gastrointestinal disorders	Abdominal discomfort	ABDOMINAL DISCOMFORT	RECOVERED/ RESOLVED	POSSIBLE
					TR-701 200mg	1	Eye disorders	Vision blurred	BLURRY VISION	RECOVERED/ RESOLVED	POSSIBLE
TR701-113-287-223	78	F	RUS	WHITE	Linezolid 1200mg	6	Reproductive system and breast disorders	Vulvovaginal burning sensation	BURNING SENSATION IN THE VAGINA	RECOVERED/ RESOLVED	DEFINITE
					Linezolid 1200mg	6	Eye disorders	Visual acuity reduced	BILATERAL REDUCED VISUAL ACUITY	RECOVERED/ RESOLVED	DEFINITE
					Linezolid 1200mg	6	Nervous system disorders	Headache	HEADACHE	RECOVERED/ RESOLVED	DEFINITE
					Linezolid 1200mg	6	Gastrointestinal disorders	Abdominal pain upper	EPIGASTRIC PAIN	RECOVERED/ RESOLVED	DEFINITE
TR701-113-444-230	33	F	ZAF	BLACK OR AFRICAN AMERICAN	Linezolid 1200mg	8	Gastrointestinal disorders	Vomiting	VOMITING	RECOVERED/ RESOLVED	NOT RELATED
					Linezolid 1200mg	15	Nervous system disorders	Somnolence	SLEEPY	RECOVERED/ RESOLVED	NOT RELATED
					Linezolid 1200mg	8	Gastrointestinal disorders	Nausea	NAUSEA	RECOVERED/ RESOLVED	NOT RELATED

					Linezolid 1200mg	14	Infections and infestations	Meningitis tuberculous	TUBERCULOSIS MENINGITIS	FATAL	NOT RELATED
					Linezolid 1200mg	12	Infections and infestations	Meningitis tuberculous	TUBERCULOSIS MENINGITIS [BECAME A SAE]	RECOVERED/ RESOLVED	NOT RELATED
TR701-126-115-185	49	M	USA	WHITE	TR-701 200mg	2	Infections and infestations	Thrombophle bitis septic	SEPTIC THROMBOPHLE BITIS OF THE GREATER SAPHENOUS VEIN	RECOVERED/ RESOLVED	NOT RELATED
TR701-126-128-073	51	M	USA	WHITE	TR-701 200mg	1	Immune system disorders	Drug hypersensitivi ty	ALLERGIC REACTION TO STUDY DRUG TREATMENT FOR ABSSSI	RECOVERED/ RESOLVED	PROBABLE

7.3.5 Submission Specific Primary Safety Concerns

The following submission specific safety concerns are addressed in this section: neurologic disorders, optic nerve disorders, myelosuppression, MAO-related drug interactions, serotonergic syndrome, lactic acidosis, convulsions and hypoglycemia. Additional details can be found throughout the review, including Section 7.4.2 Laboratory Findings, Section 7.4.5 Special Safety Studies/ Clinical Trials, Section 7.5.4 Drug-Disease Interactions, and Section 7.5.5 Drug-Drug interactions.

7.3.5.1 Neurologic Disorders

The Applicant conducted preclinical studies which supported the safety of tedizolid phosphate with respect to neurologic disorders. A 9-month vehicle-controlled rat neurotoxicology study suggested no evidence of functional or histopathologic optic or peripheral neuropathic lesions at systemic exposures equivalent to up to 8-fold that observed in humans at the therapeutic dose of 200 mg once daily. In addition, no functional nerve anomalies were observed through the 9-month assessment up to the maximum 8-fold clinical exposure. Additional information can be found in the Preclinical Pharmacology/ Toxicology review.

The Applicant conducted two Phase 1 studies where neurologic and ophthalmic safety was assessed.

The first Phase 1 study (TR701-110), studied 72 volunteers where detailed assessments of ophthalmic and peripheral neurologic function were conducted. No clinically significant differences in neurologic or ophthalmic exams were noted with administration of 200 mg once daily tedizolid phosphate for 10 days.

The second Phase 1 study (TR701-101) evaluated healthy subjects receiving 200, 300 or 400 mg oral tedizolid phosphate once daily or 600 mg linezolid twice daily or placebo for 21 days. Subjects receiving tedizolid phosphate had no signs of optic or peripheral neuropathy during the study. It should be noted that peripheral and optic neuropathies reported in patients treated with linezolid occur primarily in patients treated for longer than the maximum recommended duration of 28 days.

In the Phase 2 and 3 trials the Applicant conducted neurologic and visual examinations to assess for potential drug class related adverse events. A summary is provided in Table 7.3.5-1 (adapted from Applicant's submission).

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Table 7.3.5-1: Summary of neurologic and visual examinations

	Neurologic Examination	Visual Acuity Assessment
Phase 2		
TR701-104	General neurologic examination	No visual acuity assessment
TR701-126	Extensive neurologic examination	Snellen visual acuity assessment
Phase 3		
TR701-112	General neurologic examination	No visual acuity assessment
TR701-113	Amendment 1: General neurologic examination Amendment 4: Added cranial nerve examination	Amendment 1: Snellen visual acuity assessment

During the drug development program, the Applicant conducted neurologic examinations in several of the tedizolid phosphate studies. Neurologic examinations included general as well as extensive neurologic examinations. This included peripheral, sensory, cranial nerve and peripheral motor examinations. In the Phase 2 and Phase 3 studies, two patients were identified with abnormal neurologic examinations (Table 7.3.5-2).

Table 7.3.5-2: Abnormal Neurologic Examinations in Phase 2 and Phase 3 Studies

Analysis Unique Subject ID	Parameter	Analysis Value	Actual Treatment
TR701-112-103-657	Foot	ABNORMAL	TR-701 FA 200mg
TR701-113-143-606	Peripheral Sensory	DECREASED SENSATION LEFT LOWER EXTREMITY, CHRONIC ABNORMAL GAIT	Linezolid 1200mg

TR701-112-103-657 was a 43 year old white, Hispanic, male with IV drug use, hepatitis C, asthma, depression, occasional tension headaches who developed numbness to second and third toes (side not indicated) nine days after the study drug was initiated. This adverse event was of mild severity, considered possibly related to the study drug (tedizolid phosphate) by the Investigator. The adverse event continued through the course of the study.

TR701-113-143-606 was a 49 year old white, Hispanic or Latino, male with history of IV drug use, hepatitis C, asthma and chronic back pain who had a left thigh cellulitis/erysipelas. At the time of screening, the patient had limited range of motion due to chronic back pain. In addition, the patient had decreased sensation in the left lower extremity in comparison to the right lower extremity as well as an abnormal gait. On study day 1, the patient developed diarrhea lasting 2 days. This was considered moderate severity, possibly related to the study drug and the patient recovered without any action taken. On study day 2, the patient developed headache lasting 8 days. This

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was considered mild in severity and not related to the study drug. The patient recovered without any action taken.

In the Phase 3 studies, there were 8 (1.2%) patients in the TR-701 FA arm and 5 (0.8%) in the linezolid arm who experienced at least 1 neurologic TEAE (Table 7.3.5-3). These events included hypoesthesia, cranial nerve VII paralysis, parasthesia and sensory loss. Most events were mild and transient.

Table 7.3.5-3: Peripheral Neuropathy and Hearing and Vestibular Disorder SMQ for Phase 3 Studies

			Phase 3 studies	
SMQ Name	*Body System or Organ Class*	*Dictionary-Derived Term*	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Peripheral neuropathy (SMQ)	Nervous system disorders		8 (1.2%)	4 (0.6%)
		Hypoaesthesia	4 (0.6%)	1 (0.2%)
		Neuropathy peripheral	1 (0.2%)	0 (0.0%)
		Paraesthesia	3 (0.5%)	3 (0.5%)
		Sensory loss	0 (0.0%)	1 (0.2%)
Hearing and vestibular disorders (SMQ)	Ear and labyrinth disorders		0 (0.0%)	1 (0.2%)
		Tinnitus	0 (0.0%)	1 (0.2%)

Details of selected patients with Neurologic TEAEs are included in the table below (Table 7.3.5-4).

Table 7.3.5-4: Listing of selected patients with neurologic Treatment Emergent Adverse Events.

Analysis Unique Subject ID	Age	Sex	Country	Actual Treatment	Study Day of Start of Adverse Event	Body System or Organ Class	Dictionary-Derived Term	Reported Term for the Adverse Event	Causality
TR701-112-103-657	43	M	USA	TR-701 FA 200mg	9	Nervous system disorders	Hypoaesthesia	NUMBNESS TO SECOND AND THIRD TOES	POSSIBLE
TR701-113-143-606	49	M	USA	Linezolid 1200mg	6	Gastrointestinal disorders	Diarrhoea	DIARRHEA	POSSIBLE
					1	Nervous system disorders	Headache	HEADACHE	NOT RELATED
TR701-112-128-665	27	F	USA	TR-701 FA 200mg	25	Nervous system disorders	Headache	HEADACHE	NOT RELATED
					33	Investigations	Weight decreased	WEIGHT LOSS	NOT RELATED
					25	Musculoskeletal and connective tissue disorders	Myalgia	CERVICAL MYALGIA	NOT RELATED
					1	Gastrointestinal disorders	Nausea	NAUSEA	NOT RELATED
					26	Psychiatric disorders	Insomnia	INSOMNIA	NOT RELATED
					33	Gastrointestinal disorders	Vomiting	INTRACTABLE VOMITING	NOT RELATED
					10	Nervous system disorders	Headache	HEADACHE	POSSIBLE
					35	Investigations	Weight decreased	WEIGHT LOSS	NOT RELATED
					24	Gastrointestinal disorders	Nausea	NAUSEA	NOT RELATED
					10	Nervous system disorders	VIIth nerve paralysis	SEVENTH CRANIAL NERVE PALSY	NOT RELATED
					33	Metabolism and nutrition disorders	Dehydration	DEHYDRATION	NOT RELATED
					24	Gastrointestinal disorders	Vomiting	VOMITING	NOT RELATED
					32	Gastrointestinal disorders	Diarrhoea	DIARRHEA	NOT RELATED

A brief patient narrative of a patient with cranial nerve disorder follows.

> **TR701-112-128-665** was a 27 year old White female born 'legally blind in her left eye" with cellulitis/erysipelas of the abdomen who developed seventh cranial nerve palsy

noted as mild left sided facial droop on Study Day 9. The investigator noted clinical success of the study drug tedizolid phosphate for treatment of the ABSSSI. On Day 25, the symptoms evolved to right facial droop and weakness. In addition, severe nausea and vomiting occurred on Day 24 requiring hospitalization on Day 33. No ophthalmic or visual TEAEs were reported. Further evaluations, including a brain MRI, were not diagnostic. The Applicant reports that diagnostic evaluations including a CT scan and MRI were not conclusive. Per the Applicant, symptoms improved over time, however the event was considered ongoing at approximately 4 months after onset.

In addition, there was one patient in the tedizolid phosphate arm who discontinued study drug due to physician decision for an adverse event of 'decreased grip strength'.

TR701-112-128-159 is an 18 year old Black or African American Male with a history of myopia and headaches who presented with a major cutaneous abscess on the right knee. The patient developed decreased grip strength of the right hand approximately 5 hours after taking the first oral dose of study drug on Study Day 1. This TEAE lasted approximately 2 hours and resolved without any action taken. The patient took the second dose of study drug approximately six hours after the first dose. The patient recovered and the Investigator determined that this adverse event was mild and possibly related to the study drug.

Specialized safety assessments incorporated into select studies with tedizolid phosphate suggest that treatment emergent adverse events potentially related to neurologic disorders are similar to the comparator, linezolid, at the proposed dose (200 mg) and duration (6 days). While peripheral neuropathies have been reported in patients treated with linezolid longer than the maximum recommended duration of 28 days, tedizolid phosphate has only been studied for 21 days. Within the context of the current study design, the association of tedizolid phosphate and neurologic TEAEs at higher doses and longer durations cannot be assessed.

7.3.5.2 Optic Nerve Disorders

The Applicant conducted preclinical studies which supported the safety of tedizolid phosphate with respect to ophthalmic disorders. As described previously, the Applicant conducted a 9-month vehicle-controlled rat neurotoxicology study which showed no evidence of functional or histopathologic optic or peripheral neuropathic lesions at systemic exposures equivalent to up to 8-fold that observed in humans at the therapeutic dose of 200 mg once daily.

The Applicant conducted a Phase 1 study (TR701-110) in volunteers where detailed assessments of ophthalmic and peripheral neurologic function were conducted. No associated risk of optic neuropathy was seen with administration of 200 mg once daily tedizolid phosphate for 10 days after 4-6 weeks of follow-up after the screening examination. In addition, the FDA Division of Transplant and Ophthalmology Products was consulted during the IND Phase of

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drug development to comment on study TR701-110. They concluded that there are no clinically significant treatment-related effects on visual acuity, slit lamp examination, optic nerve, color vision, or visual field identified in this clinical trial.

MedRA SMQ

MedRA SMQs were conducted for optic nerve disorders in the Phase 2 and Phase 3 studies. Results were similar and low for tedizolid phosphate and linezolid. In Phase 3 studies, there were 2 (0.3%) patients in the tedizolid phosphate arm and 1 (0.15%) in the linezolid arm with at least 1 optic nerve disorder TEAE (Table 7.3.5-5). These events included visual acuity reduced and visual impairment.

Table 7.3.5-5: Optic Nerve Disorders SMQ for Phase 3 Studies

			Phase 3 Studies	
SMQ Name	*Body System or Organ Class*	*Dictionary-Derived Term*	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Optic nerve disorders (SMQ)	Eye disorders		2 (0.3%)	1 (0.2%)
		Visual acuity reduced	1 (0.2%)	1 (0.2%)
		Visual impairment	1 (0.2%)	0 (0.0%)

Details of the optic nerve related TEAEs noted are included in the Table 7.3.5-6. Brief patient narratives follow the table.

Table 7.3.5-6: Listing of selected patients with optic nerve related Treatment Emergent Adverse Events.

Analysis Unique Subject ID	Age	Sex	Country	Actual Treatment	Study Day of Start of Adverse Event	Body System or Organ Class	Dictionary-Derived Term	Reported Term for the Adverse Event	Causality
TR701-112-105-042	24	F	USA	TR-701 FA 200mg	39	Infections and infestations	Endophthalmitis	ENDOPHTHALMITIS	NOT RELATED
					35	Infections and infestations	Endophthalmitis	ENDOPHTHALMITIS RIGHT EYE	NOT RELATED
					26	Eye disorders	Visual acuity reduced	DECREASED VISION RT EYE	NOT RELATED
TR701-113-287-223	78	F	RUS	Linezolid 1200mg	6	Gastrointestinal disorders	Abdominal pain upper	EPIGASTRIC PAIN	DEFINITE
					6	Nervous system disorders	Headache	HEADACHE	DEFINITE
					6	Eye disorders	Visual acuity reduced	BILATERAL REDUCED VISUAL ACUITY	DEFINITE
					6	Reproductive system and breast disorders	Vulvovaginal burning sensation	BURNING SENSATION IN THE VAGINA	DEFINITE
TR701-113-289-370	56	M	RUS	TR-701 FA 200mg	2	Eye disorders	Visual impairment	SEEING SPOTS BOTH EYES	NOT RELATED

TR701-112-105-042 was a 24 year old white female with a history of IV drug use, asthma, headaches, insomnia, depression and anxiety who developed an infected wound of the right foot. The patient developed decreased vision to the right eye 26 days after study drug (tedizolid phosphate) initiation. The patient subsequently developed endophthalmitis to the right eye 35 days after study drug initiation. This adverse event was classified as severe and not related to the study drug by the Investigator. The patient did not recover from endophthalmitis during the study.

TR701-113-287-223 is a 78 year old white female with history of bilateral cataracts and intraocular lens implants, dehydration, hypertension with cellulitis/erysipelas of the right knee/ankle. The patient developed bilateral reduced visual acuity on study day 6 after receiving linezolid. The patient recovered after study drug discontinuation. The Investigator classified this event as mild, definitely related to the study drug, linezolid. In addition, the investigator classified the clinical response as failure due to a TEAE leading to study drug discontinuation.

TR701-113-289-370 is a 56 year old white male with coronary artery disease, cardiosclerosis, atherosclerosis, essential hypertension, alcoholic myocardiodystrophy, congestive heart failure, chronic bronchitis, pneumofibrosis, chronic toxic encephalopathy, polyneuropathy and alcohol addiction who had a left ankle and foot cellulitis. The patient reported seeing spots in both eyes on study day 2 while receiving tedizolid phosphate. The symptoms lasted three hours and resolved without any action taken. The TEAE was considered mild and not related to the study drug per the Investigator. The patient had a Snellen examination which showed improvement or no change in both eyes through the post-therapy evaluation.

In addition, there was one patient who discontinued study drug during the study due to adverse events (vision blurred and abdominal discomfort).

TR701-113-105-180 is a 51 year old white female with a history of IV drug use, hepatitis C, type 1 diabetes mellitus, smoking, hypertension, high cholesterol, and major cutaneous abscess caused by methicillin resistant *Staphylococcus aureus* who developed a major cutaneous abscess on the right leg. On study day 1, the patient developed blurry vision during the tedizolid phosphate infusion. The infusion was stopped and then restarted 15 minutes later. The blurry vision resolved the following day. This adverse event was considered mild and possibly related to the study drug by the investigator. Abdominal discomfort occurred at the same time, resolved the following day, and was considered moderate and possibly related to the study drug by the investigator. The investigator documented that the patient recovered from both adverse events.

There was one patient who received tedizolid phosphate and concomitant serotonin antagonist reporting ‘eye strain’ (dictionary derived term, asthenopia).

TR701-112-114-625 is a 70 year old white male with a history of chronic atrial fibrillation, coronary artery disease, hypertension, skin cancer, hypothyroidism, cardiomegaly, obesity, macular degeneration, intermittent constipation, shortness of breath, left femoral pseudoaneurysm, radiating right shoulder pain, night sweats, decreased appetite, cataracts, crackles at lung bases and prior MRSA surgical site infection. The patient had cellulitis/ erysipelas of the left lower leg. Prior and concomitant medications included ondansetron, Diltiazem, enoxaparin subcutaneous, furosemide, docusate sodium, levothyroxine, Zestoretic, metoprolol, potassium chloride, diphenhydramine, hydrochlorothiazide, lisinopril, Lutein, aspirin, and acetaminophen. On study day 1, the patient developed facial flushing and recovered in 2 days. This adverse event was considered moderate severity and possibly related to the study drug by the Investigator. The patient was treated with diphenhydramine for the flushing. The patient developed eye strain on study day 1 which lasted one day. This adverse event was considered

mild and not related to the study drug by the Investigator. The patient recovered from this adverse event without additional action taken.

In patients treated with linezolid, visual blurring has been reported in some patients treated for less than 28 days. The cases described above suggest that some patients treated with tedizolid phosphate may be also experience visual disturbances while on treatment.

Snellen Examination

Visual acuity assessments were conducted for TR701-126 and TR701-113. The Applicant defined categories of vision loss as defined in ICD-9-CM, which is based on recommendations of the WHO and International Council of Ophthalmology (see Table 7.3.5-7 below).

Table 7.3.5-7: Range of Visual Acuity Loss

Vision Category	Snellen Decimal	Examples of possible Snellen Ratios
Normal Vision	≥0.8	20/12, 20/15, 20/20, 20/25
Near-Normal Vision	<0.8 and ≥0.32	20/30, 20/40, 20/60
Moderate Low Vision	<0.32 and ≥0.125	20/70, 20/80, 20/100
Severe Low Vision	<0.125 and ≥0.05	20/200, 20/400
Profound Low Vision or Worse than Profound Low Vision	<0.05	NA

Note: All Snellen ratios will be converted to "Snellen Decimals." For example, 20/12=1.67 and 20/15=1.33. Categories of vision loss as defined in ICD-9-CM, based on recommendations of the WHO and International Council of Ophthalmology.

Source: Applicant's Statistical Analysis Plan, Table 1.

A summary of Snellen Exam results and category change by time point (48-72 hours, EOT, and PTE), as well as Worst Post-baseline in the Phase 2 and 3 trials are provided in Table 7.3.5-8.

In the Phase 2 trials, there was 1 (0.6%) patient who had improvement or no change in one eye and worsening by 2 or more categories in the other eye at EOT. There were zero patients in this category at 40 – 72 hours and PTE.

In the Phase 2 trials, the incidence of patients with worsening by 1 category in both eyes was as follows: at 48-72 hours, 5/189 (2.6%), EOT 7/175 (4.0%), and PTE 9/176 (5.1%).

In the Phase 2 trials, there were a few patients who worsening by 1 category in one eye and worsening by 2 or more categories in the other eye. At 48 – 72 hours, there were zero patients. At EOT and PTE, there was 1 (0.6%) patient each.

Finally, there were zero patients who had worsening by 2 or more categories in both eyes in the Phase 2 trials.

When worst post-baseline results of the Snellen examination were reviewed for the Phase 2 trials, the majority of the patients had 'improvement or no change in both eyes' (147/191 [77%]). The remainder had 'improvement or no change in one eye and worsening by 1 category in the other eye' (29/191 [15.2%) or 'worsening by 1 category in both eyes' (13/191 [6.8%]). Few patients had 'improvement or no change in one eye and worsening by 2 or more categories in the other eye' (1/191 [0.5%]) or 'worsening by 1 category in one eye and worsening by 2 or more categories in the other eye' (1/191 [0.5%]). There were zero patients who had worsening by 2 or more categories in both eyes.

In the Phase 3 trials, the incidence of patients with improvement or no change in both eyes was similar in both arms at 48-72 hours, (tedizolid phosphate 290/324 [89.5%]; linezolid 289/321 [90.0%]), EOT (tedizolid phosphate 277/305 [90.8%]; linezolid 261/304 [85.9%]), and PTE (tedizolid phosphate 189/212 [89.2%]; linezolid 237/278 [85.3%]).

The number of patients in Phase 3 trials who had improvement or no change in one eye and worsening by 1 category in the other eye was 22 (6.8%) for tedizolid phosphate and 21 (6.5%) for linezolid at 48 - 72 hours; 18 (5.9%) for tedizolid phosphate and 26 (8.6%) for linezolid at EOT; and 11 (5.2%) for tedizolid phosphate and 23 (8.3%) for linezolid at PTE.

In the Phase 3 trials, there were a few patients who had improvement or no change in one eye and worsening by 2 or more categories in the other eye. At 48 – 72 hours, there were no patients. At both EOT and PTE, there was 1 (0.3%) patient each in the linezolid arm.

In the Phase 3 trials, the incidence of patients with worsening by 1 category in both eyes in each arm was 48-72 hours, (tedizolid phosphate 11/324 [3.4%]; linezolid 11/321 [3.4%]), EOT (tedizolid phosphate 9/305 [3.0%]; linezolid 15/304 [4.9%]), and PTE (tedizolid phosphate 12/212 [5.7%]; linezolid 16/278 [5.8%]).

In the Phase 3 trials, there were a few patients who worsening by 1 category in one eye and worsening by 2 or more categories in the other eye. At 48 – 72 hours, there was 1 (0.3%) patient in the tedizolid phosphate arm. At EOT, there was 1 (0.3%) patient each in the tedizolid phosphate and linezolid arms. At PTE, there was 1 (0.4%) patient in the linezolid arm.

Finally, there were zero patients in both arms who had worsening by 2 or more categories in both eyes in the Phase 3 trials.

When worst post-baseline results of the Snellen examination were reviewed for the Phase 3 trials, the majority of the patients had 'improvement or no change in both eyes' (tedizolid phosphate 268/324 [82.7%]; linezolid 262/323 [81.1%]). The remainder had 'improvement or no change in one eye and worsening by 1 category in the other eye' (tedizolid phosphate 30/324 [9.3%]; linezolid 32/323 [9.9%]) or 'worsening by 1 category in both eyes' (tedizolid phosphate 24/324 [7.4%]; linezolid 26/323 [8.0%]). Few patients had 'improvement or no change in one eye and worsening by 2 or more categories in the other eye' (tedizolid phosphate 1/324 [0.3%]; linezolid 1/323 [0.3%]) or 'worsening by 1 category in one eye and worsening by 2 or more categories in the other eye' (tedizolid phosphate 1/324 [0.3%]; linezolid 2/323 [0.6%]). There were zero patients who had worsening by 2 or more categories in both eyes.

In the Phase 2 trials, the incidence of patients with improvement or no change was as follows: at 48-72 hours, 166/189 (87.8%), EOT 153/175 (87.4%), and PTE 144/176 (81.8%).

The number of patients in Phase 2 trials who had improvement or no change in one eye and worsening by 1 category in the other was 18/189 (9.5%) at 48 – 72 hours, 13/175 (7.4%) at EOT and 22/176 (12.5%) at PTE.

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Table 7.3.5-8: Summary of Snellen Exam by Time point and Worst Post Baseline in Phase 2 and 3 Trials.

	Phase 2 Studies	Phase 3 Studies	
	Tedizolid phosphate (≥200mg) n=388	Tedizolid phosphate (200mg) n=662	Linezolid (1200mg) n=662
Visit/ Category Change from Baseline			
48-72 HOUR (N)	**189**	**324**	**321**
Improvement or no change in both eyes	166 (87.8%)	290 (89.5%)	289 (90.0%)
Improvement or no change in one eye and worsening by 1 category in the other eye	18 (9.5%)	22 (6.8%)	21 (6.5%)
Improvement or no change in one eye and worsening by 2 or more categories in the other eye	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worsening by 1 category in both eyes	5 (2.7%)	11 (3.4%)	11 (3.4%)
Worsening by 1 category in one eye and worsening by 2 or more categories in the other eye	0 (0.0%)	1 (0.3%)	0 (0.0%)
Worsening by 2 or more categories in both eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)
EOT (N)	**175**	**305**	**304**
Improvement or no change in both eyes	153 (87.4%)	277 (90.8%)	261 (85.9%)
Improvement or no change in one eye and worsening by 1 category in the other eye	13 (7.4%)	18 (5.9%)	26 (8.6%)
Improvement or no change in one eye and worsening by 2 or more categories in the other eye	1 (0.6%)	0 (0.0%)	1 (0.3%)
Worsening by 1 category in both eyes	7 (4.0%)	9 (3.0%)	15 (4.9%)
Worsening by 1 category in one eye and worsening by 2 or more categories in the other eye	1 (0.6%)	1 (0.3%)	1 (0.3%)
Worsening by 2 or more categories in both eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)
PTE (N)	**176**	**212**	**278**
Improvement or no change in both eyes	144 (81.8%)	189 (89.2%)	237 (85.3%)
Improvement or no change in one eye and worsening by 1 category in the other eye	22 (12.5%)	11 (5.2%)	23 (8.3%)
Improvement or no change in one eye and worsening by 2 or more categories in the other eye	0 (0.0%)	0 (0.0%)	1 (0.4%)
Worsening by 1 category in both eyes	9 (5.1%)	12 (5.7%)	16 (5.7%)
Worsening by 1 category in one eye and worsening by 2 or more categories in the other eye	1 (0.6%)	0 (0.0%)	1 (0.4%)
Worsening by 2 or more categories in both eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worst Postbaseline (N)	**191**	**324**	**323**
Improvement or no change in both eyes	147 (77.0%)	268 (82.7%)	262 (81.1%)
Improvement or no change in one eye and worsening by 1 category in the other eye	29 (15.2%)	30 (9.3%)	32 (9.9%)
Improvement or no change in one eye and worsening by 2 or more categories in the other eye	1 (0.5%)	1 (0.3%)	1 (0.3%)
Worsening by 1 category in both eyes	13 (6.8%)	24 (7.4%)	26 (8.1%)
Worsening by 1 category in one eye and worsening by 2 or more categories in the other eye	1 (0.5%)	1 (0.3%)	2 (0.6%)
Worsening by 2 or more categories in both eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)

N=number of patients with at least one non-missing baseline and post-baseline value.

Changes in Snellen Examination categories were similar for tedizolid phosphate and linezolid at 48-72 hours, EOT, PTE and any time point post-baseline. These findings indicate that changes in visual acuity known to occur with linezolid treatment may also be associated with tedizolid phosphate.

In summary, peripheral and optic neuropathies have been reported in patients treated with linezolid, particularly when treatment exceeds the maximum recommended duration of 28 days. Some patients report visual blurring when treated with linezolid for less than 28 days. Nonclinical studies for tedizolid phosphate suggested no evidence of functional or histopathologic optic or peripheral neuropathic lesions with exposure greater than the human dose. Specialized safety assessments incorporated into select studies with tedizolid phosphate suggest that treatment emergent adverse events potentially related to ophthalmic or peripheral neuropathy were similar to the comparator, linezolid. Standard MedRA Queries for Peripheral Neuropathy and Optic Nerve Disorders revealed the incidence of Treatment Emergent Adverse Events to be similar and low in both the tedizolid phosphate and linezolid arms of the Phase 3 trials. In the drug development program, patients were not exposed to tedizolid phosphate for longer than 28 days, the time period when peripheral and ophthalmic neuropathy has been primarily reported for linezolid. Within the context of the current study design, the association of tedizolid phosphate and ophthalmic TEAEs at higher doses and longer durations cannot be assessed.

7.3.5.3 Myelosuppression

Myelosuppression, including anemia, leukopenia, pancytopenia, and thrombocytopenia, is known to occur in patients receiving linezolid, particularly when treatment is given for longer than 2 weeks.

Preclinical studies examined immunotoxicity. The results indicate that, at doses associated with TR-700 exposures 4-8 times the human therapeutic exposure, TR-701 is immunotoxic. However, results of the recovery study in the 3-month oral toxicology study indicate that the immunotoxicity appears to be reversible. Because TR-701 was immunotoxic in animals studied at high doses, immune cells may require monitoring in patients if dosed at longer durations. Additional information can be found in the Preclinical Pharmacology/ Toxicology review.

The Applicant conducted a randomized, placebo or active controlled double blind Phase 1 study (TR701-101), where subjects received tedizolid phosphate, once daily, at 200, 300, or 400 mg doses for 21 days. (See Table 7.3.5-9.)

Table 7.3.5-9: Study Drug Exposure for TR701-101.

Drug	Number of Subjects	Dose/ Duration	Total Exposure per Subject		
			Mean	Median	Range
Part A (Single Ascending Dose)					
Placebo	10	0 mg	0 mg	0 mg	NA
TR-701	6	200 mg	200 mg	200 mg	NA
TR-701	6	400 mg	400 mg	400 mg	NA
TR-701	6	600 mg	600 mg	600 mg	NA
TR-701	6	800 mg	800 mg	800 mg	NA
TR-701	6	1200 mg	1200 mg	1200 mg	NA
Part B (Multiple Ascending Dose)					
Placebo	8	0 mg QD/ 21 days	0 mg	0 mg	NA
TR-701	8	200 mg QD/ 11 to 21 days	3950 mg	4200 mg	2200 mg to 4200 mg
TR-701	8	300 mg QD/ 21 days	6300 mg	6300 mg	NA
TR-701	8	400 mg QD/ 10 to 21 days	7700 mg	8400 mg	5600 mg to 8400 mg
Linezolid	8	600 mg BID/ 18 to 21 days	24675 mg	25200 mg	21000 mg to 25200 mg

Source: Listings 16.2.5-2a and 16.2.5-2b
NOTE: NA = Not applicable.

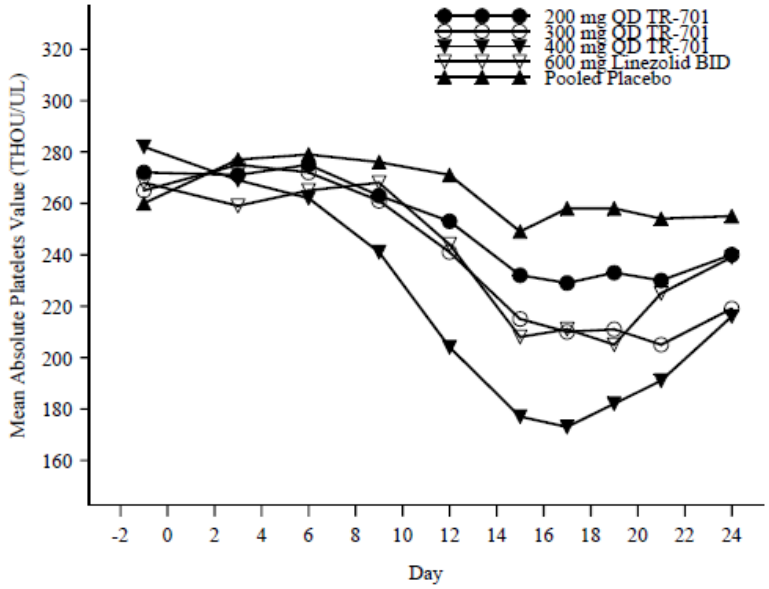
Source: Clinical Study Report for TR701-101, Table 12-1.

Several hematology parameters including platelets, absolute neutrophils, reticulocytes, red blood cells and white blood cells, decreased from baseline over time, particularly at the higher doses. Specific findings for laboratory parameters measured in TR701-101 follow.

Platelets: There was a decrease in platelets which appeared approximately 7 days after dosing and plateaued after about 2 weeks, particularly in subjects receiving the highest multiple dose of tedizolid phosphate (400 mg QD) (Figure 7.3.5-1). Significant changes in platelet count from baseline (>20% change) were noted in all 8 subjects receiving 400 mg tedizolid phosphate. Significant changes in platelet count were noted in 6 subjects receiving 300 mg tedizolid phosphate, 4 subjects receiving 200 mg tedizolid phosphate, 1 subject receiving placebo, and 5 subjects receiving 600 mg linezolid BID. One patient receiving TR701 had a platelet count of <120 thousand/µL, the pre-specified criteria for early signs of myelosuppression.

Figure 7.3.5-1 Mean platelet counts over time

Figure 12-1 Mean Platelet Counts Over Time for Part B (Multiple Ascending Dose)



Source: Figure 14.3.4-1b
Note: Normal range = 150 thousand/µL to 425 thousand/µL

Source: Clinical Study Report for TR701-101, Figure 12-1.

Absolute Neutrophil Count: There was a decline in mean ANCs in all treatment groups which was more pronounced in the subjects receiving tedizolid phosphate at 400 mg. The number of subjects which >40% decrease in ANC was 3 in the group receiving tedizolid phosphate 400 mg. In comparison, the number of subjects with >40% decrease in ANC was 2 in the group perceiving 200 mg tedizolid phosphate, and 1 in each group receiving 300 mg tedizolid phosphate or placebo. There were 5 subjects in the linezolid arm who had a >40% decrease in ANC. In all treatment groups, mean ANCs were increasing toward baseline (Figure 7.3.5-2).

Figure 7.3.5-2 Mean absolute neutrophil values over time

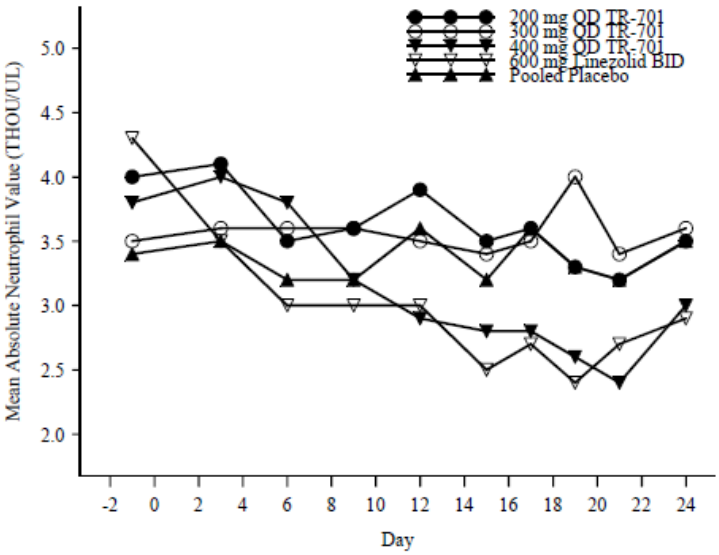


Figure 14.3.4-2b Mean Absolute Neutrophil Values over Time for Part B

Study Population: Randomized Safety

NOTE: Subjects were dosed for 21 days

Source: Clinical Study Report for TR701-101, Figure 14.3.4-2b.

Red Blood Cell Count: In all treatment groups, there was a downward trend of RBC counts over time. The decrease was greater in subjects receiving 400 mg tedizolid phosphate or 600 mg linezolid bid. This decrease was similar for both groups.

White Blood Cell Count: There was a downward trend of WBC counts in subjects receiving 200 mg tedizolid phosphate, 400 mg tedizolid phosphate, and 600 mg linezolid. The decrease was greater in subjects receiving 400 mg tedizolid phosphate or 600 mg linezolid bid. This decrease was similar for both groups.

Results of the Phase 1 trial (TR701-101) suggest that the risk of myelosuppression is comparable to placebo when tedizolid phosphate is dosed at 200 mg for 6 days. However, there was a decreasing trend in platelets, white blood cell counts, neutrophils and red blood cell counts at higher doses and longer durations of treatment.

In addition, the Applicant collected data on hematology parameters during the Phase 2 and 3 trials. Clinically significant changes in laboratory values from baseline were similar in the tedizolid phosphate and linezolid arms at the proposed dose and duration. Details of the analyses conducted on laboratory parameters can be found in Section 7.4.2 Laboratory Findings.

Myelosuppression, including anemia, leukopenia, pancytopenia, and thrombocytopenia, is known to occur in patients receiving linezolid, particularly when treatment is given for longer than 2 weeks. Nonclinical studies showed that TR-701 was immunotoxic in animals at high doses. The Applicant conducted a randomized, placebo or active controlled double blind Phase 1 study (TR701-101), where subjects received tedizolid phosphate, once daily, at 200, 300, or 400 mg doses for 21 days. Results suggest that the risk of myelosuppression is comparable to placebo when tedizolid phosphate is dosed at 200 mg for 6 days. However, there was a decreasing trend in platelets, white blood cell counts, neutrophils and red blood cell counts at higher doses and longer durations of treatment with tedizolid phosphate. In addition, the Applicant collected data on hematology parameters during the drug development program including the Phase 2 and Phase 3 trials. Potentially clinically significant changes in platelets, white blood cell counts, neutrophils, and red blood cell counts were similar for tedizolid phosphate and linezolid in the Phase 3 trials. Within the context of the current study design, the association of tedizolid phosphate and myelosuppression at higher doses and longer durations cannot be assessed.

7.3.5.4 MAO-related drug interactions

There are potential interactions with linezolid which may elevate blood pressure. Current prescribing information indicates that linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., epinephrine, norepinephrine), and dopaminergic agents (e.g., dopamine, dobutamine).

The Applicant conducted preclinical and Phase 1 studies to examine potential drug interactions with tedizolid phosphate. Additional details can be found in discipline-specific reviews for Preclinical Pharmacology/ Toxicology and Clinical Pharmacology.

The effects of tedizolid phosphate and central serotonergic potentiation and blood pressure were examined in animal models. In a mouse head-twitch experiment and a tyramine-challenge experiment in rats, linezolid doses comparable to the human therapeutic dose produced positive results (increased head twitch or increased mean arterial pressure), but tedizolid phosphate doses associated with plasma tedizolid C_{max} and AUC values greatly exceeding the equivalent clinical therapeutic exposure values did not.

The Applicant conducted two Phase 1 studies (TR701-105 and TR701-114) to examine potential drug-drug interactions.

TR701-105 was a randomized, placebo controlled, crossover, double blind study which evaluated the effect of tedizolid phosphate on blood pressure response to tyramine. Healthy subjects were treated with a single 100-mg tyramine challenge, followed by 2 treatment periods

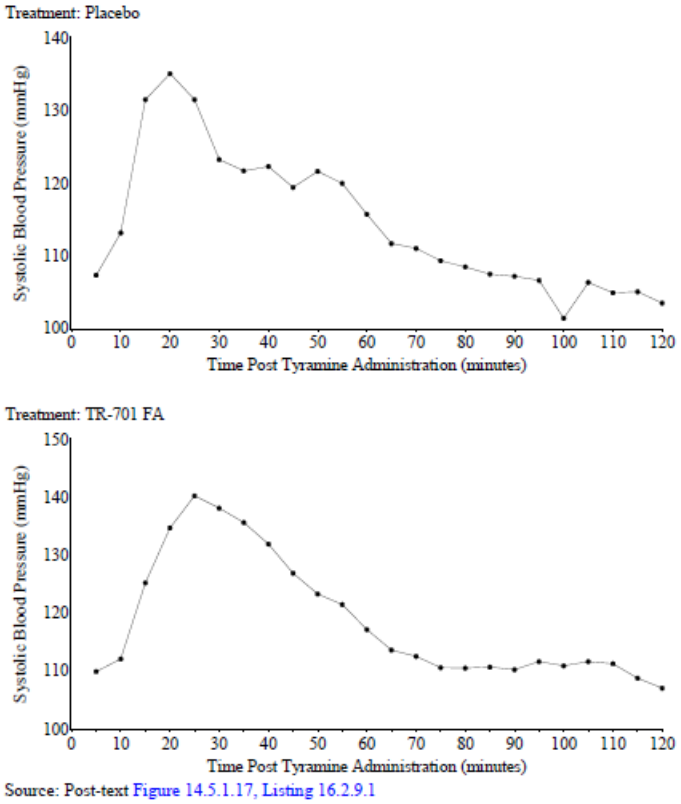
Reference ID: 3521547

where subjects received either tedizolid phosphate 200 mg or placebo daily for 14 days with ascending doses of tyramine.

TYR_{30} was defined as the midpoint between the log-transformed dose of tyramine at which a ≥30 mm Hg increase in systolic blood pressure (SBP) was observed and the previous (next lower) dose of tyramine. The tyramine sensitivity factor (TSF) was defined as the ratio of TYR_{30} following placebo administration divided by TYR_{30} following tedizolid phosphate administration. Both TYR_{30} and TSF were also calculated using the actual dose of tyramine on the day that SBP increased by ≥30 mmHg.

The Applicant observed blood pressure responses and measured the TYR_{30}, the tyramine dose required to cause an increase in SBP of ≥30 mmHg from pre-dose baseline. On the day when TYR_{30} was reached, the mean SBP reached a maximum at 20-25 minutes after tyramine administration and decreased over the next hour. This finding was similar for the placebo (n=7) and tedizolid phosphate (n=24) groups (Figure 7.3.5-3).

Figure 7.3.5-3: Mean systolic blood pressure values (mmHg) versus time post-tyramine administration on day the Tyr_{30} is reached by treatment.



Source: Clinical Study Report for TR701-105, Figure 11-2.

In the PP analysis set (N=7), the median TYR_{30} was 100 mg lower with tedizolid phosphate compared to placebo (325 mg versus 425 mg, respectively) using actual tyramine doses, as well as interpolated values (399.22 mg, tedizolid phosphate and 298.96 mg, placebo).

Six of the 7 subjects in the PP Analysis Set had TSF <2 (range 0.76 to 1.46). One subject had a TSF of 2.1, using the actual tyramine dose. In the primary analysis (PD Analysis Set), the tyramine sensitivity geometric mean ratio of 1.29 (90% CI, 0.94 to 1.76) was below the predetermined TSF ≥2, indicative of a clinically relevant positive pressor response. The upper limit of the 90% CI was <2. In all analyses, estimates of the tyramine sensitivity ratio (either mean TSF or geometric mean ratio, placebo/tedizolid phosphate) and upper limits of 90% CI were <2.

The number of TEAEs after dosing was 28/29 (96.6%) and 25/28 (89.3%) for the tedizolid phosphate and placebo arms respectively (Table 7.3.5-10). The TEAE of palpitations (tedizolid phosphate, 21/29 [72.4%]; placebo, 13/28 [46.4%]) is most likely related to the tyramine challenge. Reasons for study drug discontinuation included palpitations in three patients and chest pain with dyspnea in 1 patient, all of whom were receiving tedizolid phosphate.

Reference ID: 3521547

Table 7.3.5-10: TEAE in Study TR701-105

System Organ Class Preferred Term	Number of Distinct Subjects (%) TR-701 FA (N=29)	Placebo (N=28)	Overall (N=30)
Subjects with at least one TEAE	28 (96.6)	25 (89.3)	29 (96.7)
Cardiac Disorders	21 (72.4)	13 (46.4)	25 (83.3)
Palpitations	21 (72.4)	13 (46.4)	25 (83.3)
Gastrointestinal Disorders	16 (55.2)	14 (50.0)	23 (76.7)
Nausea	7 (24.1)	9 (32.1)	14 (46.7)
Abdominal Pain	7 (24.1)	5 (17.9)	11 (36.7)
Vomiting	6 (20.7)	4 (14.3)	10 (33.3)
Diarrhoea	6 (20.7)	2 (7.1)	8 (26.7)
Dyspepsia	3 (10.3)	0	3 (10.0)
Constipation	0	2 (7.1)	2 (6.7)
Nervous System Disorders	12 (41.4)	16 (57.1)	22 (73.3)
Headache	9 (31.0)	12 (42.9)	19 (63.3)
Dizziness	4 (13.8)	8 (28.6)	11 (36.7)
Paraesthesia	2 (6.9)	5 (17.9)	7 (23.3)
Tremor	0	2 (7.1)	2 (6.7)
General Disorders and Administration Site Conditions	11 (37.9)	13 (46.4)	17 (56.7)
Non-Cardiac Chest Pain	6 (20.7)	6 (21.4)	8 (26.7)
Chest Pain	4 (13.8)	4 (14.3)	7 (23.3)
Fatigue	0	5 (17.9)	5 (16.7)
Application Site Irritation	0	2 (7.1)	2 (6.7)
Skin and Subcutaneous Tissue Disorders	7 (24.1)	6 (21.4)	11 (36.7)
Skin Irritation	3 (10.3)	4 (14.3)	7 (23.3)
Hyperhidrosis	4 (13.8)	1 (3.6)	4 (13.3)
Musculoskeletal and Connective Tissue Disorders	4 (13.8)	7 (25.0)	9 (30.0)
Myalgia	1 (3.4)	3 (10.7)	4 (13.3)
Muscle Spasms	2 (6.9)	0	2 (6.7)
Respiratory, Thoracic and Mediastinal Disorders	6 (20.7)	4 (14.3)	7 (23.3)
Dyspnoea	4 (13.8)	4 (14.3)	6 (20.0)
Infections and Infestations	4 (13.8)	2 (7.1)	6 (20.0)
Vaginal Infection	3 (10.3)	0	3 (10.0)
Vascular Disorders	4 (13.8)	1 (3.6)	5 (16.7)
Hot Flush	4 (13.8)	1 (3.6)	5 (16.7)
Psychiatric Disorders	2 (6.9)	1 (3.6)	3 (10.0)
Ear and Labyrinth Disorders	0	2 (7.1)	2 (6.7)

Source: Post-text Table 14.3.1.5, Listing 16.2.7.1
Note: Events were coded using MedDRA (Version 13.1), TEAE=treatment-emergent adverse event. Within each group, subjects reporting a TEAE more than once are counted only once by preferred term and system organ class. TEAEs occurring in ≥2 subjects by system organ class or preferred term occurring in either treatment group are included.

Source: Clinical Study Report for TR701-105, Table 12.3.

The study noted minor increases in tyramine sensitivity with tedizolid phosphate (measured by changes in systolic blood pressure after oral tyramine administration) when compared with placebo in healthy individuals. As per FDA recommendations, the tyramine challenge was conducted under fasted conditions. The Applicant reports that sensitivity to tyramine as part of a meal is expected to be decreased approximately 2-fold. A typical tyramine-rich meal is expected to contain no more than 40 mg tyramine. It is not clear whether repeated doses of tedizolid phosphate 200 mg would produce a clinically meaningful pressor response to a tyramine-rich meal.

TR701-114 was a randomized, placebo controlled, double blind crossover trial examining pressor effects of pseudoephedrine (PSE) when administered with tedizolid phosphate in healthy adult volunteers. Eligible subjects were randomized to 1 of 2 possible treatment sequences on Study Day 1. Subjects received oral 200 mg tedizolid phosphate or placebo once daily for 5 days during each treatment period, with a 2-day washout between periods (72 hours between doses). On Study Day 5 of each treatment period, subjects received oral 60 mg PSE, a typical therapeutic dose, at the same time as study drug.

The Applicant observed no statistically significant differences in maximum PSE-induced changes in systolic blood pressure, diastolic blood pressure, and heart rate between tedizolid phosphate and placebo-treated groups (p >0.05) (Table 7.3.5-11 below)

Table 7.3.5-11: Maximum changes in blood pressure and heart rate after pseudoephedrine administration with tedizolid phosphate and placebo.

	LS Mean		Difference in LS Means		
Maximum Change	TR-701 FA N=18	Placebo N=18	TR-701 FA - Placebo	95% CI	p-value
Systolic BP (mmHg)	11.6	12.1	-0.5	[-3.8, 2.7]	0.7309
Diastolic BP (mmHg)	6.7	6.8	-0.1	[-2.0, 1.7]	0.8966
Heart Rate (beats/min)	13.6	15.2	-1.6	[-3.8, 0.7]	0.1689

Source: Post-text Table 14.5.1.3, Listing 16.2.9.1.
Abbreviations: BP=blood pressure; CI=confidence interval; LS=least squares; PD=pharmacodynamic; PSE=pseudoephedrine.
Notes: Baseline is defined as the average Day 5 predose measurement for each period. LS means, differences, and 95% CIs are derived from an analysis of variance model with average maximum change as the dependent variable and average baseline value, treatment (TR-701 FA or placebo), period, and sequence as fixed effects, and subject nested within sequence as a random effect.

Source: Clinical Study Report for TR701-114, Table 11.6.

In addition, the Applicant observed no PK or PD drug-drug interaction between tedizolid phosphate and PSE.

The number of subjects with at least one TEAE was 4/18 (22.2%) and 5/18 (27.8%) in the tedizolid phosphate and placebo arms, respectively. In each arm, there was one patient (5.6%) who had a TEAE of 'headache'. In the tedizolid phosphate arm, one subject had a TEAE of 'anxiety'. In the placebo arm, one patient had a TEAE of 'night sweats'. Preliminary results suggest that tedizolid phosphate administrations has minimal potentiation of PSE vasopressor effect in healthy individuals.

Note that in the current linezolid label (Revised 01/2014), the mean maximum increases in systolic blood pressure over baseline was 32 mm Hg (range: 20–52 mm Hg) and 38 mm Hg

(range: 18–79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

Phase 2 and Phase 3 trial design incorporated exclusion of patients on MAOIs, SSRIs, SNRIs, tricyclic antidepressants and triptans.

Nonclinical and Phase 1 studies in healthy individuals suggest that potential MAO related drug-drug interactions with tedizolid phosphate may be less than that observed with linezolid. In nonclinical studies, a tyramine challenge in rats had no significant effect on mean arterial pressure. Results from one Phase 1 study, conducted to evaluate whether tedizolid phosphate potentiates the MAO-mediated pressor response to pseudoephedrine HCl (TR701-114), suggest that there is minimal drug-drug interaction in healthy individuals. Another Phase 1 study, conducted to evaluate sensitivity to tyramine (TR701-105), showed minimal increases in blood pressure response with more TEAEs of palpitations for tedizolid phosphate versus placebo. MAO-related drug interactions were not assessed in Phase 2 and Phase 3 trials due to study design and patient exclusion criteria. Based on the available data, possible MAO related drug interactions in a clinically relevant population cannot be excluded.

7.3.5.5 Serotonergic syndrome

Current prescribing information for linezolid indicates that patients taking drugs with serotonergic potential should take the drug only if no other therapies are available, and to discontinue serotonergic drugs and monitor for serotonergic syndrome. Additional details regarding serotonergic drug –drug interactions can be found in Section 4.4 and the Clinical Pharmacology Review.

As described in the previous section, the effects of tedizolid phosphate and central serotonergic potentiation and blood pressure were examined in animal models. Data from a study examining serotonergic brain activity in a murine behavioral model suggest no increase in head twitch rates at tedizolid phosphate exposures equivalent to 30 times the human therapeutic dose.

Serotonergic drug interactions were not assessed in Phase 2 and Phase 3 trials due to study design and patient exclusion criteria. However, there were a few individuals taking concomitant $5HT_3$ antagonists.

In the Phase 2 trials, there were 12 patients taking concomitant serotonin antagonists. There were 2/662 (0.5%) patients with concomitant serotonin antagonists and at least one TEAE in the Phase 2 trials (Table 7.3.5-12). One patient had a TEAE of ‘blood pressure increased’. Irrespective of concomitant medications, there was one patient in the Phase 2 trials who had a TEAE of ‘palpitations’.

In the Phase 3 trials, the number of patients taking concomitant serotonin antagonists was small (tedizolid phosphate [10/662, (1.5%)], linezolid [7/662, (1.1%)]). In these individuals, the number of patients with concomitant ($5HT_3$) antagonists and at least one TEAE was similar in the tedizolid phosphate and linezolid arms (8/662 [1.2%] versus 5/662 [0.8%]) (Table 7.3.5-12). None of the patients in this subset had a TEAE of palpitations or blood pressure increased. One patient in the tedizolid phosphate arm had a TEAE of flushing. Irrespective of concomitant medications, there was one patient in the tedizolid phosphate arm and 2 patients in the linezolid arm with a TEAE of 'palpitations'.

Table 7.3.5-12: Number of patients with concomitant serotonin ($5HT_3$) antagonists and at least one TEAE

		Phase 2 Studies	Phase 3 Studies	
Body System or Organ Class	*Dictionary-Derived Term*	**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid 1200mg, n=662**
Number of patients with concomitant serotonin ($5HT_3$) antagonists and at least one TEAE		2 (0.5%)	8 (1.2%)	5 (0.8%)
Eye disorders		0 (0.0%)	1 (0.2%)	0 (0.0%)
	Asthenopia	0 (0.0%)	1 (0.2%)	0 (0.0%)
Gastrointestinal disorders		2 (0.5%)	4 (0.6%)	5 (0.8%)
	Abdominal pain	1 (0.3%)	0 (0.0%)	1 (0.2%)
	Constipation	0 (0.0%)	2 (0.3%)	1 (0.2%)
	Diarrhoea	0 (0.0%)	2 (0.3%)	1 (0.2%)
	Nausea	2 (0.5%)	2 (0.3%)	4 (0.6%)
	Vomiting	1 (0.3%)	1 (0.2%)	3 (0.5%)
General disorders and administration site conditions		1 (0.3%)	0 (0.0%)	1 (0.2%)
	Chills		0 (0.0%)	1 (0.2%)
	Cyst	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Fatigue	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Pain	1 (0.3%)	0 (0.0%)	0 (0.0%)
Hepatobiliary disorders		1 (0.3%)	0 (0.0%)	0 (0.0%)
	Cholecystitis acute	1 (0.3%)	0 (0.0%)	0 (0.0%)
Infections and infestations		0 (0.0%)	4 (0.6%)	2 (0.3%)
	Abscess	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Furuncle	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Herpes simplex	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Oral candidiasis	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Osteomyelitis	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Perineal abscess	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Rash pustular	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Upper respiratory tract infection	0 (0.0%)	1 (0.2%)	0 (0.0%)
Investigations		1 (0.3%)	1 (0.2%)	0 (0.0%)
	Blood pressure increased	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Weight decreased	0 (0.0%)	1 (0.2%)	0 (0.0%)

Metabolism and nutrition disorders		0 (0.0%)	1 (0.2%)	1 (0.2%)
	Dehydration	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Hypokalaemia	0 (0.0%)	0 (0.0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders		1 (0.3%)	2 (0.3%)	0 (0.0%)
	Muscle spasms	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Muscular weakness	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Myalgia	0 (0.0%)	1 (0.2%)	0 (0.0%)
Nervous system disorders		1 (0.3%)	3 (0.5%)	2 (0.3%)
	Dizziness	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Headache	1 (0.3%)	3 (0.5%)	1 (0.2%)
	Paraesthesia	0 (0.0%)	0 (0.0%)	1 (0.2%)
	VIIth nerve paralysis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Psychiatric disorders		0 (0.0%)	2 (0.3%)	1 (0.2%)
	Anxiety	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Insomnia	0 (0.0%)	2 (0.3%)	0 (0.0%)
	Major depression	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Suicidal ideation	0 (0.0%)	0 (0.0%)	1 (0.2%)
Skin and subcutaneous tissue disorders		1 (0.3%)	3 (0.5%)	2 (0.3%)
	Cold sweat	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Dermatitis	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Pruritus	0 (0.0%)	1 (0.2%)	1 (0.2%)
	Pruritus generalised	0 (0.0%)	1 (0.2%)	1 (0.2%)
	Scab	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Skin lesion	1 (0.3%)	1 (0.2%)	0 (0.0%)
Vascular disorders		0 (0.0%)	1 (0.2%)	0 (0.0%)
	Flushing	0 (0.0%)	1 (0.2%)	0 (0.0%)

Brief narratives are included for patients with concomitant serotonin ($5HT_3$) antagonists and the following TEAEs: BP increased, muscular weakness, muscle spasms, dizziness and paresthesia. The patient (**TR701-112-128-665**) experiencing VIIth nerve paralysis and myalgia has been reported previously in this review. The patient (**TR701-112-114-625**) experiencing asthenopia, flushing, headache and herpes simplex, has also been reported previously in the review.

TR701-104-001-025 is a 55 year old white male with history insulin dependent diabetes mellitus, deep vein thrombosis, hepatitis C, left axillary cyst status post incision and

drainage who had MRSA abscess of the neck. Concomitant medications reported on the CRF included Clindaymcin, Bactrim DS, Zofran, morphine, Vicodin, aspirin, Insulin 70/30, and regular insulin. Adverse events reported included nausea on study day 0 to 6, fatigue on study day 1 to 4, increased blood pressure on study day 2 to 6, body aches on study day 3 to 6, muscular weakness on study day 3 to 7, left axillary cyst worsening on study 2 to 14, vomiting on study day 12 and nausea again on study day 12. BP measurement was 136/75 at screening. On Study Day 2, 3, and 5, BP measurements were 144/85, 156/97 and 130/81, respectively. At end of therapy, BP was 109/62 and at test of cure it was 135/78.

TR701-112-128-045 is a 51 year old white male with a history of seasonal allergies, asthma, eczema, hypertension, stress headaches, insomnia, and hepatitis C who had left elbow/forearm cellulitis/erysipelas. On study day 3, the patient developed light headedness lasting 5 minutes which was considered mild and possibly related to the study drug by the Investigator. The patient recovered without any action taken. On study day 4, the patient developed headache which lasted 2 hours which was considered mild and possibly related to the study drug by the Investigator. The patient recovered without any action taken. On study day 6, the patient developed muscle spasms which continued throughout the study. This adverse event was considered mild and not related to the study drug. On study day 7, the patient developed worsening insomnia which lasted 6 days. This adverse event was considered mild and not related to the study drug by the Investigator. The patient recovered without any action taken.

TR701-112-132-543 is a 46 year old black or African-American male with a history of type 2 diabetes mellitus, hypertension and constipation who had cellulitis/erysipelas of the left thigh and left groin. On study day 1, the patient developed vomiting lasting 7 days which was considered mild and possibly related to the study drug. The patient also developed nausea on study day 1 lasting 3 days which was considered mild and probably related to the study drug. On study day 3, the patient developed chills lasting 13 days which was considered moderate in severity and not related to the study drug. The patient recovered without any action taken. On study day 5, the patient developed tingling sensation which lasted 11 hours and was noted as mild and not related to the study drug. The patient recovered without any action taken. On study day 6, the patient developed nausea again which lasted 2 days. The event was considered moderate and not related to the study drug.

The data are limited to make definitive conclusions whether there are drug-drug interactions leading to serotonin syndrome with tedizolid phosphate. Preclinical studies suggest that tedizolid phosphate may have less potential for serotonergic syndrome in comparison to linezolid. Within the context of the current study design, possible serotonergic syndrome drug interactions in a clinically relevant population cannot be assessed.

7.3.5.6 Acidosis

Lactic acidosis has been reported in patients treated with linezolid. In TR701-101, lactic acid levels were measured at check-in, Day 3 and clinic discharge. Following multiple doses of 400 mg TR701, there was a trend toward increasing plasma L-lactate values (Figure 7.3.5-4). In 6 of the 8 subjects receiving tedizolid phosphate, plasma L-lactate levels increased 1.6 to 1.8 times baseline on Day 24. Plasma L-lactate values did not exceed the upper limit of normal. These results suggest that lactic acidosis may not be associated with tedizolid phosphate with exposures at proposed doses for 21 days in healthy individuals.

Figure 7.3.5-4 Mean Plasma L-lactate values over time

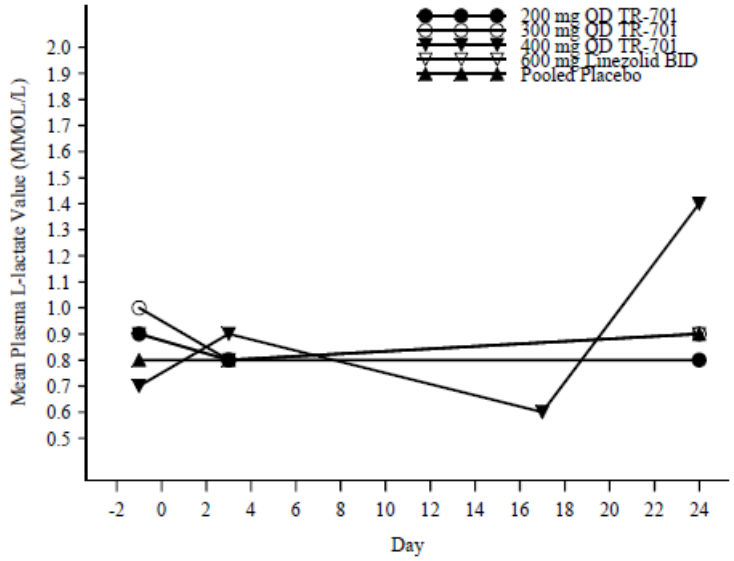


Figure 14.3.4-5 Mean Plasma L-lactate Values over Time for Part B

Study Population: Randomized Safety

NOTE: Subjects were dosed for 21 days

Source: Clinical Study Report for TR701-101, Figure 14.3.4-5.

In the Phase 2 and 3 trials, lactic acid levels were not reported and no patients were identified with substantially abnormal postbaseline bicarbonate levels. In addition, there were no patients with a treatment emergent adverse event of lactic acidosis or serum bicarbonate decreased.

In conclusion, Phase 1 studies suggest that 200 mg tedizolid phosphate may not be associated with lactic acidosis up to 21 days exposure. Within the context of the Phase 2 and 3 study design, the association of tedizolid phosphate and lactic acidosis at higher treatment doses and longer durations is unknown.

7.3.5.7 Convulsions

There have been reports of convulsions in patients treated with linezolid. In the Phase 2 and 3 trials, no treatment emergent adverse events with the dictionary derived term of ‘convulsion’ or ‘seizure’ were identified in patients receiving tedizolid phosphate or linezolid..

7.3.5.8 Hypoglycemia

Symptomatic hypoglycemia has been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid. In the Phase 2 and 3 trials, no treatment emergent adverse events with the dictionary derived term of ‘hypoglycemia’ or ‘blood sugar decreased’ were identified in patients receiving tedizolid phosphate or the comparator. In the Phase 3 trials, there was one patient in the tedizolid phosphate arm who had a TEAE of ‘blood glucose increased’. There was one patient in the linezolid arm who had a TEAE of ‘hyperglycemia’. In the Phase 2 trials, there was one patient who had a TEAE of ‘hyperglycemia’.

Clinically significant changes in glucose values from baseline were similar to the comparator for tedizolid phosphate at the proposed dose and duration. Details of the analyses conducted on laboratory parameters can be found in Section 7.4.2 Laboratory Findings. TEAEs in the subset of patients with diabetes were similar in the tedizolid phosphate and linezolid arms in the Phase 3 trials. Details can be found in Section 7.5.3 Drug-Demographic Interactions.

Due to small numbers of patients with diabetes mellitus receiving insulin or oral hypoglycemic agents, it is difficult to conclude if symptomatic hypoglycemia occurs in these patients when treated with tedizolid phosphate.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Applicant’s Approach to Eliciting Adverse Events in the Development Program

The Applicant assessed safety through Adverse Events (AEs), laboratory evaluations, vital signs (blood pressure, heart rate, respiration rate, and temperature), ECGs, and physical examinations.

The Applicant defined an AE as any untoward medical occurrence experienced by a patient, whether or not considered drug related by the Investigator. In the Phase 3 studies, adverse events were collected from the time when the ICF was signed through the Late Follow-up Visit. All AEs were recorded irrespective of whether it was volunteered, elicited, or noted on physical

Reference ID: 3521547

examination. After the first study drug administration, patients were monitored for AEs for 30 minutes.

In Phase 3 studies, the Applicant reported laboratory values, vital signs, and ECG abnormalities as AEs only if the result led to medical intervention. The Applicant did not record insufficient clinical response, efficacy, or pharmacologic action as an AE.

A central ECG laboratory evaluated and analyzed electronically transmitted ECG results. Any ECG-related safety issues were communicated to the Investigator and the Applicant. The central clinical laboratory for the Phase 3 studies identified any values outside of the reference ranges, and notified sites of values of clinical significance.

Incidence of Common Adverse Events — Assessment of Various Databases

In order to assess the incidence of common adverse events, data from the two Phase 2 studies, TR701-104 and TR701-126, and two Phase 3 studies, TR701-112 and TR701-113, were pooled. In this pooled population, patients with cSSSI or ABSSSI received ≥200 mg tedizolid phosphate once daily for an intended 5 to 7 days or 600 mg linezolid twice daily for 10 days.

The tedizolid phosphate safety database includes data from 1050 patients (1048 unique patients) enrolled in Phase 2 and 3 clinical trials as well as 438 subjects (437 unique subjects) enrolled in Phase 1 clinical trials, including both oral and IV administration routes.

Overview of Adverse Events

In the Phase 3 studies, the incidence of adverse events (after study enrollment), treatment emergent adverse events (after study drug initiation), severe treatment emergent adverse events, serious adverse events and serious treatment emergent adverse events was similar in the tedizolid phosphate and linezolid groups (Table 7.4.1-1). In the Phase 3 studies, the number of patients who had a TEAE leading to study drug discontinuation was 3 (0.45%) in the tedizolid phosphate arm and 6 (0.91%) in the linezolid arm. In addition, as described previously in the review, there were 2 (0.30%) patients in the tedizolid phosphate arm and 1 (0.15%) patient in the linezolid arm with an outcome of death.

Table 7.4.1-1: Overview of Adverse Events in Phase 2 and 3 studies

	Phase 2 Studies	Phase 3 Studies	
Category	**Tedizolid phosphate (≥200 mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
AE	221 (56.96%)	287 (43.35%)	286 (43.20%)
TEAE	221 (56.96%)	283 (42.75%)	286 (43.20%)
Severe TEAE	9 (2.32%)	13 (1.96%)	13 (1.96%)
Serious AE	7 (1.8%)	12 (1.81%)	13 (1.96%)
Serious TEAE	7 (1.8%)	12 (1.81%)	13 (1.96%)
TEAE Leading to Study Drug Discontinuation	2 (0.52%)	3 (0.45%)	6 (0.91%)
TEAE with Outcome of Death	0 (0.00%)	2 (0.30%)	1 (0.15%)

The Applicant evaluated study drug related adverse events (Table 7.4.1-2). From the data the Applicant provided for the Phase 3 studies, the incidence of AEs, TEAEs, severe TEAEs, serious AEs, serious TEAEs, and TEAEs leading to study drug discontinuation, considered related to the study drug, is slightly lower in the tedizolid phosphate arm in comparison to the linezolid arm.

Table 7.4.1-2: Overview of Adverse Events Considered Related to the Study Drug by the Applicant in Phase 2 and 3 Studies

	Phase 2 Studies	Phase 3 Studies	
Category	**Tedizolid phosphate (≥200 mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
AE	143 (36.86%)	150 (22.66%)	185 (27.95%)
TEAE	143 (36.68%)	148 (22.36%)	185 (27.95%)
Severe TEAE	3 (0.77%)	2 (0.30%)	4 (0.60%)
Serious AE	1 (0.26%)	0 (0.00%)	2 (0.30%)
Serious TEAE	1 (0.26%)	0 (0.00%)	2 (0.30%)
TEAE Leading to Study Drug Discontinuation	1 (0.26%)	2 (0.30%)	5 (0.76%)
TEAE with Outcome of Death	0 (0.00%)	0 (0.00%)	0 (0.00%)

Treatment Emergent Adverse Events with ≥1% and ≥2% Incidence in Phase 2 and 3 Studies

In the Phase 3 studies, the overall incidence of TEAEs was similar between groups (42.7% [283 patients] in the tedizolid phosphate group and 43.2% [286] in the linezolid group (Table 7.4.1-3 and Table 7.4.1-4). The highest incidence of TEAEs was in the GI disorders SOC (16.0% in the tedizolid phosphate group and 23.0% in the linezolid group).

TEAEs occurring at ≥1% in Phase 2 and 3 studies for tedizolid phosphate or linezolid included constipation, diarrhea, dyspepsia, nausea, vomiting, fatigue, abscess, cellulitis, vulvovaginal mycotic infection, dizziness, headache, insomnia, pruritus, and pruritus generalized. TEAEs occurring at ≥2% in Phase 2 and 3 studies included diarrhea, nausea, vomiting, abscess, cellulitis, dizziness, and headache (Table 7.4.1-3 and Table 7.4.1-4).

TEAEs occurring at ≥5% incidence included nausea, headache, and abscess in the tedizolid phosphate group and nausea, headache, diarrhea, and vomiting in the linezolid group. The Body System or Organ Class for TEAEs occurring at ≥1% incidence were similar in the tedizolid phosphate and linezolid arms of the Phase 3 studies. However, TEAEs occurring in the Gastrointestinal Disorder SOC was numerically lower in the tedizolid phosphate arm (16.01%) than the linezolid arm (22.96%) in the Phase 3 trials. Specifically, nausea and vomiting were lower in the tedizolid phosphate group (8.16% and 2.87%, respectively) compared to the linezolid group (12.24% and 5.59%, respectively).

In the Phase 2 studies, the overall incidence of TEAEs was 36.9% (143/388 patients) (Table 10a and b). In general, TEAEs for tedizolid phosphate occurred at a higher incidence in the Phase 2 versus the Phase 3 studies. This is likely due to the higher doses given to patients in TR-701 104 In the Phase 2 studies, treatment-emergent AEs with an incidence ≥5% occurred in the SOCs of GI Disorders (nausea, diarrhea, vomiting), Infections and Infestations (abscess), and Nervous System Disorders (headache).

Table 7.4.1-3: Treatment Emergent Adverse Events with ≥1% Incidence in Phase 2 and 3 Studies.

Body System or Organ Class	*Dictionary-Derived Term*	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200mg) n=388	Tedizolid phosphate (200mg) n=662	Linezolid (1200mg) n=662
Gastrointestinal disorders		115 (29.64%)	106 (16.01%)	152 (22.96%)
	Constipation	7 (1.8%)	9 (1.36%)	6 (0.91%)
	Diarrhea	29 (7.47%)	26 (3.93%)	35 (5.29%)
	Dyspepsia	3 (0.77%)	4 (0.60%)	8 (1.21%)
	Nausea	57 (14.69%)	54 (8.16%)	81 (12.24%)
	Vomiting	28 (7.22%)	19 (2.87%)	37 (5.59%)
General disorders and administration site conditions		31 (7.99%)	36 (5.44%)	39 (5.89%)
	Fatigue	8 (2.1%)	9 (1.36%)	12 (1.81%)
Infections and infestations		68 (17.52%)	91 (13.75%)	78 (11.78%)
	Abscess	28 (7.22%)	35 (5.29%)	26 (3.93%)
	Cellulitis	13 (3.35%)	17 (2.57%)	14 (2.11%)
	Vulvovaginal mycotic infection	3 (0.77%)	2 (0.30%)	9 (1.36%)
Nervous system disorders		48 (12.3%)	65 (9.82%)	67 (10.12%)
	Dizziness	12 (3.09%)	12 (1.81%)	14 (2.11%)
	Headache	29 (7.47%)	41 (6.19%)	39 (5.89%)
Psychiatric disorders		19 (4.90%)	17 (2.57%)	8 (1.21%)
	Insomnia	9 (2.32%)	10 (1.51%)	5 (0.76%)
Skin and subcutaneous tissue disorders		30 (7.73%)	47 (7.10%)	40 (6.04%)
	Pruritus	5 (1.29%)	3 (0.45%)	9 (1.36%)
	Pruritus generalised	3 (0.77%)	11 (1.66%)	7 (1.06%)

Table 7.4.1-4: Incidence of Treatment Emergent Adverse Events with ≥2% Incidence in Phase 2 and 3 Studies.

		Phase 2 Studies	Phase 3 Studies	
Body System or Organ Class	*Dictionary-Derived Term*	**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Gastrointestinal disorders		115 (29.64%)	106 (16.01%)	152 (22.96%)
	Diarrhea	29 (7.47%)	26 (3.93%)	35 (5.29%)
	Nausea	57 (14.69%)	54 (8.16%)	81 (12.24%)
	Vomiting	28 (7.22%)	19 (2.87%)	37 (5.59%)
Infections and infestations		68 (17.53%)	91 (13.75%)	78 (11.78%)
	Abscess	28 (7.22%)	35 (5.29%)	26 (3.93%)
	Cellulitis	13 (3.35%)	17 (2.57%)	14 (2.11%)
Nervous system disorders		48 (12.37%)	65 (9.82%)	67 (10.12%)
	Dizziness	12 (3.09%)	12 (1.81%)	14 (2.11%)
	Headache	29 (7.47%)	41 (6.19%)	39 (5.89%)

In summary, tedizolid phosphate is similar to linezolid with respect to adverse events. The incidence of adverse events, treatment emergent adverse events, severe treatment emergent adverse events, serious adverse events and serious treatment emergent adverse events was similar in the tedizolid phosphate and linezolid groups in the Phase 3 trials. Furthermore, TEAEs occurred in the same body system or organ class for both tedizolid phosphate and linezolid. The incidence of TEAEs in the Gastrointestinal Disorders SOC was numerically lower in the tedizolid phosphate arm versus linezolid in the Phase 3 trials.

Drug-Related Treatment Emergent Adverse Events

As described previously, the overall incidence of TEAEs considered by the investigator as related to the study drug was 22.4% (148 patients) in the tedizolid phosphate group and 27.9% (185 patients) in the linezolid group) in Phase 3 studies. With the exception of nausea, drug-related TEAE were similar in the tedizolid phosphate and linezolid arms in the Phase 3 studies. Drug related nausea occurred in 6.95% of the patients in the tedizolid phosphate arm 9.82% of the patients in the linezolid arm. In the Phase 2 studies, the overall incidence of TEAEs considered by the investigator as related to the study drug was 36.9% (143/388).

In Phase 3 studies, TEAEs considered related to the study drug by the investigator with ≥5% incidence included nausea (Table 7.4.1-5). In Phase 2 studies, TEAEs considered related to the study drug by the investigator with ≥5% incidence included diarrhea, nausea, and vomiting (Table 7.4.1-5).

Table 7.4.1-5: Treatment Emergent Adverse Events Considered Related to the Study Drug with ≥1% Incidence in Phase 2 and 3 Studies.

		Phase 2 studies	Phase 3 studies	
Body System or Organ Class	*Dictionary-Derived Term*	**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Gastrointestinal disorders		100 (25.77%)	84 (12.69%)	122 (18.43%)
	Diarrhea	26 (6.70%)	21 (3.17%)	31 (4.68%)
	Nausea	51 (13.14%)	46 (6.95%)	65 (9.82%)
	Vomiting	21 (5.41%)	15 (2.27%)	32 (4.83%)
General disorders and administration site conditions		10 (2.58%)	15 (2.27%)	17 (2.57%)
	Fatigue	4 (1.03%)	7 (1.06%)	8 (1.21%)
Infections and infestations		8 (2.06%)	10 (1.51%)	21 (3.17%)
	Vulvovaginal mycotic infection	3 (0.77%)	2 (0.30%)	8 (1.21%)
Nervous system disorders		34 (8.76%)	36 (5.44%)	41 (6.19%)
	Dizziness	10 (2.58%)	8 (1.21%)	12 (1.81%)
	Headache	18 (4.64%)	23 (3.47%)	22 (3.32%)

In summary, TEAEs considered related to the study drug are similar for tedizolid phosphate and linezolid. In the Phase 2 trials, there appears to be a higher incidence of TEAEs with tedizolid phosphate doses greater than 200 mg.

Severity of Treatment Emergent Adverse Events

In the Phase 2 Studies, most patients with a TEAE, experienced events with a maximum severity of mild (162/221 [73.2%]) (Table 7.4.1-6). Fewer patients experienced a moderate or severe event (50/221 [22.6%] and 9/221 [4.1%], respectively). In an analysis of causality of TEAEs considered severe reported by the investigator, study drug may have contributed for 3 patients receiving tedizolid phosphate.

The distribution of events in mild, moderate, and severe categories was similar between the tedizolid phosphate and linezolid arms. In the Phase 3 trials, most patients with a TEAE experienced events with a maximum severity of mild (195/283 [68.9%] tedizolid phosphate group and 193/286 [67.5%] linezolid group) (Table 7.4.1-6). Fewer patients experienced a moderate or severe event (75/283 [26.5%] tedizolid phosphate group, 80/286 [28.0%] linezolid group; 13/286 [4.5%], 13/283 [4.6%], respectively). In an analysis of causality of TEAEs

considered severe reported by the investigator, study drug may have contributed for 2 patients in the tedizolid phosphate arm and 4 patients in the linezolid arm.

Table 7.4.1-6: Treatment Emergent Adverse Events by Severity in Phase 2 and 3 Studies

		Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200mg) n=388	Tedizolid phosphate (200mg) n=662	Linezolid (1200mg) n=662
*Number of patients (%) with at least one TEAE**	*Severity*	221	283	286
	Mild	162 (73.30%)	195 (68.90%)	193 (67.48%)
	Moderate	50 (22.62%)	75 (26.50%)	80 (27.97%)
	Severe	9 (4.07 %)	13 (4.59 %)	13 (4.55 %)

*Number of patients with at least one TEAE used as denominator for percentages.

Multiple TEAEs occurred in various body system or organ classes (Table 7.4.1-7). Most of the patients with a severe TEAE were considered to have a serious adverse event.

Table 7.4.1-7: TEAE in patients with at least one TEAE of maximum severity of 'severe'

		Phase 2 Studies	Phase 3 Studies	
Body System or Organ Class	*Dictionary-Derived Term*	**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
*Number of patients with at least one TEAE of maximum severity of 'severe'**		9 (100.00%)	13 (100.00%)	13 (100.00%)
Cardiac disorders		0 (0.00%)	2 (15.38%)	1 (7.69%)
	Acute coronary syndrome	0 (0.00%)	0 (0.00%)	1 (7.69%)
	Cardiac arrest	0 (0.00%)	1 (7.69%)	0 (0.00%)
	Myocardial infarction	0 (0.00%)	1 (7.69%)	0 (0.00%)
Eye disorders		0 (0.00%)	1 (7.69%)	0 (0.00%)
	Visual acuity reduced	0 (0.00%)	1 (7.69%)	0 (0.00%)
Gastrointestinal disorders		1 (11.11%)	2 (15.38%)	1 (7.69%)
	Nausea	1 (11.11%)	2 (15.38%)	1 (7.69%)
	Vomiting	0 (0.00%)	1 (7.69%)	1 (7.69%)
Hepatobiliary disorders		1 (11.11%)	0 (0.00%)	0 (0.00%)
	Cholecystitis acute	1 (11.11%)	0 (0.00%)	0 (0.00%)
Immune system disorders		0 (0.00%)	0 (0.00%)	1 (7.69%)
	Anaphylactic reaction	0 (0.00%)	0 (0.00%)	1 (7.69%)
Infections and infestations		6 (66.67%)	7 (53.85%)	4 (30.77%)
	Abscess	3 (33.33%)	4 (30.77%)	1 (7.69%)
	Cellulitis	2 (22.22%)	0 (0.00%)	0 (0.00%)
	Endophthalmitis	0 (0.00%)	1 (7.69%)	0 (0.00%)
	Meningitis tuberculous	0 (0.00%)	0 (0.00%)	1 (7.69%)
	Osteomyelitis	0 (0.00%)	1 (7.69%)	0 (0.00%)
	Pneumonia	0 (0.00%)	1 (7.69%)	0 (0.00%)
	Pulpitis dental	0 (0.00%)	0 (0.00%)	1 (7.69%)
	Septic shock	0 (0.00%)	2 (15.38%)	0 (0.00%)
	Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (7.69%)
Investigations		0 (0.00%)	0 (0.00%)	1 (7.69%)
	Blood glucose increased	0 (0.00%)	0 (0.00%)	1 (7.69%)
Musculoskeletal and connective tissue disorders		0 (0.00%)	0 (0.00%)	2 (15.38%)
	Arthritis	0 (0.00%)	0 (0.00%)	1 (7.69%)
	Muscle spasms	0 (0.00%)	0 (0.00%)	1 (7.69%)
Nervous system disorders		0 (0.00%)	0 (0.00%)	2 (15.38%)
	Headache	0 (0.00%)	0 (0.00%)	2 (15.38%)
Psychiatric disorders		0 (0.00%)	1 (7.69%)	1 (7.69%)
	Insomnia	0 (0.00%)	1 (7.69%)	0 (0.00%)
	Suicidal ideation	0 (0.00%)	0 (0.00%)	1 (7.69%)
Renal and urinary disorders			1 (7.69%)	1 (7.69%)
	Dysuria	0 (0.00%)	0 (0.00%)	1 (7.69%)

	Nephrolithiasis	0 (0.00%)	1 (7.69%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			1 (7.69%)	0 (0.00%)
	Bronchospasm	0 (0.00%)	1 (7.69%)	0 (0.00%)
Skin and subcutaneous tissue disorders		1 (11.11%)	1 (7.69%)	0 (0.00%)
	Dermatitis	0 (0.00%)	1 (7.69%)	0 (0.00%)
	Hyperhidrosis	1 (11.11%)	0 (0.00%)	0 (0.00%)
	Pruritus generalised	0 (0.00%)	1 (7.69%)	0 (0.00%)
Vascular disorders			1 (7.69%)	0 (0.00%)
	Hypertension	0 (0.00%)	1 (7.69%)	0 (0.00%)

*Number of patients with at least one TEAE used as denominator for percentages.

In summary, the distribution of treatment emergent adverse events in mild, moderate, and severe categories was similar between the tedizolid phosphate and linezolid arms. Severe TEAEs occurred in various body system or organ classes with most considered to also have a serious adverse event.

Time of Onset of Treatment Emergent Adverse Events with ≥1% Incidence in Phase 2 and 3 Studies

In Phase 2 and Phase 3 Studies, most TEAEs with ≥1% incidence occurred by 6 days in both treatment groups (Table 7.4.1-8). For the SOC Infections and Infestations, the TEAE abscess and cellulitis occurred more frequently at >10 days in both treatment arms (8.16% for tedizolid phosphate and 6.95% for linezolid). For the TEAE of abscess, the time of onset of >10 days was 3.47% in the tedizolid phosphate arm and 2.87% in the linezolid arm. For the TEAE of cellulitis, the time of onset of >10 days was 1.36% in the tedizolid phosphate arm and 1.51% in the linezolid arm. A similar trend was noted in the Phase 2 Studies where patients receiving tedizolid phosphate developed abscess (5.67%) and cellulitis (2.58%) at > 10 days.

Table 7.4.1-8: Time of Onset of Treatment Emergent Adverse Events with ≥1% Incidence in Phase 2 and 3 Studies

Body System or Organ Class	*Dictionary-Derived Term*	*Time of Onset*	**Phase 2 Studies**	**Phase 3 Studies**	
			Tedizolid phosphate (≥200mg) n=388	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
General disorders and administration site conditions		0-6 days	22 (5.67%)	23 (3.47%)	25 (3.78%)
		7-10 days	2 (0.52%)	5 (0.76%)	9 (1.36%)
		>10 days	7 (1.08%)	8 (1.21%)	7 (1.06%)
	Fatigue	0-6 days	8 (2.06%)	9 (1.36%)	9 (1.36%)
		7-10 days	0 (0.00%)	0 (0.00%)	3 (0.45%)
		>10 days	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders		0-6 days	107 (27.58%)	86 (12.99%)	125 (18.88%)
		7-10 days	11 (2.84%)	11 (1.66%)	26 (3.93%)
		>10 days	9 (2.32%)	15 (2.27%)	13 (1.96%)
	Constipation	0-6 days	6 (1.55%)	8 (1.21%)	5 (0.76%)
		7-10 days	1 (0.26%)	0 (0.00%)	1 (0.15%)
		>10 days	0 (0.00%)	1 (0.15%)	0 (0.00%)
	Diarrhoea	0-6 days	24 (6.19%)	19 (2.87%)	27 (4.08%)
		7-10 days	4 (1.03%)	5 (0.76%)	8 (1.21%)
		>10 days	2 (0.52%)	2 (0.30%)	1 (0.15%)
	Dyspepsia	0-6 days	3 (0.77%)	2 (0.30%)	6 (0.91%)
		7-10 days	0 (0.00%)	2 (0.30%)	1 (0.15%)
		>10 days	0 (0.00%)	0 (0.00%)	1 (0.15%)
	Nausea	0-6 days	52 (13.4%)	47 (7.10%)	70 (10.57%)
		7-10 days	3 (0.77%)	3 (0.45%)	11 (1.66%)
		>10 days	6 (1.55%)	6 (0.91%)	4 (0.60%)
	Vomiting	0-6 days	26 (6.70%)	13 (1.96%)	31 (4.68%)
		7-10 days	1 (0.26%)	3 (0.45%)	2 (0.30%)
		>10 days	2 (0.52%)	4 (0.60%)	4 (0.60%)
Nervous system disorders		0-6 days	40 (10.3%)	48 (7.25%)	52 (7.85%)
		7-10 days	4 (1.03%)	16 (2.42%)	10 (1.51%)

		>10 days	7 (1.80%)	5 (0.76%)	9 (1.36%)
	Dizziness	0-6 days	12 (3.09%)	10 (1.51%)	11 (1.66%)
		7-10 days	0 (0.00%)	2 (0.30%)	0 (0.00%)
		>10 days	0 (0.00%)	0 (0.00%)	3 (0.45%)
	Headache	0-6 days	20 (5.15%)	29 (4.38%)	32 (4.83%)
		7-10 days	3 (0.77%)	10 (1.51%)	7 (1.06%)
		>10 days	6 (1.55%)	3 (0.45%)	3 (0.45%)
Psychiatric disorders		0-6 days	16 (4.12%)	10 (1.51%)	4 (0.60%)
		7-10 days	2 (0.52%)	3 (0.45%)	2 (0.30%)
		>10 days	1 (0.26%)	5 (0.76%)	2 (0.30%)
	Insomnia	0-6 days	8 (2.06%)	5 (0.76%)	3 (0.45%)
		7-10 days	1 (0.26%)	1 (0.15%)	2 (0.30%)
		>10 days	0 (0.00%)	4 (0.60%)	0 (0.00%)
Skin and subcutaneous tissue disorders		0-6 days	22 (5.67%)	34 (5.14%)	25 (3.78%)
		7-10 days	0 (0.00%)	2 (0.30%)	6 (0.91%)
		>10 days	9 (2.32%)	12 (1.81%)	11 (1.66%)
	Pruritus	0-6 days	5 (1.29%)	3 (0.45%)	6 (0.91%)
		7-10 days	0 (0.00%)	0 (0.00%)	1 (0.15%)
		>10 days	0 (0.00%)	0 (0.00%)	2 (0.30%)
	Pruritus generalised	0-6 days	3 (0.77%)	11 (1.66%)	6 (0.91%)
		7-10 days	0 (0.00%)	0 (0.00%)	1 (0.15%)
		>10 days	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations		0-6 days	21 (5.41%)	30 (4.53%)	24 (3.63%)
		7-10 days	9 (2.32%)	19 (2.87%)	16 (2.42%)
		>10 days	46 (11.86%)	54 (8.16%)	46 (6.95%)
	Abscess	0-6 days	5 (1.29%)	11 (1.66%)	5 (0.76%)
		7-10 days	2 (0.52%)	5 (0.76%)	3 (0.45%)
		>10 days	22 (5.67%)	23 (3.47%)	19 (2.87%)
	Cellulitis	0-6 days	4 (1.03%)	5 (0.76%)	3 (0.45%)
		7-10 days	1 (0.26%)	3 (0.45%)	2 (0.30%)
		>10 days	10 (2.58%)	9 (1.36%)	10 (1.51%)

	Vulvovaginal mycotic infection	0-6 days	1 (0.26%)	2 (0.30%)	4 (0.60%)
		7-10 days	2 (0.52%)	0 (0.00%)	3 (0.45%)
		>10 days	0 (0.00%)	0 (0.00%)	2 (0.30%)

In summary, for both Phase 2 and Phase 3 studies, most TEAEs with ≥1% incidence occurred while the patient was on treatment (by 6 days for both tedizolid phosphate and linezolid). However, the TEAEs of abscess and cellulitis occurred more frequently at >10 days for patients receiving either tedizolid phosphate or linezolid in the Phase 2 and 3 trials. Please refer to the efficacy section for further sensitivity analyses carried out regarding this finding.

Gastrointestinal Disorders TEAE

Because a numerical difference was noted in TEAEs occurring at ≥1 % incidence in the Gastrointestinal Disorders Body System or Organ Class, an overview of Gastrointestinal treatment emergent adverse events by subgroups in Phase 3 studies is provided in the Table 7.4.1-9 below.

In Phase 3 studies, there was an overall lower incidence of gastrointestinal TEAEs in the tedizolid phosphate arm compared to the linezolid arm (16.0% versus 23.0%, respectively). This was true in most subgroups studied, with the exception of patients with moderate to severely impaired renal function where GI TEAEs were higher in the tedizolid phosphate arm (15.0%) versus linezolid (10.3%).

Table 7.4.1-9: Incidence of Gastrointestinal Disorders TEAEs by Subgroup in Phase 3 Studies

Subgroup	Patients with at Least 1 Gastrointestinal Disorder TEAE			
	Tedizolid phosphate (200 mg) (N=662)		Linezolid (1200 mg) (N=662)	
	N1	n (%)	N1	n (%)
All patients	662	106 (16.0%)	662	152 (23.0%)
< 65 years	590	101 (17.1%)	603	144 (23.9%)
≥ 65 years	72	5 (6.9%)	59	8 (13.6%)
≥ 75 years	24	0 (0.0%)	25	4 (16.0%)
Male	429	55 (12.8%)	408	77 (18.9%)
Female	233	51 (21.9%)	254	75 (29.5%)
White	563	95 (16.9%)	555	130 (23.4%)
Black or African American	77	7 (9.1%)	71	11 (15.5%)
Asian	6	1 (16.7%)	14	7 (50.0%)
Other	16	3 (18.8%)	22	4 (18.2%)
<18.5 kg/m^2	12	1 (8.3%)	7	2 (28.6%)
≥18.5 kg/m^2 to <30 kg/m^2	450	72 (16.0%)	426	94 (22.1%)
≥30 kg/m^2	200	33 (16.5%)	229	56 (24.5)
US/ Canada	424	93 (21.9%)	421	124 (29.5%)
Europe	165	8 (4.8%)	166	13 (7.8%)
Other	73	5 (6.8%)	75	15 (20.0%)
Normal/Mild Renal Impairment	633	103 (16.3%)	612	147 (24.0%)
Moderate/Severe Renal Impairment	20	3 (15.0%)	29	3 (10.3%)
Normal Hepatic Function	474	72 (15.2%)	443	100 (22.6%)
Hepatic Impairment	14	0 (0.0%)	12	2 (16.7%)
Hepatic Disease	175	34 (19.4%)	209	50 (23.9%)
IV Drug Use	182	37 (20.3%)	203	51 (25.1)
No IV Drug Use	480	69 (14.4%)	459	101 (22.0)
Diabetes	58	9 (15.5%)	67	18 (26.9%)
No diabetes	604	97 (16.1%)	595	134 (22.5%)

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup, used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

In summary, for most patient subgroups, there was an overall lower incidence of gastrointestinal TEAEs in the tedizolid phosphate arm compared to the linezolid arm in the Phase 3 studies.

One exception is in patients with moderate to severely impaired renal function where GI TEAEs were higher in the tedizolid phosphate arm versus linezolid. Additional study will be required in a larger population to provide better clarity on these preliminary findings.

Venous Tolerability

The Applicant evaluated venous tolerability of intravenous tedizolid phosphate in a Phase 1 study (TR701-107) and in a Phase 3 study (TR701-113).

TR701-107 was a randomized placebo-controlled cross-over sub-study where study drug was administered under standardized conditions in 10 healthy subjects. Each subject was his/her own control and received 3 days of 200 mg IV tedizolid phosphate or 3 days of placebo through a dorsal vein of one hand, followed by the alternate regimen under the same conditions in the other hand. The most frequently reported adverse events included infusion site pain, infusion site swelling, and infusion site erythema. The incidence of infusion site-related adverse events, as well as the number and severity of infusion site examination findings, increased with multiple dosing. The Applicant conjectures that this may be possibly due to the presence of the IV catheter, the numerous venous punctures, or the study drug itself. However, Visual Infusion Phlebitis scores did not differ between 200 mg tedizolid phosphate and placebo. Nine of ten subjects in the tedizolid phosphate group and six of ten subjects in the placebo group experienced infusion-site related adverse event, all of which were considered mild. Infusion-site erythema, hematoma, pain, and swelling were adverse events occurring in more than 1 subject in a group.

TR701-113 was a Phase 3 trial where patients received IV tedizolid phosphate and were switched to the oral formulation. The number of patients with a TEAE in the General disorders and administration site conditions SOC was similar in the tedizolid phosphate and linezolid arms (23 [6.95%] and 25 [7.65%], respectively) (Table 7.4.1-10). In the tedizolid phosphate arm, TEAEs occurring in more than one patient included fatigue (n=8, 2.42%), infusion related reaction (n=2, 0.60%), infusion site pain (n=2, 0.60%) and infusion site phlebitis (n=2, 0.60%).

Reference ID: 3521547

Table 7.4.1-10: Treatment emergent adverse events in the General disorders and administration site conditions body system or organ class in TR701-113.

Dictionary-Derived Term	Tedizolid phosphate (200mg) n=331	Linezolid (1200mg) n=327
Number of patients with a TEAE in the General disorders and administration site conditions SOC	23 (6.95%)	25 (7.65%)
Asthenia	1 (0.30%)	1 (0.31%)
Catheter site pain	0 (0.00%)	1 (0.31%)
Chest pain	1 (0.30%)	1 (0.31%)
Chills	1 (0.30%)	2 (0.61%)
Drug withdrawal syndrome	1 (0.30%)	0 (0.00%)
Fatigue	8 (2.42%)	7 (2.14%)
Infusion related reaction	2 (0.60%)	0 (0.00%)
Infusion site dermatitis	0 (0.00%)	1 (0.31%)
Infusion site erythema	0 (0.00%)	1 (0.31%)
Infusion site extravasation	1 (0.30%)	0 (0.00%)
Infusion site induration	0 (0.00%)	1 (0.31%)
Infusion site pain	2 (0.60%)	1 (0.31%)
Infusion site phlebitis	2 (0.60%)	1 (0.31%)
Infusion site swelling	1 (0.30%)	1 (0.31%)
Infusion site urticaria	0 (0.00%)	1 (0.31%)
Injection site haematoma	0 (0.00%)	1 (0.31%)
Localised oedema	1 (0.30%)	0 (0.00%)
Oedema peripheral	3 (0.91%)	4 (1.22%)
Pain	0 (0.00%)	3 (0.92%)
Pyrexia	2 (0.60%)	3 (0.92%)

In summary, findings from Phase 3 trials suggest that venous tolerability is similar to linezolid at the proposed dose (200 mg IV) and duration (6 days). Venous tolerability of tedizolid phosphate is unknown at higher doses and longer durations.

7.4.2 Laboratory Findings

Overview of Laboratory Testing in the Development Program

The Applicant collected data on chemistry and hematology parameters during the drug development program. Laboratory evaluations included shift table analyses as well as abnormal/substantially abnormal category analyses. In addition, analyses of laboratory related TEAEs was conducted.

Selection of Clinical Trials and Analyses for Drug-Control Comparisons of Laboratory Values

Analyses of laboratory values were conducted on pooled Phase 2 trials (TR701-104 and TR701-126) and pooled Phase 3 trials (TR701-112 and TR701-113). The data were examined for changes from baseline of clinical significance. Separate analyses in select patient subgroups were also conducted.

7.4.2.1 Analyses Focused on Measures of Central Tendency

An analysis of central tendency was conducted to examine mean changes from baseline across treatment groups for hematology and chemistry parameters (Table 7.4.2-1 and Table 7.4.2-2). In the Phase 3 trials, mean changes from baseline for reported hematology and chemistry parameters were similar and minor in the tedizolid phosphate and linezolid arms. Lactic acid levels were not reported during the Phase 2 and Phase 3 trials.

Table 7.4.2-1: Mean Change from Baseline for Select Hematology Parameters in Phase 2 and Phase 3 Trials.

	Phase 2 Studies			Phase 3 Studies					
	Tedizolid phosphate (≥200mg) n=388			Tedizolid phosphate (200mg) n=662			Linezolid (1200mg) n=662		
Parameter	N	Mean Baseline Value	Mean Change from Baseline	N	Mean Baseline Value	Mean Change from Baseline	N	Mean Baseline Value	Mean Change from Baseline
Hemoglobin (g/dL)	356	13.8	0.0	602	13.5	0.0	597	13.5	-0.1
Hematocrit (%)	356	44.5	-0.2	583	44.3	-0.3	581	44.2	-0.8
Erythrocytes (10^6/uL)	356	4.7	0.0	583	4.6	0.0	581	4.6	0.0
Platelets (10^3/uL)	346	246.4	9.6	579	250.1	20.4	577	248.2	12.3
Leukocytes (10^3/uL)	356	9.0	-2.1	583	9.4	-2.2	581	8.8	-1.9
Neutrophils (10^3/uL)	346	6.4	-2.1	567	6.8	-2.2	554	6.2	-1.9
Lymphocytes (10^3/uL)	346	1.9	0.1	567	1.8	0.1	554	1.8	0.1
Monocytes (10^3/uL)	346	0.5	-0.1	567	0.6	-0.1	554	0.5	-0.1
Basophils (10^3/uL)	346	0.1	0.0	567	0.1	0.0	554	0.1	0.0
Eosinophils (10^3/uL)	346	0.2	0.0	567	0.2	0.0	554	0.2	0.0

N represents the number of subjects who had the laboratory value assessed at baseline and at least one follow-up time.

Table 7.4.2-2: Mean Change from Baseline for Select Chemistry Parameters in Phase 2 and Phase 3 Trials.

	Phase 2 Studies			Phase 3 Studies					
	Tedizolid phosphate (≥200mg) n=388			Tedizolid phosphate (200mg) n=662			Linezolid (1200mg) n=662		
Parameter	**N**	**Mean Baseline Value**	**Mean Change from Baseline**	**N**	**Mean Baseline Value**	**Mean Change from Baseline**	**N**	**Mean Baseline Value**	**Mean Change from Baseline**
Alanine Aminotransferase (U/L)	363	30.0	2.7	628	28.4	3.0	616	30.5	3.3
Albumin (g/dL)	369	4.2	0.0	639	4.2	0.0	630	4.2	0.0
Alkaline Phosphatase (U/L)	369	85.8	-3.0	639	86.3	-2.8	630	87.0	-4.6
Aspartate Aminotransferase (U/L)	363	28.6	3.1	622	27.7	2.0	608	30.1	1.6
Bicarbonate (mmol/L)	369	23.6	0.5	638	23.3	1.4	631	23.2	1.1
Bilirubin (mg/dL)	368	0.4	-0.1	639	0.5	-0.1	631	0.5	-0.1
Blood Urea Nitrogen (mg/dL)	177	12.2	0.7	318	13.9	0.0	317	13.6	0.3
Calcium (mg/dL)	369	9.4	0.0	638	9.2	0.1	630	9.3	0.0
Chloride (mEq/L)	177	100.7	0.8	253	99.7	1.4	248	99.9	0.9
Cholesterol (mg/dL)	369	165.4	1.7	639	165.4	3.6	631	165.1	0.3
Creatine Kinase (U/L)	365	149.0	13.0	631	133.9	-14.7	622	145.9	-16.0
Creatinine (mg/dL)	369	0.8	0.0	639	0.9	0.0	630	0.9	0.0
Direct Bilirubin (mg/dL)	344	0.1	0.0	618	0.2	0.0	600	0.2	0.0
Gamma Glutamyl Transferase (U/L)	368	38.3	0.9	637	50.5	-2.2	627	55.2	-2.6
Glucose (mg/dL)	369	108.8	3.9	629	111.0	3.8	623	113.9	0.1
Indirect Bilirubin (mg/dL)	356	0.3	-0.1	618	0.3	-0.1	599	0.3	0.0
Lactate Dehydrogenase (U/L)	362	167.8	-5.5	628	183.8	-10.1	616	181.0	-10.1
Magnesium (mg/dL)	368	2.0	0.0	639	1.9	0.0	627	1.9	0.0
Phosphate (mg/dL)	368	3.6	0.0	637	3.5	0.1	628	3.6	0.0
Potassium (mmol/L)	365	4.0	0.1	631	4.1	0.1	616	4.2	0.1
Protein (g/dL)	369	7.3	-0.1	639	7.2	-0.1	630	7.2	-0.1
Sodium (mmol/L)	369	137.3	0.8	639	138.8	0.7	630	138.7	0.6
Urate (mg/dL)	369	5.1	0.4	639	5.1	0.4	631	5.2	0.4

N represents the number of subjects who had the laboratory value assessed at baseline and at least one follow-up time.

In summary, an analysis of central tendency examining mean changes from baseline across treatment groups for hematology and chemistry parameters in Phase 3 trials suggest that mean changes from baseline for reported hematology and chemistry parameters were similar and minor in the tedizolid phosphate and linezolid arms.

7.4.2.2 Analyses Focused on Shifts From Normal to Abnormal

Shifts of ≥2 toxicity grades from baseline to the worst postbaseline were examined for select hematology and chemistry parameters in the Phase 3 trials (Tables 7.4.2-3 and 7.4.2-4). The Applicant used toxicity grades defined by a modified Division of Microbiology and Infectious Diseases Adult Toxicity Scale, November 2007 criteria.

Hematology

For the toxicity grades, changes for most parameters indicated a decreasing value.

In the Phase 2 trials, shifts of ≥2 toxicity grades were observed for leukocytes and neutrophils.

- Leukocytes: There were 10 (2.8%) of 356 patients with a ≥2 grade toxicity increase: tedizolid phosphate Grade 0 to 2 (6/356, 1.7%), Grade 0 to 3 (2/356, 0.6%), Grade 1 to 3 (2/356, 0.6%).
- Neutrophils: There were 3 (0.9%) of 346 patients with a ≥2 grade toxicity increase: tedizolid phosphate Grade 0 to 2 (2/346, 0.6%), Grade 0 to 3 (1/346, 0.3%).

Analyses of select hematology parameters showed that shifts of ≥2 toxicity grades in the Phase 3 trials were similar and low in the tedizolid phosphate and linezolid arms (Table 7.4.2-3). There was one patient in the tedizolid phosphate arm who had a Grade 4 toxicity grade for neutrophils at baseline and throughout the study. In addition, there was one patient in the linezolid arm who had a Grade 4 toxicity grade for leukocytes at baseline and throughout the study.

Table 7.4.2-3: Shift ≥2 Tox Grades from Baseline to Worst Post-Baseline for select Hematology Parameters in Phase 3 Studies

Parameter Category Hematology		Phase 3 Studies	
Parameter	**Shift ≥ 2 Tox Grades from Baseline to Worst Post Baseline**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Hemoglobin (g/dL)	N	602	597
	Grade 0 to Grade 2	3 (0.5%)	4 (0.7%)
	Grade 0 to Grade 3	1 (0.2%)	0 (0%)
	Grade 0 to Grade 4	1 (0.2%)	0 (0%)
	Grade 1 to Grade 3	1 (0.2%)	0 (0%)
	Total	*6 (1.0%)*	*4 (0.7%)*
Platelets (10^3/uL)	N	579	577
	Grade 0 to Grade 2	3 (0.5%)	3 (0.5%)
	Grade 0 to Grade 3	4 (0.7%)	0 (0%)
	Grade 0 to Grade 4	1 (0.2%)	1 (0.2%)
	Total	*8 (1.4%)*	*4 (0.7%)*
Leukocytes (10^3/uL)	N	583	581
	Grade 0 to Grade 2	6 (1.0%)	7 (1.2%)
	Grade 0 to Grade 3	6 (1.0%)	1 (0.2%)
	Grade 1 to Grade 3	3 (0.5%)	2 (0.3%)
	Grade 1 to Grade 4	1 (0.2%)	0 (0%)
	Total	*15 (2.6%)*	*10 (1.7%)*
Neutrophils (10^3/uL)	N	567	554
	Grade 0 to Grade 2	0 (0%)	2 (0.4%)
	Grade 0 to Grade 3	1 (0.2%)	3 (0.5%)
	Grade 0 to Grade 4	1 (0.2%)	2 (0.4%)
	Grade 1 to Grade 4	1 (0.2%)	0 (0%)
	Total	*3 (0.5%)*	*7 (1.3%)*

N=Number of patients in the subgroup with nonmissing data and is used as the denominator to calculate percentage;
Note: Shift grades ≥2 with 0 patients in both treatment arms are not shown in the table.

Chemistry

Analyses of select chemistry parameters showed that shifts of ≥2 toxicity grades in the Phase 3 trials were similar and low in the tedizolid phosphate and linezolid arms (Table 7.4.2-4). There was one patient each in the tedizolid phosphate and linezolid arms who had a Grade 4 toxicity grade for gamma glutamyl transferase at baseline and throughout the study. In addition, there was one patient in the linezolid arm who had a Grade 4 toxicity grade for glucose at baseline and throughout the study.

Reference ID: 3521547

Table 7.4.2-4: Shift ≥2 Tox Grades from Baseline to Worst Post-Baseline for Select Chemistry Parameters in Phase 2 and Phase 3 Studies

Parameter Category Chemistry		Phase 2 Studies	Phase 3 Studies	
Parameter	**Shift ≥2 Tox Grades from Baseline to Worst Post Baseline**	**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Alanine Aminotransferase (U/L)	N	363	628	616
	Grade 0 to Grade 2	4 (1.1%)	10 (1.6%)	11 (1.8%)
	Grade 0 to Grade 3	0 (0.0%)	3 (0.5%)	1 (0.2%)
	Grade 1 to Grade 4	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Grade 2 to Grade 4	0 (0.0%)	1 (0.2%)	0 (0.0%)
	*Total**	4 (1.1%)	13 (2.1%)	12 (2.0%)
Alkaline Phosphatase (U/L)	N	369	638	629
	Grade 0 to Grade 2	1 (0.3%)	1 (0.2%)	0 (0.0%)
	Total	1 (0.3%)	1 (0.2%)	0 (0.0%)
Aspartate Aminotransferase (U/L)	N	363	622	608
	Grade 0 to Grade 2	2 (0.6%)	7 (1.1%)	7 (1.2%)
	Grade 0 to Grade 3	1 (0.3%)	2 (0.3%)	1 (0.2%)
	Grade 0 to Grade 4	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Grade 1 to Grade 3	0 (0.0%)	0 (0.0%)	3 (0.5%)
	Grade 1 to Grade 4	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Grade 2 to Grade 4	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Total	4 (1.1%)	8 (1.3%)	11 (1.8%)
Bilirubin (mg/dL)	N	368	639	631
	Grade 0 to Grade 2	0 (0.0%)	0 (0.0%)	1 (0.16%)
	Grade 1 to Grade 3	0 (0.0%)	0 (0.0%)	1 (0.16%)
	Total	0 (0.0%)	0 (0.0%)	2 (0.32%)
Calcium (mg/dL)	N	369	638	630
	Grade 0 to Grade 2	0 (0.0%)	2 (0.3%)	4 (0.6%)
	Grade 0 to Grade 4	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Grade 1 to Grade 3	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Total	0 (0.0%)	2 (0.3%)	6 (1.0%)
Creatinine (mg/dL)	N	369	639	630

	Grade 0 to Grade 2	0 (0.0%)	2 (0.3%)	4 (0.6%)
	Grade 0 to Grade 3	1 (0.3%)	1 (0.2%)	0 (0.0%)
	Total	1 (0.3%)	2 (0.3%)	4 (0.6%)
Gamma Glutamyl Transferase (U/L)	N	368	637	627
	Grade 0 to Grade 2	1 (0.3%)	3 (0.5%)	4 (0.6%)
	Grade 0 to Grade 3	1 (0.3%)	1 (0.2%)	1 (0.2%)
	Grade 1 to Grade 3	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Grade 2 to Grade 4	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Total	1 (0.3%)	6 (0.9%)	4 (0.6%)
Glucose (mg/dL)	N	369	629	623
	Grade 0 to Grade 2	12 (3.3%)	31 (4.9%)	41 (6.6%)
	Grade 0 to Grade 3	0 (0.0%)	4 (0.6%)	1 (0.16%)
	Grade 0 to Grade 4	4 (1.1%)	2 (0.3%)	0 (0.0%)
	Grade 1 to Grade 3	2 (0.5%)	5 (0.8%)	4 (0.6%)
	Grade 2 to Grade 4	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Total	18 (4.9%)	41 (6.5%)	46 (7.4%)
Phosphate (mg/dL)	N	368	636	628
	Grade 0 to Grade 2	2 (0.5%)	4 (0.6%)	4 (0.6%)
	Total	2 (0.5%)	4 (0.6%)	4 (0.6%)
Potassium (mmol/L)	N	365	631	616
	Grade 0 to Grade 2	1 (0.27%)	6 (1.0%)	4 (0.7%)
	Grade 0 to Grade 3	0 (0.0%)	0 (0.0%)	3 (0.5%)
	Grade 0 to Grade 4	0 (0.0%)	1 (0.2%)	1 (0.2%)
	Total	1 (0.3%)	7 (1.1%)	6 (1.0%)
Sodium (mmol/L)	N	369	639	630
	Grade 0 to Grade 2	0 (0.0%)	2 (0.3%)	0 (0.0%)
	Grade 0 to Grade 3	0 (0.0%)	1 (0.2%)	1 (0.2%)
	Grade 0 to Grade 4	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Total	0 (0.0%)	3 (0.5%)	2 (0.3%)
Urate (mg/dL)	N	369	639	631
	Grade 0 to Grade 2	1 (0.3%)	1 (0.2%)	4 (0.6%)
	Grade 0 to Grade 3	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Grade 0 to Grade 4	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Grade 1 to Grade 3	1 (0.3%)	0 (0.0%)	1 (0.2%)
	Total	3 (0.8%)	1 (0.2%)	5 (0.8%)

N=Number of patients in the subgroup with nonmissing data and is used as the denominator to calculate percentages.

*Total indicates number of patients with shifts of ≥2 Tox Grades from Baseline to Worst Post-Baseline. Note: Shift grades ≥2 with 0 patients in both treatment arms are not shown in the table.

In summary, shifts of ≥2 toxicity grades from baseline to the worst postbaseline for select hematology and chemistry parameters in the Phase 3 trials were similar and low for both tedizolid phosphate and linezolid.

7.4.2.3 Analyses Focused on Outliers

Analyses were conducted to evaluate outliers in laboratory parameters.

In the multiple ascending dose Phase 1 study, tedizolid phosphate, mean ALT values increased for subjects receiving 200 (n=8) or 300 mg (n=8) TR701 for 21 days. These changes were not considered clinically significant by the Investigator. One subject receiving 200 mg tedizolid phosphate had an ALT 5.3 x ULN; however was asymptomatic and did not have concomitant increases in bilirubin and alkaline phosphatase. In the group receiving 400 mg (n=8) tedizolid phosphate, the highest dose, there were no increasing trends of ALT.

The incidences of substantially abnormal postbaseline results for select hematology and chemistry parameters were examined for Phase 2 and 3 trials (Tables 7.4.2-5 and 7.4.2-6). Additional analyses were performed for patients with hepatic disease or impairment, as well as moderate/severe renal function. In Phase 3 trials, the incidence of substantially abnormal hematology parameters was similar in the tedizolid phosphate and linezolid arms.

The Applicant used the following definitions for substantially abnormal values:

1. Hemoglobin and platelet counts: <75% of lower limit of normal (LLN) for values normal at baseline or <75% of the LLN and <75% of baseline for values abnormal at baseline.
2. Absolute neutrophil count (ANC): <50% of LLN for values normal at baseline or <50% of the LLN and <50% of baseline for values abnormal at baseline.
3. Chemistry: substantially abnormal values were defined as >2 × the upper limit of normal (ULN) for values normal at baseline; or >2 × ULN and >2 × baseline value for values abnormal at baseline.

Table 7.4.2-5: Incidence of Substantially Abnormal Postbaseline Results for Select Hematology Parameters in Phase 2 and Phase 3 Studies

			Phase 2 Studies	Phase 3 Studies	
Parameter	**Population**		**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Hemoglobin (g/dL)					
	Overall	N	378	642	642
		Substantially Abnormal	0 (0.0%)	4 (0.6%)	3 (0.5%)
	Hepatic Disease or Impairment	N	105	186	212
		Substantially Abnormal	0 (0.0%)	1 (0.5%)	1 (0.5%)
	Moderate/ Severe Renal Function	N	4	20	29
		Substantially Abnormal	0 (0.0%)	0 (0.0%)	1 (3.5%)
Platelets (10^3/uL)					
	Overall	N	374	639	636
		Substantially Abnormal	5 (1.3%)	16 (2.5%)	20 (3.1%)
	Hepatic Disease or Impairment	N	104	185	211
		Substantially Abnormal	3 (2.9%)	10 (5.4%)	8 (3.8%)
	Moderate/ Severe Renal Function	N	4	20	28
		Substantially Abnormal	1 (25.0%)	0 (0.0%)	1 (3.6%)
Neutrophils (10^3/uL)					
	Overall	N	376	637	627
		Substantially Abnormal	1 (0.3%)	3 (0.5%)	5 (0.8%)
	Hepatic Disease or Impairment	N	105	183	208
		Substantially Abnormal	0 (0.0%)	1 (0.6%)	0 (0.0%)
	Moderate/ Severe Renal Function	N	4	20	28

	Substantially Abnormal	0 (0.0%)	0 (0.0%)	1 (3.6%)

N=Number of patients in the subgroup with nonmissing data is used as the denominator to calculate percentages.
Substantially abnormal criteria:
'HGB','PLAT': <75% of LLN for values normal at baseline; or <75% of the LLN and <75% of baseline for values abnormal at baseline.
'NEUT': <50% of LLN for values normal at baseline; or <50% of the LLN and <50% of baseline for values abnormal at baseline. (There were no patients identified with substantially abnormal postbaseline white blood cell counts in Phase 2 and Phase 3 Studies.)

The incidence of substantially abnormal aspartate aminotransferase levels was lower in the tedizolid phosphate arm versus the linezolid arm in the Phase 3 trials (7/186 [3.8%] and 13/212 [6.1%]). For the remainder of the chemistry parameters, the incidence of substantially abnormal postbaseline result was similar in both treatment arms in the Phase 3 trials (Table 7.4.2-6).

Table 7.4.2-6: Incidence of Substantially Abnormal Postbaseline Results for Select Chemistry Parameters in Phase 2 and Phase 3 Studies

			Phase 2 Studies	Phase 3 Studies	
Parameter	**Population**		**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Alkaline phosphatase (U/L)					
	Overall	N	378	646	644
		Substantially Abnormal*	1 (0.26%)	1 (0.2%)	0 (0.0%)
	Hepatic Disease or Impairment	N	105	186	212
		Substantially Abnormal	0 (0.00%)	1 (0.5%)	0 (0.0%)
Alanine Aminotransferase (U/L)					
	Overall	N	378	646	643
		Substantially Abnormal	10 (2.65%)	25 (3.9%)	20 (3.1%)
	Hepatic Disease or Impairment	N	104	186	212
		Substantially Abnormal	2 (1.92%)	8 (4.3%)	7 (3.3%)
Aspartate Aminotransferase (U/L)					
	Overall	N	378	646	643
		Substantially Abnormal	7 (1.85%)	17 (2.6%)	18 (2.8%)
	Hepatic Disease or Impairment	N	104	186 (100.0%)	212 (100.0%)
		Substantially Abnormal	2 (1.92%)	7 (3.8%)	13 (6.1%)
	Moderate/ Severe Renal Function	N	4	20	29
		Substantially Abnormal	0 (0.00%)	1 (5.0%)	0 (0.0%)

Bilirubin (mg/dL)					
	Overall	N	379	646	644
		Substantially Abnormal	0 (0.00%)	0 (0.0%)	1 (0.2%)
	Hepatic Disease or Impairment	N	105	186	212
		Substantially Abnormal	0 (0.00%)	1 (0.0%)	1 (0.5%)
Blood Urea Nitrogen (mg/dL)					
	Overall	N	185	322	324
		Substantially Abnormal	0 (0.00%)	0 (0.0%)	1 (0.3%)
Creatinine (mg/dL)					
	Overall	N	379	646	644
		Substantially Abnormal	1 (0.26%)	1 (0.2%)	3 (0.5%)

N=Number of patients in the subgroup with nonmissing data and is used as the denominator to calculate percentages.
*Substantially abnormal criteria:
'AST','ALT','ALP','','CREAT','BUN','BILI': > 2 × ULN for values normal at baseline; or > 2 × ULN and > 2 × baseline value for values abnormal at baseline.
(There were no patients identified with substantially abnormal postbaseline bicarbonate, glucose, cholesterol, and GGT results in Phase 2 and Phase 3 Studies. For patients with moderate/severe renal function, there were no substantially abnormal results for ALP, ALT, AST, BILI, BICARB and CREAT in Phase 2 and Phase 3 Studies.)

Additional analyses on post-dose liver function tests elevations in Phase 2 and 3 studies were requested from the Applicant (Table 7.4.2-7). The results are as follows:

Table 7.4.2-7: Post-dose liver function tests elevations in Phase 2 and 3 studies

Parameter	Phase 2 TR-701/FA (>=200 mg) (N=388) n (%)	Phase 3 TR-701/FA (200 mg) (N=662) n (%)	Phase 3 Linezolid (1200 mg) (N=662) n (%)
Alanine Aminotransferase (U/L), N1	378	646	643
>= ULN	107 (28.3)	195 (30.2)	219 (34.1)
>= 2x ULN	27 (7.1)	47 (7.3)	59 (9.2)
>= 3x ULN	12 (3.2)	21 (3.3)	25 (3.9)
>= 5x ULN	1 (0.3)	5 (0.8)	5 (0.8)
>= 10x ULN	0	2 (0.3)	1 (0.2)
Aspartate Aminotransferase (U/L), N1	378	646	643
>= ULN	92 (24.3)	185 (28.6)	188 (29.2)
>= 2x ULN	25 (6.6)	37 (5.7)	55 (8.6)
>= 3x ULN	8 (2.1)	16 (2.5)	22 (3.4)
>= 5x ULN	2 (0.5)	4 (0.6)	8 (1.2)
Alkaline Phosphatase (U/L), N1	379	645	643
>= ULN	50 (13.2)	109 (16.9)	98 (15.2)
>= 2x ULN	3 (0.8)	8 (1.2)	5 (0.8)
>= 3x ULN	1 (0.3)	1 (0.2)	0
>= 5x ULN	0	0	0
Bilirubin (mg/dL), N1	379	646	644
>= ULN	8 (2.1)	17 (2.6)	19 (3.0)
>= 1.5x ULN	0	0	4 (0.6)
>= 2x ULN	0	0	1 (0.2)
>= 3x ULN	0	0	1 (0.2)

Note: TR-701/FA refers to both TR-701 and TR-701 FA. N=Number of patients in Safety Analysis Set. N1=Number of patients with at least one non-missing post-baseline result with a non-missing upper limit of normal, and is used for percentages.
n=Number of patients in each category.
The upper limit of normal (ULN) for Alanine Aminotransferase is 30 U/L for males <=18 years of age, 20 U/L for females <=18 years of age, and 45 U/L for males and females > 18 years of age. The ULN for Aspartate Aminotransferase is 41 U/L. The ULN for Alkaline Phosphatase is 129 U/L for males and 104 U/L for females. The ULN for total bilirubin is 1.2 mg/dL.

Source: NDA 205435, SN 0036, Integrated Summary of Safety, Table 1

In addition, the Applicant was requested to provide data on selected baseline liver disease in Phase 2 and 3 trials (Table 7.4.2-8). The results are as follows:

Table 7.4.2-8: Selected Baseline Liver Disease in Phase 2 and 3 Trials

	Phase 2 TR-701/FA (>=200 mg) (N=388) n (%)	Phase 3 TR-701/FA (200 mg) (N=662) n (%)	Phase 3 Linezolid (1200 mg) (N=662) n (%)
Number of events	218	380	458
Number of subjects with at least one event	111 (28.6)	202 (30.5)	238 (36.0)
Number of subjects with hepatitis B	2 (0.5)	6 (0.9)	11 (1.7)
Number of subjects with hepatitis C	99 (25.5)	165 (24.9)	195 (29.5)
Number of subjects with alcohol abuse/use	7 (1.8)	15 (2.3)	24 (3.6)
Number of subjects with hepatic disease	107 (27.6)	180 (27.2)	216 (32.6)
Number of subjects with hepatic impairment	3 (0.8)	14 (2.1)	12 (1.8)

Note: TR-701/FA refers to both TR-701 and TR-701 FA. N=Number of patients in Safety Analysis Set.
n=Number of patients in each category.
Hepatic Impairment: Child-Pugh grade B or C (total score >=7) at baseline.
Hepatic Disease: ALT or AST >=2 x ULN at baseline; or subjects with positive results for Hepatitis B

Source: NDA 205435, SN 0036, Integrated Summary of Safety, Table 2

Furthermore, the Applicant was requested to provide information on post-dose alanine aminotransferase elevations in subjects with normal baseline transaminase levels in the Phase 2 and 3 studies (Table 7.4.2-9). The results are as follows:

Table 7.4.2-9: Post-dose alanine aminotransferase elevations in subjects with normal baseline transaminase levels in the Phase 2 and 3 studies

Parameter	Phase 2 TR-701/FA (>=200 mg) (N=388) n (%)	Phase 3 TR-701/FA (200 mg) (N=662) n (%)	Phase 3 Linezolid (1200 mg) (N=662) n (%)
Alanine Aminotransferase (U/L), N1	306	536	522
>3x ULN - 5x ULN	1 (0.3)	2 (0.4)	5 (1.0)
>5x ULN - 10x ULN	0	0	1 (0.2)
>10x ULN	0	1 (0.2)	0
Total	1 (0.3)	3 (0.6)	6 (1.1)

Note: TR-701/FA refers to both TR-701 and TR-701 FA. N=Number of patients in Safety Analysis Set. N1=Number of patients with non-missing baseline ALT below the upper limit of normal and at least one non-missing post-baseline result, and is used for percentages. n=Number of patients in each category. For trials 112 and 113 the measurements are obtained from Day 1 through the Late Follow-Up visit (18-25 days after end of therapy). For trial 126 measurements are obtained through the Post Therapy Evaluation Visit (7-14 days following the completion of study medication). For trial 104 measurements are obtained through the Test of Cure Visit (6-15 days following the completion of study medication).
The upper limit of normal (ULN) for Alanine Aminotransferase is 30 U/L for males <=18 years of age, 20 U/L for females <=18 years of age, and 45 U/L for males and females > 18 years of age.

Source: NDA 205435, SN 0036, Integrated Summary of Safety, Table 3

In summary, the incidences of potentially clinically significant laboratory parameters were similar and low for tedizolid phosphate and linezolid in the Phase 2 and 3 trials. This trend was also observed in the small numbers of patients with hepatic disease or impairment, as well as moderate/ severe renal function.

7.4.2.4 Analyses Focused on Hy's Law

Analyses for patients meeting Hy's Law criteria were conducted for the Phase 2 and Phase 3 trials.

Hy's Law criteria were defined as:

1. ALT or AST >3 x upper limit of normal
2. Bilirubin > 2 x upper limit of normal, and
3. Alkaline phosphatase < 2 x upper limit of normal

There were no patients receiving tedizolid phosphate in the Phase 2 and Phase 3 trials who met Hy's Law criteria. There was one patient in the Phase 3 trial in the linezolid arm who met Hy's law criteria. This patient, TR701-113-141-437 had Grade 0 baseline ALT, AST, and bilirubin values at baseline) which changed to Grades 2, 3, and 3, respectively, on Day 1. No TEAEs related to these laboratory results were reported. Details regarding this patient follow.

> **TR701-113-141-437**, was a 78-year-old white male who received 10 days of linezolid 600 mg twice daily for treatment of cellulitis/erysipelas of his left lower leg. Past medical history was significant for a cholecystectomy and scattered angioma. Baseline serology tests were negative for hepatitis B and hepatitis C. Concomitant medications included paracetamol (Day -1 to Day 8), ibuprofen (Day 3), morphine, docusate, and heparin. Baseline ALT and AST values were normal (19 and 21 U/L, respectively). On Day 1, ALT and AST were 200 U/L and 305 U/L, measured after receiving the first infusions of study medication. ALT and AST returned to normal by Day 7. Baseline ALP values were normal (64 U/L) rose to 221 U/L on Day 1, and returned to normal by Day 18. Baseline total bilirubin was slightly elevated (24 umol/L), increased to 72 umol/L on Day 1, then decreased to normal during the study. There were no TEAEs reported regarding liver test abnormalities. The one reported TEAE was a gastrointestinal syndrome on Day 1 which resolved without additional treatment. The patients developed elevated ALT and AST values >5x ULN and elevated bilirubin levels during treatment, meeting clinical criteria for Hy's Law.

7.4.2.5 Analyses of Laboratory Related TEAEs

The incidence of laboratory related TEAEs was examined in Phase 2 and Phase 3 trials (Table 7.4.2-10). No patients discontinued study drug or the study due to laboratory abnormalities.

In Phase 3 trials, the incidence of laboratory related TEAEs was similar in both treatment arms (6/662 [0/9%] for tedizolid phosphate and 11/662 [1.7%] for linezolid).

There was one (0.2%) patient in the Phase 3 trial who developed the TEAE of 'white blood cell count decreased'. The narrative for this patient is as follows:

> **TR701-112-115-453** was a 53 year old white female with a prior history of cellulitis/erysipelas of the right leg which was treated with ceftriaxone and amoxicillin/clavulanate. Nine days later, the patient received tedizolid phosphate for the treatment of erysipelas/ cellulitis of the right leg. On study day 2, the patient developed diarrhea which lasted 2 days. This adverse event was considered moderate in severity and definitely related to the study drug by the Investigator. The patients was treated with Imodium for the diarrhea and recovered. On study day 13, the patient developed fever which lasted one day. This event was considered moderate and not related to the study drug by the Investigator. The patient was treated with acetaminophen and

recovered. On study day 13, the patient developed 'antibiotic associated diarrhea clostridium dificile' which lasted 20 days. This event was considered moderate in severity and probably related to the study drug. The patient recovered with metronidazole. On study day 2, the patient developed 'irritation on the right knee. New site.' This event was considered mild in severity and not related to the study drug. The patient recovered in 11 days with no new action taken. On study day 4, the patient developed 'decreased white blood cell' which lasted 4 days. On study day 1, the patient's leukocyte count was 10.6 (10^3/µl). The leukocyte count decreased to 2.4 (10^3/µl) by study day 4. By study 18, the leukocyte count rose to 5.6 (10^3/µl). This adverse event was considered moderate and possibly related to the study drug by the Investigator. No action was taken and the patient recovered.

There was one patient (0.2%) each in the tedizolid phosphate and linezolid arms with a TEAE of 'transaminases increased'. There was one (0.2%) patient in the linezolid arm with a TEAE of 'hyperglycemia'. There was one (0.2%) patient in the tedizolid phosphate arm with a TEAE of 'blood glucose increased'.

In the Phase 2 trials, there was only one patient with a laboratory related TEAE. This TEAE was reported as hyperglycemia.

In the Phase 2 and Phase 3 trials, no patients were identified with hypoglycemia or blood glucose decreased.

Table 7.4.2-10: Incidence of laboratory related TEAEs in Phase 2 and Phase 3 studies

		Phase 3 trials	
Body System or Organ Class	*Dictionary-Derived Term*	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Number of patients with at least one laboratory related TEAE		6 (0.9%)	11 (1.7%)
Hepatobiliary disorders			
	Hyperbilirubinaemia	0 (0.0%)	1 (0.2%)
Investigations			
	Blood creatine phosphokinase increased	0 (0.0%)	2 (0.3%)
	Blood creatinine increased	0 (0.0%)	1 (0.2%)
	Blood glucose increased	0 (0.0%)	1 (0.2%)
	Blood magnesium decreased	0 (0.0%)	1 (0.2%)
	Blood potassium decreased	0 (0.0%)	1 (0.2%)
	Transaminases increased	1 (0.2%)	1 (0.2%)
	White blood cell count decreased	1 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders			
	Electrolyte imbalance	0 (0.0%)	1 (0.2%)
	Hyperglycaemia	1 (0.2%)	0 (0.0%)
	Hyperkalaemia	1 (0.2%)	0 (0.0%)
	Hypokalaemia	2 (0.3%)	5 (0.8%)
	Hypomagnesaemia	0 (0.0%)	2 (0.3%)
	Hyponatraemia	0 (0.0%)	1 (0.2%)

In summary, the incidence of laboratory related TEAEs in Phase 2 and Phase 3 trials was similar and low for tedizolid phosphate and linezolid.

7.4.3 Vital Signs

In the Phase 2 and 3 studies, vital signs were measured at all study visits. This includes systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate. For both tedizolid phosphate and linezolid, the EOT values were defined as values within 4 days of the last administration of active study drug. For tedizolid phosphate, the EOT visit is defined as Day 7. For linezolid, the EOT visit is defined as Day 11.

In the Phase 2 and 3 studies, analyses were conducted for the following vital signs systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate by the Safety Reviewer. Identical results were obtained as reported by the Applicant. Hence, tables are taken verbatim directly from the Applicant's Integrated Summary of Safety (5.3.5.3).

Drug-drug interactions which may result in increased blood pressure could not be evaluated in the Phase 2 and Phase 3 trials due to patient exclusion criteria. Additional information regarding the potential effect of tedizolid phosphate on blood pressure can be found in Section 7.3.5 Submission Specific Safety Concerns where drug-drug interactions are discussed. Details can also be found in the Clinical Pharmacology Review.

7.4.3.1 Changes in Blood Pressure from Baseline

Changes in systolic blood pressure (SBP) by time point are summarized in Table 7.4.3-1. In the Phase 2 studies, the mean largest increase from baseline at any time point was +11.4 mm Hg. The mean largest decrease at any time point was -8.4 mm Hg.

In the Phase 3 studies, mean values for SBP were similar at 48-72 hours (+1.1 mm Hg for tedizolid phosphate; -1.2 mm Hg for linezolid) and EOT (+0.8 mm Hg for tedizolid phosphate; -0.88 mm Hg). At any time point, the mean largest increase from baseline for SBP was +11.0 mm Hg for tedizolid phosphate and +9.5 mm Hg for linezolid. The largest decrease from baseline at any time point was -9.5 and -10.9 mm Hg for tedizolid phosphate and linezolid, respectively.

Table 7.4.3-1: Change in Systolic Blood Pressure by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388)	TR-701/FA (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
SBP (mmHg): 48-72 Hours	**n=370**	**n=646**	**n=644**
Baseline			
Mean (SD)	126.8 (15.93)	125.8 (15.52)	127.2 (16.84)
Median	126.0	125.0	125.0
(Min, Max)	(91, 182)	(74, 180)	(90, 212)
48-72 Hours			
Mean (SD)	128.5 (17.06)	126.9 (15.06)	126.0 (14.77)
Median	127.5	125.0	125.0
(Min, Max)	(81, 189)	(90, 187)	(89, 181)
Change from Baseline for 48-72 Hours			
Mean (SD)	1.7 (14.67)	1.1 (13.60)	-1.2 (13.35)
Median	1.0	0.0	-0.5
(Min, Max)	(-52, 62)	(-48, 57)	(-52, 47)
SBP (mmHg): EOT	**n=377**	**n=639**	**n=631**
Baseline			
Mean (SD)	127.0 (16.13)	125.9 (15.63)	127.1 (16.89)
Median	126.0	125.0	125.0
(Min, Max)	(91, 182)	(74, 180)	(90, 212)
EOT			
Mean (SD)	128.5 (16.96)	126.7 (15.13)	126.3 (14.61)
Median	126.0	125.0	124.0
(Min, Max)	(77, 188)	(84, 189)	(83, 189)
Change from Baseline for EOT			
Mean (SD)	1.5 (15.47)	0.8 (14.13)	-0.8 (14.93)
Median	1.0	0.0	0.0
(Min, Max)	(-42, 56)	(-47, 71)	(-80, 58)
SBP (mmHg): Worst Result	**n=381**	**n=655**	**n=654**
Baseline			
Mean (SD)	126.9 (16.23)	126.0 (15.61)	127.1 (16.84)
Median	126.0	125.0	125.0
(Min, Max)	(91, 182)	(74, 180)	(90, 212)
Highest Postbaseline Value			
Mean (SD)	138.3 (16.20)	136.9 (15.88)	136.6 (15.49)
Median	136.0	135.0	134.0
(Min, Max)	(106, 193)	(95, 196)	(98, 209)
Lowest Postbaseline Value			
Mean (SD)	118.5 (14.19)	116.5 (11.98)	116.2 (12.10)
Median	118.0	116.0	115.0
(Min, Max)	(77, 173)	(74, 156)	(83, 167)
Largest Increase from Baseline			
Mean (SD)	11.4 (14.36)	11.0 (13.82)	9.5 (13.20)
Median	11.0	9.0	8.0
(Min, Max)	(-34, 62)	(-31, 83)	(-50, 58)
Largest Decrease from Baseline			
Mean (SD)	-8.4 (13.39)	-9.5 (12.96)	-10.9 (13.49)
Median	-8.0	-8.0	-10.0
(Min, Max)	(-52, 40)	(-93, 48)	(-93, 24)

Source: Post-text Table 1.6.1
Abbreviations: EOT=end of treatment; min=minimum; max=maximum; N=Number of patients in the Safety Analysis Set; n=Number of patients with nonmissing data; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. Largest increase (decrease) corresponds to numerically largest (smallest) change.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 49).

Changes in diastolic blood pressure (DBP) by time point are summarized in Table 7.4.3-2. In the Phase 2 studies, the mean largest increase from baseline at any time point was +7.0 mm Hg. The mean largest decrease at any time point was -6.8 mm Hg.

In the Phase 3 studies, mean values for DBP were similar at 48-72 hours (+0.8 mm Hg for tedizolid phosphate; -0.4 mm Hg for linezolid) and EOT (+0.5 mm Hg for tedizolid phosphate; +0.2 mm Hg). At any time point, the largest increase from baseline for DBP was +8.2 and +7.6 mm Hg for tedizolid phosphate and linezolid, respectively. The largest decrease from baseline at any time point was -7.6 and -7.7 mm Hg for tedizolid phosphate and linezolid, respectively.

Table 7.4.3-2: Change in Diastolic Blood Pressure by Time Point in Phase 2/3 Studies.

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388)	TR-701/FA (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
DBP (mmHg): 48-72 Hours	**n=370**	**n=646**	**n=644**
Baseline			
Mean (SD)	76.9 (11.06)	76.4 (10.28)	77.2 (11.08)
Median	77.0	77.0	77.5
(Min, Max)	(48, 115)	(46, 106)	(42, 159)
48-72 Hours			
Mean (SD)	77.7 (11.17)	77.2 (10.49)	76.9 (9.85)
Median	77.0	78.0	77.0
(Min, Max)	(53, 115)	(42, 114)	(44, 112)
Change from Baseline for 48-72 Hours			
Mean (SD)	0.7 (10.48)	0.8 (10.49)	-0.4 (10.15)
Median	1.0	0.0	0.0
(Min, Max)	(-37, 32)	(-37, 50)	(-65, 34)
DBP (mmHg): EOT	**n=377**	**n=639**	**n=631**
Baseline			
Mean (SD)	77.1 (11.09)	76.5 (10.33)	77.3 (11.01)
Median	78.0	77.0	78.0
(Min, Max)	(48, 115)	(46, 106)	(42, 159)
EOT			
Mean (SD)	77.6 (11.77)	77.0 (10.16)	77.4 (10.09)
Median	78.0	78.0	78.0
(Min, Max)	(46, 120)	(48, 110)	(48, 112)
Change from Baseline for EOT			
Mean (SD)	0.5 (10.68)	0.5 (10.58)	0.2 (10.28)
Median	0.0	0.0	0.0
(Min, Max)	(-35, 31)	(-35, 50)	(-69, 31)
DBP (mmHg): Worst Result	**n=381**	**n=655**	**n=654**
Baseline			
Mean (SD)	77.0 (11.12)	76.5 (10.32)	77.1 (11.07)
Median	78.0	77.0	77.0
(Min, Max)	(48, 115)	(46, 106)	(42, 159)
Highest Postbaseline Value			
Mean (SD)	84.0 (10.42)	84.7 (9.50)	84.7 (9.27)
Median	84.0	85.0	85.0
(Min, Max)	(57, 120)	(59, 117)	(56, 114)
Lowest Postbaseline Value			
Mean (SD)	70.2 (10.18)	68.9 (9.26)	69.5 (9.16)
Median	70.0	70.0	70.0
(Min, Max)	(46, 107)	(35, 104)	(44, 101)
Largest Increase from Baseline			
Mean (SD)	7.0 (9.85)	8.2 (10.05)	7.6 (9.46)
Median	6.0	7.0	6.0
(Min, Max)	(-35, 39)	(-29, 50)	(-62, 36)
Largest Decrease from Baseline			
Mean (SD)	-6.8 (9.98)	-7.6 (9.73)	-7.7 (9.24)
Median	-7.0	-6.0	-6.0
(Min, Max)	(-40, 19)	(-48, 20)	(-74, 22)

Source: Post-text Table 1.6.1
Abbreviations: EOT=end of treatment; min=minimum; max=maximum; N=Number of patients in the Safety Analysis Set; n=Number of patients with nonmissing data; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. Largest increase (decrease) corresponds to numerically largest (smallest) change.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 50).

Details of potentially clinically significant blood pressure abnormalities by time point in the Phase 2 and 3 trials are presented in Table 7.4.3-3.

Table 7.4.3-3: Potentially clinically significant blood pressure abnormalities by time point in the Phase 2 and 3 studies

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388) n (%)	TR-701/FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Systolic Blood Pressure (mmHg)			
48-72 Hours	**N1=370**	**N1=646**	**N1=644**
Potentially Clinically Significant Abnormal	4 (1.1)	3 (0.5)	4 (0.6)
≥180 mmHg and increase ≥20 mmHg from baseline	3 (0.8)	3 (0.5)	0
≤90 mmHg and decrease ≥20 mmHg from baseline	1 (0.3)	0	4 (0.6)
EOT	**N1=377**	**N1=639**	**N1=631**
Potentially Clinically Significant Abnormal	5 (1.3)	1 (0.2)	2 (0.3)
≥180 mmHg and increase ≥20 mmHg from baseline	3 (0.8)	1 (0.2)	1 (0.2)
≤90 mmHg and decrease ≥20 mmHg from baseline	2 (0.5)	0	1 (0.2)
Worst Postbaseline Result	**N1=381**	**N1=655**	**N1=654**
Potentially Clinically Significant Abnormal	12 (3.1)	9 (1.4)	12 (1.8)
≥180 mmHg and increase ≥20 mmHg from baseline	7 (1.8)	8 (1.2)	4 (0.6)
≤90 mmHg and decrease ≥20 mmHg from baseline	5 (1.3)	1 (0.2)	8 (1.2)
Diastolic Blood Pressure (mmHg)			
48-72 Hours	**N1=370**	**N1=646**	**N1=644**
Potentially Clinically Significant Abnormal	2 (0.5)	5 (0.8)	2 (0.3)
≥105 mmHg and increase ≥15 mmHg from baseline	2 (0.5)	4 (0.6)	1 (0.2)
≤50 mmHg and decrease ≥15 mmHg from baseline	0	1 (0.2)	1 (0.2)
EOT	**N1=377**	**N1=639**	**N1=631**
Potentially Clinically Significant Abnormal	5 (1.3)	3 (0.5)	4 (0.6)
≥105 mmHg and increase ≥15 mmHg from baseline	3 (0.8)	2 (0.3)	1 (0.2)
≤50 mmHg and decrease ≥15 mmHg from baseline	2 (0.5)	1 (0.2)	3 (0.5)
Worst Postbaseline Result	**N1=381**	**N1=655**	**N1=654**
Potentially Clinically Significant Abnormal	10 (2.6)	23 (3.5)	19 (2.9)
≥105 mmHg and increase ≥15 mmHg from baseline	6 (1.6)	16 (2.4)	11 (1.7)
≤50 mmHg and decrease ≥15 mmHg from baseline	4 (1.0)	7 (1.1)	9 (1.4)

Source: Post-text Table 1.6.2
Abbreviations: EOT=end of treatment; min=minute; N=number of patients in the Safety Analysis Set; N1=number of patients with nonmissing data at the summarized visit and is used as the denominator to calculate percentage; n=number of patients in the specified category

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 51).

7.4.3.2 TEAEs Related to blood pressure

The number of patients with TEAE of blood pressure increased or hypertension was examined (Table 7.4.3-4). In Phase 3 trials, there were 7/662 (1.1%) in the tedizolid phosphate arm and 4/662 (0.6%) who developed a TEAE of 'blood pressure increased' or 'hypertension'.

In Phase 2 trials, 8/388 (2.1%) patients had a TEAE of blood pressure increased (7/388 [1.8%]) or hypertension (1/388 [0.3%]).

Table 7.4.3-4: Number of patients with TEAE of 'blood pressure increased' or 'hypertension'

		Phase 2 Studies	**Phase 3 Studies**	
Body System or Organ Class	*Dictionary-Derived Term*	**Tedizolid phosphate (≥200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Number of patients with TEAE of 'blood pressure increased' or 'hypertension'		8 (2.1%)	7 (1.1%)	4 (0.6%)
Investigations	Blood pressure increased	7 (1.8%)	2 (0.3%)	2 (0.3%)
Vascular disorders	Hypertension	1 (0.3%)	5 (0.8%)	2 (0.3%)

Patients experiencing a TEAE of 'blood pressure increased' or 'hypertension' were on a wide range of concomitant medications (Table 7.4.3-5). The TEAE was considered serious in one elderly patient (**TR701-113-147-639**) and is described.

> **TR701-113-147-639** was an 82 year old white male with a history of cholelithiasis, resected colon cancer, appendectomy, hypertension, stable angina, infrarenal aortic aneurysm, abdominal aortic aneurysm, hypothyroidism, pulmonary fibrosis, rib fracture, malignant skin cancer, obesity, chronic renal insufficiency, gastroespohageal reflux disease, and a non-healing ulcer and right leg cellulitis from a bedrail injury at the primary ABSSSI site. The patient developed serious and severe hypertension which resolved with other drug therapy.

Reference ID: 3521547

Table 7.4.3-5: Line listing of patients with TEAE of 'blood pressure increased' or 'hypertension' and concomitant medications

Analysis Unique Subject ID	Age	Sex	Country	Pooled Actual Treatment	Study Day of Start of Adverse Event	Dictionary-Derived Term	Serious Event	Outcome of Adverse Event	Causality	Standardized Medication Name
TR701-104-001-025	54	M	USA	TR-701 ≥ 200mg	3	Blood pressure increased	N	RECOVERED/ RESOLVED	POSSIBLE	VICODIN INSULIN INSULIN NOVOLIN 70/30 CLINDAMYCIN ACETYLSALICYLIC ACID LIDOCAINE ONDANSETRON IBUPROFEN MORPHINE BACTRIM
TR701-104-002-012	57	M	USA	TR-701 ≥ 200mg	5	Blood pressure increased	N	RECOVERED/ RESOLVED	PROBABLE	BACLOFEN SULFASALAZINE XYLOCAINE-EPINEPHRINE
TR701-104-004-033	45	F	USA	TR-701 ≥ 200mg	2	Blood pressure increased	N	RECOVERED/ RESOLVED	POSSIBLE	BACTRIM ATORVASTATIN CALCIUM
TR701-104-004-053	38	F	USA	TR-701 ≥ 200mg	4	Blood pressure increased	N	NOT RECOVERED/ NOT RESOLVED	POSSIBLE	LIDOCAINE MEDROXYPROGESTERONE ACETATE DOZOL /00435101/
TR701-104-004-054	22	M	USA	TR-701 ≥ 200mg	2	Blood pressure increased	N	NOT RECOVERED/ NOT RESOLVED	NOT RELATED	DIHYDROXYALUMINUM SODIUM CARBONATE LIDOCAINE IBUPROFEN VICODIN DEXTROMETHORPHAN HYDROBROMIDE

										DOXYLAMINE SUCCINATE NAPROXEN APOREX
TR701-104-005-009	52	M	USA	TR-701 ≥ 200mg	5	Hypertension	N	NOT RECOVERED/ NOT RESOLVED	POSSIBLE	VICODIN POVIDONE-IODINE XYLOCAINE-EPINEPHRINE DOXYCYCLINE BACTRIM
TR701-104-005-027	67	M	USA	TR-701 ≥ 200mg	7	Blood pressure increased	N	RECOVERED/ RESOLVED	NOT RELATED	VICODIN HYDROCHLOROTHIAZIDE NABUMETONE ECONAZOLE NITRATE CEFALEXIN CHLORHEXIDINE GLUCONATE LINEZOLID HYDROCODONE SIMVASTATIN INSULIN GLARGINE VICODIN INSULIN LISPRO MUPIROCIN BACTRIM LISINOPRIL LIDOCAINE
TR701-104-005-031	30	M	USA	TR-701 ≥ 200mg	3	Blood pressure increased	N	RECOVERED/ RESOLVED	POSSIBLE	LIDOCAINE MUPIROCIN CHLORHEXIDINE GLUCONATE THOMAPYRIN N
TR701-112-102-181	50	M	USA	TR-701 200mg	7	Hypertension	N	NOT RECOVERED/ NOT RESOLVED	NOT RELATED	ACETYLSALICYLIC ACID AMLODIPINE BESILATE VICODIN CARVEDILOL

										LISINOPRIL METOPROLOL TARTRATE BACTRIM
TR701-112-103-131	46	M	USA	Linezolid 1200mg	20	Blood pressure increased	N	RECOVERED/ RESOLVED	NOT RELATED	PARACETAMOL
TR701-112-103-277	55	M	USA	TR-701 200mg	4	Hypertension	N	RECOVERED/ RESOLVED	NOT RELATED	CLONIDINE VICODIN LIDOCAINE LISINOPRIL HUMAN MIXTARD /00806401/
TR701-112-130-301	51	M	USA	Linezolid 1200mg	4	Hypertension	N	NOT RECOVERED/ NOT RESOLVED	NOT RELATED	LIDOCAINE ETHANOL POVIDONE-IODINE
TR701-112-173-414	84	F	CAN	TR-701 200mg	1	Blood pressure increased	N	RECOVERED/ RESOLVED	NOT RELATED	POTASSIUM CHLORIDE SENNOSIDE A+B BETAMETHASONE DIPROPIONATE CITALOPRAM HYDROMORPHONE LORAZEPAM FLUDROCORTISONE ACETATE GLYCEROL FOSAVANCE PARACETAMOL CALCIUM CARBONATE DOMPERIDONE PANTOPRAZOLE SODIUM CIPROFLOXACIN CARMELLOSE SODIUM ACETYLSALICYLIC ACID DOCUSATE SODIUM
TR701-113-147-639	82	M	USA	TR-701 200mg	2	Hypertension	Y	RECOVERED/ RESOLVED	NOT RELATED	HYDROMORPHONE HYDROCHLORIDE TYLOX

										HYDROMORPHONE HYDROCHLORIDE MULTIVITAMINS ACETYLSALICYLIC ACID NIFEDIPINE ISOSORBIDE MONONITRATE TYLOX ENOXAPARIN SODIUM AMLODIPINE BESILATE METOPROLOL TARTRATE SODIUM CHLORIDE PANTOPRAZOLE SODIUM TYLOX PNEUMOCOCCAL VACCINE POLYVALENT
TR701-113-165-598	45	M	USA	TR-701 200mg	2	Hypertension	N	NOT RECOVERED/ NOT RESOLVED	NOT RELATED	ONDANSETRON SODIUM CHLORIDE ZOLPIDEM TARTRATE OXYCODONE BENAZEPRIL VANCOMYCIN CEFAZOLIN SODIUM VANCOMYCIN CLINDAMYCIN DOXYCYCLINE
TR701-113-211-208	29	M	POL	TR-701 200mg	3	Blood pressure increased	N	RECOVERED/ RESOLVED	NOT RELATED	RAMIPRIL
TR701-113-286-392	80	F	RUS	Linezolid 1200mg	17	Hypertension	N	RECOVERED/ RESOLVED	NOT RELATED	BARALGINA IBUPROFEN KETOPROFEN LISINOPRIL VINPOCETINE BETAHISTINE HYDROCHLORIDE

										NICOTINIC ACID
TR701-113-286-545	53	M	RUS	TR-701 200mg	26	Hypertension	N	NOT RECOVERED/ NOT RESOLVED	NOT RELATED	AZTREONAM KETOPROFEN KETOROLAC TROMETHAMINE PARACETAMOL KETOROLAC TROMETHAMINE PARACETAMOL DIMETHYL SULFOXIDE LIDOCAINE HYDROCHLORIDE ENALAPRIL
TR701-113-289-562	43	M	RUS	Linezolid 1200mg	6	Blood pressure increased	N	RECOVERED/ RESOLVED	NOT RELATED	ENALAPRIL SODIUM CHLORIDE TORASEMIDE
TR701-113-358-500	70	F	ARG	Linezolid 1200mg	1	Hypertension	N	RECOVERED/ RESOLVED	NOT RELATED	METFORMIN ENALAPRIL FUROSEMIDE AMLODIPINE CARVEDILOL
TR701-113-359-244	51	M	ARG	Linezolid 1200mg	1	Hypertension	N	RECOVERED/ RESOLVED	NOT RELATED	DICLOFENAC SODIUM NALBUPHINE HYDROCHLORIDE HEPARIN RANITIDINE ACENOCOUMAROL ENALAPRIL
TR701-113-448-241	37	M	ZAF	TR-701 200mg	-1	Blood pressure increased	N	NOT RECOVERED/ NOT RESOLVED	NOT RELATED	NIFEDIPINE AZTREONAM

TR701-113-448-378	49	M	ZAF	Linezolid 1200mg	-1	Blood pressure increased	N	RECOVERED/ RESOLVED	NOT RELATED	NIFEDIPINE

In summary, analyses of blood pressure changes on treatment indicate that clinically significant changes were infrequent and similar for both tedizolid phosphate and linezolid. Refer to Section 7.3.5 regarding drug-drug interactions which may influence blood pressure.

7.4.3.3 Changes in Heart and Respiratory Rates from Baseline

Changes in heart rate by time point are summarized in Table 7.4.3-6. In the Phase 2 studies, the mean change from baseline heart rate was -0.9 at 48-72 hours and -2.8 at EOT. The mean largest increase at any time point postbaseline was +8.3 bpm. The mean largest decrease at any time point postbaseline was -10.2 bpm.

In the Phase 3 studies, the mean change from baseline at 48-72 hours was -4.2 bpm and -3.1 bpm for tedizolid phosphate and linezolid, respectively. At EOT, the mean change from baseline was -4.9 bpm and -2.1 bpm for tedizolid phosphate and linezolid, respectively. The mean highest heart rate at any time point postbaseline was 88.1 bpm for tedizolid phosphate and 88.2 bpm for linezolid. The mean lowest heart rate at any time point postbaseline was 69.1 bpm for tedizolid phosphate and 70.2 bpm for linezolid. The mean largest increase in heart rate was +7.0 bpm and +7.6 bpm for tedizolid phosphate and linezolid, respectively. The mean largest decrease in heart rate was -12.1 bpm and -10.4 bpm for tedizolid phosphate and linezolid, respectively.

Table 7.4.3-6: Change in Heart Rate by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies TR-701/FA ≥200 mg (N=388)	Controlled Studies TR-701/FA (200 mg) (N=662)	Controlled Studies Linezolid (1200 mg) (N=662)
HR (beats/min): 48-72 Hours	**n=370**	**n=646**	**n=642**
Baseline			
Mean (SD)	79.6 (14.05)	81.0 (13.39)	80.6 (13.04)
Median	79.0	80.0	80.0
(Min, Max)	(42, 131)	(48, 120)	(45, 129)
48-72 Hours			
Mean (SD)	78.7 (13.97)	76.9 (12.21)	77.4 (11.44)
Median	77.5	75.0	76.0
(Min, Max)	(41, 142)	(43, 124)	(45, 126)
Change from Baseline for 48-72 Hours			
Mean (SD)	-0.9 (14.31)	-4.2 (13.33)	-3.1 (12.19)
Median	-1.0	-3.0	-2.0
(Min, Max)	(-47, 48)	(-60, 50)	(-56, 52)
HR (beats/min): EOT	**n=377**	**n=638**	**n=630**
Baseline			
Mean (SD)	79.8 (14.06)	81.3 (13.45)	80.5 (13.08)
Median	79.0	80.0	80.0
(Min, Max)	(42, 131)	(48, 120)	(45, 129)
EOT			
Mean (SD)	77.0 (13.26)	76.4 (12.32)	78.4 (11.69)
Median	75.0	75.0	77.0
(Min, Max)	(45, 121)	(47, 124)	(50, 120)
Change from Baseline for EOT			
Mean (SD)	-2.8 (14.73)	-4.9 (14.72)	-2.1 (13.97)
Median	-2.0	-4.0	-1.0
(Min, Max)	(-68, 39)	(-55, 55)	(-54, 41)
HR (beats/min): Worst Result	**n=381**	**n=655**	**n=652**
Baseline			
Mean (SD)	79.8 (14.15)	81.1 (13.42)	80.6 (13.08)
Median	79.0	80.0	80.0
(Min, Max)	(42, 131)	(48, 120)	(45, 129)
Highest Postbaseline Value			
Mean (SD)	88.1 (13.75)	88.1 (12.77)	88.2 (12.26)
Median	88.0	87.0	87.0
(Min, Max)	(46, 142)	(58, 130)	(58, 135)
Lowest Postbaseline Value			
Mean (SD)	69.6 (11.17)	69.1 (9.48)	70.2 (9.07)
Median	69.0	69.0	70.0
(Min, Max)	(35, 121)	(43, 109)	(44, 108)
Largest Increase from Baseline			
Mean (SD)	8.3 (14.02)	7.0 (13.25)	7.6 (12.74)
Median	7.0	6.0	7.0
(Min, Max)	(-41, 48)	(-36, 55)	(-32, 56)
Largest Decrease from Baseline			
Mean (SD)	-10.2 (13.14)	-12.1 (12.44)	-10.4 (11.20)
Median	-9.0	-10.0	-8.0
(Min, Max)	(-68, 28)	(-60, 29)	(-56, 31)

Source: Post-text Table 1.6.1
Abbreviations: EOT=end of treatment; Min=minimum; Max=maximum; N=Number of patients in the Safety Analysis Set; n=Number of patients with nonmissing data; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. Largest increase (decrease) corresponds to numerically largest (smallest) change.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 52).

Changes in respiratory rate by time point are summarized in Table 7.4.3-7. In the Phase 2 studies, the mean change from baseline respiratory rate was 0.0 breaths per minute at 48-72 hours and 0.1 breaths per minute at EOT. The mean largest increase at any time point postbaseline was 1.2 breaths per minute. The mean largest decrease at any time point postbaseline was -1.0 breaths per minute.

In the Phase 3 studies, the mean change from baseline at 48-72 hours was -0.4 breaths per minute for both tedizolid phosphate and linezolid. At EOT, the mean change from baseline was -0.6 breaths per minute and -0.4 breaths per minute for tedizolid phosphate and linezolid, respectively. The mean highest respiratory rate at any time point postbaseline was 18.5 breaths per minute for tedizolid phosphate and 18.3 breaths per minute for linezolid. The mean lowest respiratory rate at any time point postbaseline was 16.0 breaths per minute for tedizolid phosphate and 15.9 breaths per minute for linezolid. The mean largest increase in respiratory rate was 0.9 and 0.8 breaths per minute for tedizolid phosphate and linezolid, respectively. The mean largest decrease in respiratory rate was -1.6 breaths per minute for both tedizolid phosphate and linezolid.

Table 7.4.3-7: Change in Respiratory Rate by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies TR-701/FA ≥200 mg (N=388)	Controlled Studies TR-701/FA (200 mg) (N=662)	Controlled Studies Linezolid (1200 mg) (N=662)
RR (breaths/min): 48-72 Hours	**n=370**	**n=642**	**n=644**
Baseline			
Mean (SD)	17.1 (1.85)	17.6 (2.02)	17.5 (2.17)
Median	16.0	18.0	18.0
(Min, Max)	(12, 22)	(12, 27)	(12, 30)
48-72 Hours			
Mean (SD)	17.1 (1.77)	17.2 (1.87)	17.1 (1.87)
Median	16.0	17.0	17.0
(Min, Max)	(12, 24)	(12, 28)	(11, 26)
Change from Baseline for 48-72 Hours			
Mean (SD)	0.0 (1.94)	-0.4 (2.06)	-0.4 (2.21)
Median	0.0	0.0	0.0
(Min, Max)	(-6, 8)	(-10, 8)	(-12, 6)
RR (breaths/min): EOT	**n=377**	**n=634**	**n=632**
Baseline	17.1 (1.85)	17.6 (2.03)	17.5 (2.16)
Mean (SD)	16.0	18.0	18.0
Median	(12, 22)	(12, 27)	(12, 30)
(Min, Max)			
EOT	17.2 (1.81)	17.0 (1.90)	17.1 (1.87)
Mean (SD)	17.0	17.0	17.0
Median	(12, 22)	(11, 26)	(10, 23)
(Min, Max)			
Change from Baseline for EOT	0.1 (1.92)	-0.6 (2.19)	-0.4 (2.26)
Mean (SD)	0.0	0.0	0.0
Median	(-6, 6)	(-12, 8)	(-14, 6)
(Min, Max)	377	634	632
RR (breaths/min): Worst Result	**n=381**	**n=651**	**n=654**
Baseline			
Mean (SD)	17.1 (1.85)	17.6 (2.01)	17.5 (2.16)
Median	16.0	18.0	18.0
(Min, Max)	(12, 22)	(12, 27)	(12, 30)
Highest Postbaseline Value			
Mean (SD)	18.2 (1.74)	18.5 (2.73)	18.3 (1.90)
Median	18.0	18.0	18.0
(Min, Max)	(12, 24)	(13, 69)	(12, 27)
Lowest Postbaseline Value			
Mean (SD)	16.0 (1.73)	16.0 (1.67)	15.9 (1.69)
Median	16.0	16.0	16.0
(Min, Max)	(12, 20)	(11, 22)	(10, 20)
Largest Increase from Baseline			
Mean (SD)	1.2 (1.79)	0.9 (2.81)	0.8 (1.97)
Median	1.0	0.0	1.0
(Min, Max)	(-6, 8)	(-6, 52)	(-8, 8)
Largest Decrease from Baseline			
Mean (SD)	-1.0 (1.85)	-1.6 (2.04)	-1.6 (2.07)
Median	-1.0	-1.0	-1.0
(Min, Max)	(-8, 4)	(-12, 6)	(-16, 2)

Source: Post-text Table 1.6.1
Abbreviations: EOT=end of treatment; Min=minimum; Max=maximum; N=Number of patients in the Safety Analysis Set; n=Number of patients with nonmissing data; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. Largest increase (decrease) corresponds to numerically largest (smallest) change.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 53).

Details of potentially clinically significant heart and respiratory rate abnormalities by time point in the Phase 2 and 3 trials are presented in Table 7.4.3-8.

Table 7.4.3-8: Potentially clinically significant heart and respiratory rate abnormalities by time point in the Phase 2 and 3 studies

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388) n (%)	TR-701/FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
Heart Rate (beats/min)			
48-72 Hours	N1=370	N1=646	N1=642
Potentially Clinically Significant Abnormal	3 (0.8)	3 (0.5)	2 (0.3)
≥120 beats/min and increase ≥15 beats/min from BL	2 (0.5)	0	1 (0.2)
≤50 beats/min and decrease ≥15 beats/min from BL	1 (0.3)	3 (0.5)	1 (0.2)
EOT	N1=377	N1=638	N1=630
Potentially Clinically Significant Abnormal	1 (0.3)	6 (0.9)	1 (0.2)
≥120 beats/min and increase ≥15 beats/min from BL	0	3 (0.5)	0
≤50 beats/min and decrease ≥15 beats/min from BL	1 (0.3)	3 (0.5)	1 (0.2)
Worst Postbaseline Result	N1=381	N1=655	N1=652
Potentially Clinically Significant Abnormal	6 (1.6)	16 (2.4)	11 (1.7)
≥120 beats/min and increase ≥15 beats/min from BL	2 (0.5)	9 (1.4)	8 (1.2)
≤50 beats/min and decrease ≥15 beats/min from BL	4 (1.0)	7 (1.1)	3 (0.5)
Respiratory Rate (breaths/min)			
48-72 Hours	N1=370	N1=642	N1=644
Potentially Clinically Significant Abnormal	0	0	0
≥30 breaths/min and increase ≥10 breaths/min from BL	0	0	0
≤8 breaths/min and decrease ≥4 breaths/min from BL	0	0	0
EOT	N1=377	N1=634	N1=632
Potentially Clinically Significant Abnormal	0	0	0
≥30 breaths/min and increase ≥10 breaths/min from BL	0	0	0
≤8 breaths/min and decrease ≥4 breaths/min from BL	0	0	0
Worst Postbaseline Result	N1=381	N1=651	N1=654
Potentially Clinically Significant Abnormal	0	2 (0.3)	0
≥30 breaths/min and increase ≥10 breaths/min from BL	0	2 (0.3)	0
≤8 breaths/min and decrease ≥4 breaths/min from BL	0	0	0

Source: Post-text Table 1.6.2
Abbreviations: BL=baseline; EOT=end of treatment; min=minute; N=number of patients in the Safety Analysis Set; N1=number of patients with nonmissing data at the summarized visit; n=number of patients in the specified category
Note: All patients in the safety analysis set with nonmissing data at the summarized visit are used as the denominator to calculate percentages.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 54).

7.4.4 Electrocardiograms (ECGs)

The Applicant collected 12 lead ECGs in all studies conducted during the drug development program. In addition, the Applicant conducted a Phase 1 cardiac safety and thorough QT study (TR701-115). The same central ECG laboratory interpreted ECG results for TR701-112, TR701-113, and TR701-126. An independent cardiologist interpreted ECGs for TR701-104.

TR701-115 was a Phase 1 randomized sequence crossover study which evaluated the potential for QT interval prolongation in healthy subjects with a continuous Holter monitor. Subjects received a single administration of each study drug: tedizolid phosphate 200 mg (n=44), tedizolid phosphate 1200 mg (n=46), moxifloxacin (n=47), and placebo (n=44). There was no effect on heart rate, atrioventricular conduction, or cardiac depolarization as measured by PR, QRS, and QTcF intervals when tedizolid phosphate was administered at therapeutic (200 mg) or supratherapeutic (1200 mg) doses.

In the Phase 2 and 3 studies, analyses were conducted for the following ECG parameters: heart rate, PR duration, QT interval corrected for heart rate using Bazett's (QTcB) formula and the QT interval corrected for heart rate using Fridericia's (QTcF) formula. The Safety Reviewer carried out analyses of data on these ECG parameters for the Phase 2 and Phase 3 studies. Identical results were obtained as reported by the Applicant. Hence, tables are taken verbatim directly from the Applicant's Integrated Summary of Safety (5.3.5.3).

7.4.4.1 Changes from Baseline

For Phase 2 and 3 studies, ECG parameters of heart rate, PR interval, QTcB and QTcF were analyzed by time point. In the Phase 3 trials, ECGs were performed at screening, 48-72 hours, and Day 7. It should be noted that in the Phase 3 trials, Day 7 corresponds to EOT for tedizolid phosphate. For linezolid, EOT is at 10 days, when ECGs were not typically obtained. Per the Applicant, ECG values on Day 7 are captured in the 'Worst Result' category. In the Phase 2 study, TR701-104, ECGs were performed at screening and EOT (Day 6). In the second Phase 2 study, TR701-126, ECGs were performed at screening and 48-72 hours. Results for worst postbaseline values for high and low values for heart rate, QTcB and QTcF and high values for the PR interval are presented.

Changes in heart rate by ECG are summarized in Table 7.4.4-1. In Phase 2 studies, the mean change from baseline was <3 bpm at all time points.

In Phase 3 studies, heart rate decreased from baseline to the 48-72 hour visit (mean -6.1 bpm tedizolid phosphate; -4.2 bpm linezolid). The mean greatest decrease from baseline was -11.9

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bpm for tedizolid phosphate and -10.3 bpm for linezolid. The mean greatest increase in heart rate from baseline was +1.8 and +3.7 bpm for tedizolid phosphate and linezolid, respectively.

Table 7.4.4-1: Changes in ECG Heart Rate by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies TR-701/FA ≥200 mg (N=388)	Controlled Studies TR-701/FA (200 mg) (N=662)	Controlled Studies Linezolid (1200 mg) (N=662)
Heart Rate (beats/min): 48-72 Hours	**n=186**	**n=630**	**n=626**
Baseline			
Mean (SD)	74.9 (13.49)	76.8 (14.04)	76.9 (13.65)
Median	74.7	75.3	75.3
(Min, Max)	(50, 121)	(44, 127)	(45, 133)
48-72 Hours: Postbaseline			
Mean (SD)	72.8 (12.31)	70.7 (12.89)	72.7 (12.37)
Median	71.7	69.0	72.0
(Min, Max)	(48, 120)	(39, 126)	(43, 118)
48-72 Hours: Change from Baseline			
Mean (SD)	-2.1 (10.78)	-6.1 (12.46)	-4.2 (12.20)
Median	-2.0	-5.3	-3.3
(Min, Max)	(-52, 22)	(-58, 43)	(-49, 38)
Heart Rate (beats/min): EOT	**n=171**	**n=610**	**n=34[a]**
Baseline			
Mean (SD)	72.5 (13.09)	76.6 (14.07)	76.9 (12.31)
Median	72.0	75.3	75.5
(Min, Max)	(39, 107)	(44, 127)	(54, 106)
EOT: Postbaseline			
Mean (SD)	69.9 (13.25)	72.4 (12.85)	76.4 (10.54)
Median	69.0	71.7	76.5
(Min, Max)	(40, 104)	(43, 123)	(58, 100)
EOT: Change from Baseline			
Mean (SD)	-2.6 (12.12)	-4.3 (13.45)	-0.6 (8.92)
Median	-3.0	-4.0	-0.5
(Min, Max)	(-32, 34)	(-58, 53)	(-18, 17)
Heart Rate (beats/min): Worst Result	**n=357**	**n=632**	**n=626**
Baseline			
Mean (SD)	73.7 (13.33)	76.7 (14.04)	76.9 (13.65)
Median	73.0	75.3	75.3
(Min, Max)	(39, 121)	(44, 127)	(45, 133)
Postbaseline – Low Value			
Mean (SD)	71.4 (12.84)	64.8 (11.21)	66.6 (10.78)
Median	70.7	63.7	66.0
(Min, Max)	(40, 120)	(39, 111)	(41, 111)
Change from Baseline – Low Value			
Mean (SD)	-2.3 (11.54)	-11.9 (11.38)	-10.3 (11.08)
Median	-2.7	-10.7	-8.7
(Min, Max)	(-52, 34)	(-69, 29)	(-52, 25)
Postbaseline – High Value			
Mean (SD)	71.5 (12.89)	78.5 (13.33)	80.7 (12.46)
Median	71.0	77.3	80.0
(Min, Max)	(40, 120)	(47, 127)	(52, 125)
Change from Baseline – High Value			
Mean (SD)	-2.3 (11.51)	1.8 (12.49)	3.7 (12.32)
Median	-2.3	1.7	4.0
(Min, Max)	(-52, 34)	(-52, 53)	(-48, 47)

Source: Post-text Table 1.7.1.
Abbreviations: EOT=end of therapy; min=minute; Min=minimum; Max=maximum; N=number of patients in the Safety Analysis Set; n=number of patients with nonmissing data; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. There are no scheduled ECG results for TR701-104 at 48-72 hours, for TR701-126 at EOT, and for linezolid patients in Controlled Studies at EOT Change from baseline high (low) value corresponds to numerically largest (smallest) change.
[a] Unscheduled ECGs.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 59).

Changes in PR interval are summarized in Table 7.4.4-2. In Phase 2 studies, the mean PR interval change from baseline was 1.2 msec at 48-72 hours and 1.0 msec at EOT. The high mean change from baseline at any time point was 1.2 msec.

In Phase 3 studies, PR interval changed from baseline at the 48-72 hour visit (+2.2 msec tedizolid phosphate; +2.6 msec linezolid). The mean change from baseline at EOT was+0.3 msec and -2.3 msec for tedizolid phosphate and linezolid, respectively. The mean greatest change from baseline at any time was +8.3 msec for tedizolid phosphate and +9.5 for linezolid.

Table 7.4.4-2: Changes in PR Interval by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388)	TR-701/FA (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
PR Interval (msec): 48-72 Hours	**n=186**	**n=617**	**n=615**
Baseline			
Mean (SD)	154.1 (18.26)	156.3 (21.89)	156.5 (21.50)
Median	152.2	155.3	154.7
(Min, Max)	(102, 216)	(104, 275)	(87, 276)
48-72 Hours: Postbaseline			
Mean (SD)	155.3 (20.34)	158.5 (21.95)	159.2 (21.55)
Median	153.8	156.3	156.7
(Min, Max)	(97, 263)	(101, 254)	(92, 257)
48-72 Hours: Change from Baseline			
Mean (SD)	1.2 (13.11)	2.2 (10.95)	2.6 (10.79)
Median	0.5	1.7	1.7
(Min, Max)	(-42, 114)	(-39, 48)	(-41, 58)
PR Interval (msec): EOT	**n=170**	**n=599**	**n=33[a]**
Baseline			
Mean (SD)	154.2 (23.21)	156.6 (21.96)	156.8 (22.01)
Median	151.0	155.3	154.7
(Min, Max)	(70, 256)	(104, 275)	(118, 202)
EOT: Postbaseline			
Mean (SD)	155.2 (23.82)	157.0 (21.60)	154.5 (21.49)
Median	152.0	154.7	154.0
(Min, Max)	(60, 240)	(103, 270)	(121, 199)
EOT: Change from Baseline			
Mean (SD)	1.0 (10.67)	0.3 (11.18)	-2.3 (9.36)
Median	2.0	0.7	1.0
(Min, Max)	(-38, 38)	(-39, 42)	(-19, 13)
PR Interval (msec): Worst Result	**n=356**	**n=620**	**n=615**
Baseline			
Mean (SD)	154.1 (20.72)	156.3 (21.87)	156.5 (21.50)
Median	152.0	155.3	154.7
(Min, Max)	(70, 256)	(104, 275)	(87, 276)
Postbaseline – High Value			
Mean (SD)	155.3 (21.99)	164.7 (22.10)	166.0 (21.50)
Median	152.0	162.0	163.7
(Min, Max)	(60, 263)	(114, 270)	(100, 264)
Change from Baseline – High Value			
Mean (SD)	1.2 (11.89)	8.3 (10.17)	9.5 (10.93)
Median	0.8	8.0	8.0
(Min, Max)	(-42, 114)	(-39, 48)	(-28, 114)

Source: Post-text Table 1.7.1.
Abbreviations: EOT=end of treatment; Max=maximum; Min=minimum; msec=millisecond; N=number of patients in the Safety Analysis Set; n=number of patients with nonmissing data; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. There are no scheduled ECG results for patients in TR701-104 at 48-72 hours, TR701-126 at EOT, and linezolid group of Controlled Studies at EOT. Change from baseline high value corresponds to numerically largest change.
[a] Unscheduled ECGs.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 60).

Changes in QTcB interval are summarized in Table 7.4.4-3. In Phase 2 studies, the mean QTcB interval change from baseline was -2.3 msec at 48-72 hours and 3.6 msec at EOT. The high mean change from baseline at any time point was -2.1 msec.

In Phase 3 studies, QTcB interval changed from baseline at the 48-72 hour visit (mean change -0.8 msec tedizolid phosphate; +1.7 msec linezolid). The mean change from baseline at EOT was +0.2 msec and +0.9 msec for tedizolid phosphate and linezolid, respectively. The mean greatest change from baseline at any time was +10.4 msec for tedizolid phosphate and +13.6 for linezolid.

Table 7.4.4-3: Changes in QTcB Interval by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388)	TR-701/FA (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
QTcB Interval (msec): 48-72 Hours	**n=185**	**n=630**	**n=626**
Baseline			
Mean (SD)	424.7 (22.12)	424.9 (24.01)	426.1 (24.64)
Median	424.0	423.2	425.3
(Min, Max)	(368, 516)	(365, 542)	(359, 537)
48-72 Hours: Postbaseline			
Mean (SD)	422.4 (23.31)	424.1 (23.44)	427.8 (24.84)
Median	422.7	423.7	428.0
(Min, Max)	(376, 506)	(351, 501)	(341, 509)
48-72 Hours: Change from Baseline			
Mean (SD)	-2.3 (14.76)	-0.8 (17.12)	1.7 (17.59)
Median	-2.0	-1.0	2.0
(Min, Max)	(-41, 34)	(-82, 69)	(-79, 64)
QTcB Interval (msec): EOT	**n=4[a]**	**n=610**	**n=34[b]**
Baseline			
Mean (SD)	435.8 (10.17)	424.9 (23.98)	426.2 (29.59)
Median	433.3	422.7	421.0
(Min, Max)	(427, 449)	(365, 542)	(359, 491)
EOT: Postbaseline			
Mean (SD)	439.3 (24.01)	425.1 (23.91)	427.1 (23.23)
Median	435.8	424.8	430.2
(Min, Max)	(419, 467)	(341, 507)	(373, 469)
EOT: Change from Baseline			
Mean (SD)	3.6 (14.39)	0.2 (18.31)	0.9 (17.83)
Median	3.3	0.2	2.4
(Min, Max)	(-10, 17)	(-75, 72)	(-32, 37)
QTcB Interval (msec): Worst Result	**n=190**	**n=632**	**n=626**
Baseline			
Mean (SD)	425.0 (21.92)	424.9 (24.01)	426.1 (24.64)
Median	425.5	423.2	425.3
(Min, Max)	(368, 516)	(365, 542)	(359, 537)
Postbaseline – High Value			
Mean (SD)	423.0 (23.46)	435.3 (22.92)	439.7 (23.96)
Median	422.8	434.7	438.3
(Min, Max)	(376, 506)	(376, 531)	(361, 527)
Change from Baseline – High Value			
Mean (SD)	-2.1 (14.83)	10.4 (16.06)	13.6 (15.90)
Median	-1.8	9.3	13.7
(Min, Max)	(-41, 34)	(-63, 72)	(-39, 69)

Source: Post-text Table 1.7.1.
Abbreviations: EOT=end of treatment; Max=maximum; Min=minimum; msec=millisecond; N=number of patients in the Safety Analysis Set; n=number of patients with nonmissing data; QTcB=QT interval corrected for heart rate by Bazett's formula; SD=standard deviation
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. There were no scheduled ECG results for patients in TR701-104 at 48-72 hours, TR701-126 at EOT, and linezolid group of Controlled Studies at EOT. Insufficient data from Study TR701-104 precluded calculation of QTcB. Change from baseline high value corresponds to numerically largest change.
[a]Unscheduled ECGs from patients in Study TR701-126.
[b]Unscheduled ECGs.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 61).

Changes in QTcF interval are summarized in Table 7.4.4-4. In Phase 2 studies, the mean QTcF interval change from baseline was -0.5 msec at 48-72 hours and +9.3 msec at EOT. The high mean change from baseline at any time point was -0.3 msec.

In Phase 3 studies, QTcF interval changed from baseline at the 48-72 hour visit (+4.8 msec tedizolid phosphate; +5.4 msec linezolid). The mean change from baseline at EOT was +4.1 msec and +1.3 msec for tedizolid phosphate and linezolid, respectively. The mean greatest change from baseline at any time was +13.7 msec for tedizolid phosphate and +14.8 for linezolid.

Table 7.4.4-4: Changes in QTcF Interval by Time Point in Phase 2/3 Studies

Parameter Visit	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388)	TR-701/FA (200 mg) (N=662)	Linezolid (1200 mg) (N=662)
QTcF Interval (msec): 48-72 Hours	**n=185**	**n=630**	**n=626**
Baseline			
Mean (SD)	410.4 (20.13)	408.8 (22.27)	409.8 (22.68)
Median	409.0	408.0	408.5
(Min, Max)	(356, 481)	(347, 515)	(353, 518)
48-72 Hours: Postbaseline			
Mean (SD)	409.9 (20.41)	413.7 (21.89)	415.2 (22.91)
Median	408.0	412.3	413.7
(Min, Max)	(366, 484)	(346, 499)	(346, 496)
48-72 Hours: Change from Baseline			
Mean (SD)	-0.5 (13.02)	4.8 (15.97)	5.4 (16.29)
Median	-0.3	5.3	5.5
(Min, Max)	(-42, 33)	(-78, 61)	(-63, 79)
QTcF Interval (msec): EOT	**n=4[a]**	**n=610**	**n=34[b]**
Baseline			
Mean (SD)	422.8 (14.55)	408.9 (22.33)	409.4 (23.28)
Median	418.0	408.0	406.3
(Min, Max)	(411, 444)	(347, 515)	(365, 460)
EOT: Postbaseline			
Mean (SD)	432.1 (27.01)	413.0 (22.09)	410.7 (18.79)
Median	426.0	411.8	410.7
(Min, Max)	(407, 469)	(347, 489)	(362, 447)
EOT: Change from Baseline			
Mean (SD)	9.3 (12.70)	4.1 (16.53)	1.3 (15.85)
Median	8.0	3.7	0.7
(Min, Max)	(-4, 26)	(-53, 56)	(-36, 30)
QTcF Interval (msec): Worst Result	**n=190**	**n=632**	**n=626**
Baseline			
Mean (SD)	410.7 (20.05)	408.9 (22.27)	409.8 (22.68)
Median	409.7	408.0	408.5
(Min, Max)	(356, 481)	(347, 515)	(353, 518)
Postbaseline – High Value			
Mean (SD)	410.4 (20.69)	422.6 (21.67)	424.6 (22.51)
Median	408.3	421.0	422.7
(Min, Max)	(366, 484)	(365, 512)	(357, 520)
Change from Baseline – High Value			
Mean (SD)	-0.3 (13.02)	13.7 (15.03)	14.8 (14.45)
Median	0.0	13.0	14.0
(Min, Max)	(-42, 33)	(-53, 65)	(-36, 79)

Source: Post-text Table 1.7.1.
Abbreviations: EOT=end of treatment; Max=maximum; Min=minimum; msec=millisecond; N=number of patients in the Safety Analysis Set; n=number of patients with nonmissing data; QTcF=QT interval corrected for heart rate by Fridericia's formula; SD=standard deviation.
Note: Change from baseline is calculated for patients with data at both baseline and postbaseline visit. There are no scheduled ECG results for patients in TR701-104 at 48-72 hours, TR701-126 at EOT, and linezolid group of Controlled Studies at EOT. Insufficient data from Study TR701-104 precluded calculation of QTcF. Change from baseline high value corresponds to numerically largest change.
[a] Unscheduled ECGs from patients in Study TR701-126.
[b] Unscheduled ECGs.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 62).

The Applicant defined potentially clinically significant abnormal QTcB or QTcF as <350 msec or >500 msec in the Phase 2 and 3 trials. Findings are summarized in Table 7.4.4-5. In the Phase 2 trials, there was 1 patient at baseline and postbaseline with a QTcB >500 msec (the same patient). There were no potentially clinically significant abnormalities in QTcF.

In the Phase 3 trials, there were 6 patients (0.9%) in the tedizolid phosphate group and 10 (1.6%) in the linezolid group with a QTcB >500 msec for at least 1 evaluation after the first dose of study drug. This twice the number of patients with potentially clinically significant QTcB values at baseline in both arms.

In the Phase 3 trials, there was 1 patient (0.2%) in the tedizolid phosphate arm and 1 patient (0.2%) in the linezolid arm with a QTcF >500 msec, compared to 1 and 2 patients, respectively, at baseline.

Table 7.4.4-5: Potentially Clinically Significant ECG Abnormalities in Phase 2 and 3 Trials

Parameter	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388) n (%)	TR-701/FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
QTcB (msec)			
Baseline	N1=200	N1=658	N1=660
Potentially Clinically Significant Abnormal	1 (0.5)	3 (0.5)	5 (0.8)
<350 msec	0	0	0
>500 msec	1 (0.5)	3 (0.5)	5 (0.8)
Worst Postbaseline Result	N1=190	N1=632	N1=626
Potentially Clinically Significant Abnormal	1 (0.5)	6 (0.9)	10 (1.6)
<350 msec	0	0	0
>500 msec	1 (0.5)	6 (0.9)	10 (1.6)
QTcF (msec)			
Baseline	N1=200	N1=658	N1=660
Potentially Clinically Significant Abnormal	0	2 (0.3)	2 (0.3)
<350 msec	0	1 (0.2)	0
>500 msec	0	1 (0.2)	2 (0.3)
Worst Postbaseline Result	N1=190	N1=632	N1=626
Potentially Clinically Significant Abnormal	0	1 (0.2)	1 (0.2)
<350 msec	0	0	0
>500 msec	0	1 (0.2)	1 (0.2)

Source: Post-text Table 1.7.2
Abbreviations: msec=milliseconds; N=Number of patients in the Safety Analysis Set; N1=Number of subjects with nonmissing data at the summarized visit; n=Number of patients in each specific category; QTcB=QT interval corrected for heart rate using Bazett's formula; QTcF=QT interval corrected for heart rate using Fridericia's formula

Note: In cases where ECGs were collected in triplicate, the average value for eachpatient is used to categorize patients. All patients in the safety analysis set with nonmissing data at the summarized visit are used as the denominator to calculate percentages.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 63).

Details regarding worst postbaseline results and increases from baseline for QTcB and QTcF are provided in Table 7.4.4-6.

Table 7.4.4-6: Worst Post-Baseline Changes in QTcB and QTcF in Phase 2 and 3 Studies

Parameter	Uncontrolled Studies	Controlled Studies	
	TR-701/FA ≥200 mg (N=388) n (%)	TR-701/FA (200 mg) (N=662) n (%)	Linezolid (1200 mg) (N=662) n (%)
QTcB (msec)			
Worst Postbaseline Result	N1=190	N1=632	N1=626
≤ 450 msec	167 (87.9)	477 (75.5)	425 (67.9)
>450 msec and ≤ 480 msec	20 (10.5)	133 (21.0)	171 (27.3)
>480 msec and ≤ 500 msec	2 (1.1)	16 (2.5)	20 (3.2)
>500 msec	1 (0.5)	6 (0.9)	10 (1.6)
Increase from Baseline	N1=190	N1=632	N1=626
0 or less (no increase)	104 (54.7)	163 (25.8)	112 (17.9)
1-29 msec	84 (44.2)	407 (64.4)	415 (66.3)
30-60 msec	2 (1.1)	56 (8.9)	95 (15.2)
>60 msec	0	6 (0.9)	4 (0.6)
QTcF (msec)			
Worst Postbaseline Result	N1=190	N1=632	N1=626
≤ 450 msec	185 (97.4)	568 (89.9)	548 (87.5)
>450 msec and ≤ 480 msec	4 (2.1)	57 (9.0)	65 (10.4)
>480 msec and ≤ 500 msec	1 (0.5)	6 (0.9)	12 (1.9)
>500 msec	0	1 (0.2)	1 (0.2)
Increase from Baseline	N1=190	N1=632	N1=626
0 or less (no increase)	98 (51.6)	100 (15.8)	91 (14.5)
1-29 msec	91 (47.9)	447 (70.7)	446 (71.2)
30-60 msec	1 (0.5)	83 (13.1)	85 (13.6)
>60 msec	0	2 (0.3)	4 (0.6)

Source: Post-text Table 1.7.3
Abbreviations: msec=milliseconds; N=Number of subjects in the Safety Analysis Set. N1=Number of subjects with nonmissing data at the summarized visit. n=Number of subjects; QTcB=QT interval corrected for heart rate using Bazett's formula; QTcF=QT interval corrected for heart rate using Fridericia's formula
Note: In cases where ECGs were collected in triplicate, the average value for each patient is summarized. All patients in the safety analysis set with nonmissing data at the summarized visit are used as the denominator to calculate percentages.

Source: Applicant's Integrated Summary of Safety (5.3.5.3, Table 64).

In summary, safety analyses of ECG results suggest that tedizolid phosphate does not contribute to prolongation of the QT interval. A thorough Phase 1 QT study showed that a single therapeutic or supratherapeutic dose of tedizolid phosphate did not prolong the QT interval in healthy individuals. Furthermore, Phase 2 and Phase 3 trials suggest that potentially clinically relevant QTc interval prolongation is low and similar in patients receiving tedizolid phosphate and tedizolid phosphate.

7.4.5 Special Safety Studies/Clinical Trials

Submission specific safety concerns are addressed in section 7.3.5 including neurologic disorders, optic nerve disorders, myelosuppression, lactic acidosis, convulsions and hypoglycemia. Additional details can be found throughout the review, including Section 7.4.2 Laboratory Findings, Section 7.5.4 Drug-Disease Interactions, and Section 7.5.5 Drug-Drug interactions.

7.4.6 Immunogenicity

Tedizolid phosphate is a member of the oxazolidinone class of antibacterials and not considered a protein or polysaccharide. The tendency of the molecule to provoke a humoral and/or cell mediated immune response has not been adequately studied and is unknown. There was one patient in the Phase 2 trial who developed drug hypersensitivity after receiving a single dose of tedizolid phosphate 200 mg. None of the patients in the Phase 3 trials who received tedizolid phosphate had a TEAE in the Immune System Disorders SOC. In the patients who received linezolid in the Phase 3 trials, there was one patient who experienced a TEAE of anaphylactic reaction and one patient with a TEAE of hypersensitivity.

7.5 Other Safety Explorations

Additional safety explorations included dose and time dependency for adverse events, drug-demographic interactions, drug-disease interactions, and drug-drug interactions.

7.5.1 Dose Dependency for Adverse Events

In the drug development program, the maximum dose administered was 1200 mg one time in 2 studies. TR701-115 was a QT study where 41.3% of the subjects experienced a TEAE after receiving 1200 mg tedizolid phosphate (n=46) compared to 22.7% in the subjects receiving 200 mg tedizolid phosphate (n=44). GI TEAEs were more common in the 1200 mg tedizolid phosphate group (23.9%) versus the 200 mg tedizolid phosphate group (4.5%) including diarrhea (13.0% versus 2.3%) and nausea (6.5% versus 2.3%). Headaches occurred more frequently in the 1200 mg tedizolid phosphate group (10.9%) versus the 200 mg tedizolid phosphate group (4.5%). There were no clinically significant changes in heart rate or blood pressure at the 1200 mg tedizolid phosphate dose in this study with healthy adult subjects.

In the Phase 2 randomized, double-blind, no-control study, TR701-104, patients with cSSSI received 200, 300 or 400 mg tedizolid phosphate capsules qd orally for 5 to 7 days. TEAEs increased with escalating dose, particularly for gastrointestinal disorders (200mg [30.16%], 300 mg [38.10%], 400 mg [45.16%]). Nausea and diarrhea were the most common TEAEs under

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the gastrointestinal disorder system organ class occurring at 15.87%, 19.05%, 20.97% and 11.11%, 4.76%, 9.68% for the 200, 300 and 400 mg tedizolid phosphate doses, respectively. When examining data from the pooled Phase 2 trials (TR701-104 and TR701-126), patients receiving 200 mg tedizolid phosphate had a lower incidence of nausea in comparison to patients receiving 300 or 400 mg (12.2% versus 20.0%) respectively (Table 7.5.1-1).

Table 7.5.1-1: Incidence of Treatment Emergent Adverse Events in the Gastrointestinal Disorders SOC by Dose in Pooled Phase 2 Studies

	Dose of tedizolid phosphate	
Gastrointestinal disorders SOC	**200 mg N=263**	**>200 mg N=125**
Dictionary-Derived Term	63 (24.0%)	52 (41.6%)
Diarrhea	20 (7.6%)	9 (7.2%)
Nausea	32 (12.2%)	25 (20.0%)
Vomiting	16 (6.1%)	12 (9.6%)

In the Phase 2 trials, higher doses of tedizolid phosphate were associated with a higher incidence of nausea.

7.5.2 Time Dependency for Adverse Events

Potential long term safety issues were explored based on experience from linezolid, the only approved oxazolidinone. Class specific safety concerns include optic nerve and peripheral neurotoxicity, myelosuppression, and lactic acidosis. Additional information can be found in Sections 7.3.5 Submission Specific Safety Concerns, 7.4.2 Laboratory Findings and discipline specific reviews.

7.5.3 Drug-Demographic Interactions

The incidence of TEAEs was similar in the tedizolid phosphate and linezolid arms with consideration to age < 65 years (44.1% versus 44.3%, respectively), sex and race. There is a slightly higher incidence of TEAEs in patients ≥ 75 years (37.5% for tedizolid phosphate versus 32% for linezolid). There is a slightly lower incidence of TEAEs in patients with BMI ≥30 kg/m^2 (43.5% tedizolid phosphate and 48.5% linezolid).

7.5.3.1 Age

An overview of treatment emergent adverse events by age in Phase 2 and Phase 3 studies is provided in Table 7.5.3-1. Overall, TEAEs were similar in the tedizolid phosphate and linezolid

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arms. In the ≥ 75 years age group, there was a higher incidence of TEAEs (37.5% versus 32%), severe TEAE (12.5% versus 0%), serious TEAEs (16.0% versus 0%) in the tedizolid phosphate compared to the linezolid arm respectively. There were 2 patients who died in the tedizolid phosphate arm and 1 patient in the linezolid arm who were >65 years of age; however all of these deaths do not appear to be related to the study drug. The four patients ≥ 65 years with severe TEAEs were the same as those with serious TEAEs. Three of these patients were ≥ 75 years.

Narratives for patients **TR701-113-451-258** and **TR701-112-342-605** are provided earlier in section 7.3.1 Deaths. Narrative for patient **TR701-113-105-073** is provided earlier in section 7.3.2 Nonfatal Serious Adverse Events.

Table 7.5.3-1: Treatment Emergent Adverse Events by Age Group in Phase 2 and Phase 3 Studies

Category	Age Group	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388	Tedizolid phosphate (200 mg) N=662	Linezolid (1200 mg) N=662 n (%)
N1	< 65 years	379	590	603
	≥ 65 years	9	72	59
	≥ 75 years	0	24	25
	All	388	662	662
TEAE	< 65 years	217 (57.3%)	260 (44.1%)	267 (44.3%)
	≥ 65 years	4 (44.4%)	23 (31.9%)	19 (32.2%)
	≥ 75 years	0	9 (37.5%)	8 (32.0%)
	All	221 (57.0%)	283 (42.7%)	286 (43.2%)
Severe TEAE	< 65 years	9 (2.4%)	9 (1.5%)	13 (2.2%)
	≥ 65 years	0	4 (5.6%)	0
	≥ 75 years	0	3 (12.5%)	0
	All	9 (2.3%)	13 (2.0%)	13 (2.0%)
Serious TEAE	< 65 years	7 (1.8%)	6 (1.0%)	12 (2.0%)
	≥ 65 years	0	6	1 (1.7%)
	≥ 75 years	7		
	All			
TEAE Leading to Study Drug Discontinuation	< 65 years	0		
	≥ 65 years	0		

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

Overall, the incidence of TEAEs was similar for patients receiving tedizolid phosphate and linezolid in the Phase 3 trails. Although there was a slight increase in serious adverse events in patients ≥ 65 years, limited numbers preclude definitive conclusions about safety in this subgroup.

7.5.3.2 Sex

An overview of treatment emergent adverse events by sex in Phase 2 and Phase 3 studies is provided in Table 7.5.3-2. Overall, the incidence of TEAEs was slightly higher in females than in males in Phase 3 studies; however TEAEs were similar between treatment groups (males [TR-701 FA 41.7% and linezolid 40.2%], and in females [44.6% and 48.0%, respectively]).

Table 7.5.3-2: Treatment Emergent Adverse Events by Sex in Phase 2 and Phase 3 Studies

Category	Sex	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
N1	Male	251	429	408
	Female	137	233	254
TEAE	Male	137 (54.6%)	179 (41.7%)	164 (40.2%)
	Female	84 (61.3%)	104 (44.6%)	122 (48.0%)
Severe TEAE	Male	5 (2.0%)	7 (1.6%)	8 (2.0%)
	Female	4 (2.9%)	6 (2.6%)	5 (2.0%)
Serious TEAE	Male	4 (1.6%)	5 (1.2%)	7 (1.7%)
	Female	3 (2.2%)	7 (3.0%)	6 (2.4%)
TEAE Leading to Study Drug Discontinuation	Male	2 (0.8%)	1 (0.2%)	3 (0.7%)
	Female	0	2 (0.9%)	3 (1.2%)
TEAE with Outcome of Death	Male	0	2 (0.5%)	0
	Female	0	0	1 (0.4%)

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

In summary, the incidence of TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death was similar for patients treated with tedizolid phosphate and linezolid with respect to sex in the Phase 3 studies.

7.5.3.3 Race

An overview of treatment emergent adverse events by race in Phase 2 and Phase 3 studies is provided in the Table 7.5.3-3 below. In Phase 2 studies, the incidence of TEAEs by race was similar in both treatment arms.

In the Phase 3 studies, the incidence of TEAES was similar in the tedizolid phosphate and linezolid groups for White and Black/African American subgroups. The most common TEAEs were Gastrointestinal Disorders, Infections and Infestations, and Nervous System Disorders for both White and Black/African American subgroups with a lower incidence, in general, for patients of the Black/African American subgroup in both treatment arms.

Table 7.5.3-3: Treatment Emergent Adverse Events by Race in Phase 2 and Phase 3 Studies

Category	Race	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate(≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
Number of patients in subgroup (N1)	White	294	563	555
	Black or African American	79	77	71
	Asian	4	6	14
	Other	11	16	22
Number (%) of patients with at least one TEAE	White	167 (56.8%)	256 (45.5%)	250 (45.0%)
	Black or African American	46 (58.2%)	23 (29.9%)	21 (29.6%)
	Asian	2 (50.0%)	1 (16.7%)	7 (50.0%)
	Other	6 (54.5)	3 (18.8)	8 (36.4%)

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

In summary, limited data suggest that the incidence of TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death was similar for patients treated with tedizolid phosphate and linezolid with respect to race in the Phase 3

studies. The number of patients who were considered Black or African American or Asian were very small so meaningful comparisons could not be made. Definitive conclusions regarding unique safety signals which may occur in patient subgroups such as race cannot be made.

7.5.3.4 Geographic Region

An overview of treatment emergent adverse events by geographic region in Phase 2 and Phase 3 studies is provided in Table 7.5.3-4. The incidence of TEAEs were higher in the US and Canada in comparison to Europe for both tedizolid phosphate and linezolid. In addition, the majority of severe TEAEs, SAEs, and TEAEs leading to study drug discontinuation occurred in the US or Canada The specific reason for this is not clear.

There was one patient in Peru and two in South Africa (septic shock, tuberculous meningitis, and myocardial infarction) with fatal severe and serious TEAEs. Details have been described previously in Section 7.3.1 Deaths.

Table 7.5.3-4: Treatment Emergent Adverse Events by Geographic Region in Phase 2 and Phase 3 Studies

Category	Geographic Region	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
Number of Patients in Subgroup (N1)	US/Canada	388	424	421
	Europe	0	165	166
	Other	0	73	75
TEAE	US/Canada	221 (57.0%)	220 (51.9%)	219 (52.0%)
	Europe	0	41 (24.8%)	37 (22.3%)
	Other	0	22 (30.1%)	30 (40.0%)
Severe TEAE	US/Canada	9 (2.3%)	11 (2.6%)	11 (2.6%)
	Europe	0	0	1 (0.6%)
	Other	0	2 (2.7)	1 (1.3%)
Serious TEAE	US/Canada	7 (1.8%)	8 (1.9%)	8 (1.9%)
	Europe	0	1 (0.6%)	3 (1.8%)
	Other	0	3 (4.1%)	2 (2.7%)
TEAE Leading to Study Drug Discontinuation	US/Canada	2 (0.5%)	3 (0.7%)	4 (1.0%)
	Europe	0	0	1 (0.6%)
	Other	0	0	1 (1.3%)
TEAE with Outcome of Death	US/Canada	0	0	0
	Europe	0	0	0
	Other	0	2 (2.7%)	1 (1.3%)

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

In summary, the incidence of TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death were similar for patients treated with tedizolid phosphate and linezolid with respect to geographic region in the Phase 3 studies.

7.5.3.5 BMI

An overview of treatment emergent adverse events by BMI in Phase 2 and Phase 3 studies is provided in Table 7.5.3-5. In Phase 2 studies, the incidence of TEAEs was greater for the obese subgroup (61.4%) than the normal/overweight subgroup (55.9%).

In Phase 3 trials, the incidence of TEAEs was similar for obese (43.5%) and normal/overweight (43.1%) subgroups in the tedizolid phosphate treatment group, but was greater for obese subjects in the linezolid group (48.5% and 40.1%, respectively). In both treatment arms, the most common TEAEs were in the Gastrointestinal Disorders, Infections and Infestations and Nervous Disorders. The incidence of diarrhea was greater in obese patients (8.7%) than normal/overweight patients (3.5%) within the linezolid arm and similar (4.0%) in both subgroups of the tedizolid phosphate arm.

Table 7.5.3-5: Treatment Emergent Adverse Events by Body Mass Index in Phase 2 and Phase 3 Studies

Category	BMI Subgroup	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
Number of patients in subgroup (N1)	<18.5 kg/m^2	4	12	7
	≥18.5 kg/m^2 to <30 kg/m^2	270	450	426
	≥30 kg/m^2	114	200	229
Number (%) of patients with at least one TEAE	<18.5 kg/m^2	0	2 (16.7%)	4 (57.1%)
	≥18.5 kg/m^2 to <30 kg/m^2	151 (55.9%)	194 (43.1%)	171 (40.1%)
	≥30 kg/m^2	70 (61.4%)	87 (43.5%)	111 (48.5%)

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

In summary, the number of patients with at least one TEAE was similar for patients treated with tedizolid phosphate and linezolid with respect to BMI in the Phase 3 studies.

7.5.4 Drug-Disease Interactions

Drug disease interactions were examined. There was a higher incidence of TEAEs in patients with moderate to severe renal impairment receiving tedizolid phosphate (55.0%) versus linezolid (27.6%). TEAEs were similar in patients with hepatic disease (44.6% for tedizolid phosphate and 46.9% for linezolid). TEAEs were slightly lower in patients with diabetes receiving tedizolid phosphate (44.8%) versus linezolid (47.8%). Among IVDU, 46.2% of patients in the TR-701 FA arm and 47.8% in the linezolid arm experienced at least 1 TEAE.

7.5.4.1 Renal Function

An overview of treatment emergent adverse events by Renal Function in Phase 2 and Phase 3 studies is provided in Table 7.5.4-1. In the Phase 2 and 3 studies, there were 53 patients with moderate to severe renal impairment. In Phase 2 studies, the incidence of TEAEs was lower in patients with moderate/severe renal impairment (50.0%) than patients with normal/mild renal impairment (57.4%).

In Phase 3 studies, 11 of 20 (55.0%) patients in the tedizolid phosphate arm with moderate to severe renal impairment experienced TEAEs, compared with 8 of 29 patients (27.6%) in the linezolid arm. In addition, there were 2 and 5 patients with severe and serious TEAEs, respectively, in the tedizolid phosphate arm versus none in the linezolid in the arm.

Table 7.5.4-1: Treatment Emergent Adverse Events by Renal Function Status in Phase 2 and Phase 3 Studies

Category	Renal Function Status	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
Number in Subgroup (N1):	Normal/Mild	376	633	612
	Moderate/Severe	4	20	29
TEAE	Normal/Mild	216 (57.4%)	270 (42.7%)	273 (44.6%)
	Moderate/Severe	2 (50.0%)	11 (55.0%)	8 (27.6%)
Severe TEAE	Normal/Mild	9 (2.4%)	11 (1.7%)	13 (2.1%)
	Moderate/Severe	0	2 (10.0%)	0
Serious TEAE	Normal/Mild	7 (1.9%)	7 (1.1%)	13 (2.1%)
	Moderate/Severe	0	5 (25.0%)	0
TEAE Leading to Study Drug Discontinuation	Normal/Mild	2 (0.5%)	3 (0.5)	6 (1.0%)
	Moderate/Severe	0	0	0
TEAE with Outcome of Death	Normal/Mild	0	1 (0.2%)	1 (0.2%)
	Moderate/Severe	0	1 (5.0%)	0

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.
Normal/Mild renal impairment = baseline creatinine clearance (CLcr) ≥60 mL/min
Moderate/Severe renal impairment = baseline CLcr <60 mL/min

In summary, limited data suggest that the incidence of TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death were similar for patients treated with tedizolid phosphate and linezolid with respect to renal function in the

Phase 3 studies. The number of patients who had moderate/ severe renal impairment was very small so meaningful comparisons could not be made. Definitive conclusions regarding unique safety signals which may occur in patient subgroups with moderate to severe renal impairment cannot be made.

7.5.4.2 Hepatic Function

An overview of treatment emergent adverse events by Hepatic Function in Phase 2 and Phase 3 studies is provided in Table 7.5.4-2. In Phase 2 studies, the incidence of TEAEs was higher among patients with normal hepatic function (60.1%) than those with hepatic disease (49.1%).

In Phase 3 studies, one third of the patients had hepatic impairment and/or hepatic disease, the majority of whom were hepatitis C positive. In Phase 3 studies, 44.6% and 42.6% of patients with hepatic disease and patients with normal function experienced TEAEs in the TR-701 FA arm, compared with 46.9% and 41.3%, respectively, in the linezolid arm.

Table 7.5.4-2: Treatment Emergent Adverse Events by Hepatic Impairment or Disease in Phase 2 and Phase 3 Studies

Category	Hepatic Function Status/Disease	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
Number in Subgroup (N1)	Normal	276	474	443
	Hepatic Impairment	3	14	12
	Hepatic Disease	106	175	209
Treatment-Emergent Adverse Events (TEAE)	Normal	166 (60.1%)	202 (42.6%)	183 (41.3%)
	Hepatic Impairment	1 (33.3%)	3 (21.4%)	5 (41.7%)
	Hepatic Disease	52 (49.1%)	78 (44.6%)	98 (46.9%)
Severe TEAE	Normal	5 (1.8%)	8 (1.7%)	5 (1.1%)
	Hepatic Impairment	0	1 (7.1%)	1 (8.3%)
	Hepatic Disease	4 (3.8%)	4 (2.3%)	7 (3.3%)
Serious TEAE	Normal	5 (1.8%)	9 (1.9%)	7 (1.6%)
	Hepatic Impairment	0	1 (7.1%)	2 (16.7%)
	Hepatic Disease	2 (1.9%)	2 (1.1%)	4 (1.9%)
TEAE Leading to Study Drug Discontinuation	Normal	2 (0.7%)	1 (0.2%)	3 (0.7%)
	Hepatic Impairment	0	0	0
	Hepatic Disease	0	2 (1.1%)	3 (1.4%)
TEAE with Outcome of Death	Normal	0	1 (0.2%)	1 (0.2%)
	Hepatic Impairment	0	1 (7.1%)	0
	Hepatic Disease	0	0	0

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.
Hepatic Impairment = baseline Child-Pugh classification B or C (total score ≥7).
Hepatic Disease = alanine aminotransferase or aspartate aminotransferase >2× upper limit of normal at baseline or are positive for hepatitis C at baseline.

In summary, limited data suggest that the incidence of TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death were similar

for patients treated with tedizolid phosphate and linezolid with respect to hepatic impairment or disease in the Phase 3 studies. The number of patients who had hepatic impairment was very small so meaningful comparisons could not be made. Definitive conclusions regarding unique safety signals which may occur in patient subgroups with hepatic impairment cannot be made.

7.5.4.3 Diabetes

An overview of treatment emergent adverse events by Diabetes in Phase 2 and Phase 3 studies is provided in Table 7.5.4-3. In Phase 2 studies, the incidence of TEAES in patients with diabetes was higher than in patients without (66.7% versus 56.1% respectively).

Patients with diabetes had a slightly higher incidence of TEAEs in comparison to patients without diabetes in both treatment arms. In addition, the number of patients with diabetes and at least one TEAE was similar in the tedizolid phosphate arm compared to the linezolid arm (44.8% versus 47.8%, respectively).

Table 7.5.4-3: Treatment Emergent Adverse Events by Diabetes in Phase 2 and Phase 3 Studies

Category	Diabetes Status	Phase 2 Studies	Phase 3 Studies	
		Tedizolid phosphate (≥200 mg) N=388 n (%)	Tedizolid phosphate (200 mg) N=662 n (%)	Linezolid (1200 mg) N=662 n (%)
Number of patients in subgroup (N1)	Yes	30	58	67
	No	358	604	595
Number (%) of patients with at least one TEAE	Yes	20 (66.7%)	26 (44.8%)	32 (47.8%)
	No	201 (56.1%)	257 (42.5%)	254 (42.7%)

N=Number of patients in the Safety Analysis Set;
n=Number of patients in the category;
N1=Number of patients in the subgroup and is used as the denominator to calculate percentage;
TEAE=Treatment emergent adverse event.

Table 7.5.4-4: Treatment Emergent Adverse Events by Diabetes and Body System or Organ Class in Phase 2 and Phase 3 Studies

	Phase 2 Studies	Phase 3 Studies	
Body System or Organ Class	**Tedizolid phosphate (≥ 200mg) n=388**	**Tedizolid phosphate (200mg) n=662**	**Linezolid (1200mg) n=662**
Number of patients with Diabetes	30	58	67
Blood and lymphatic system disorders	0 (0.0%)	2 (3.5%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	1 (1.7%)	0 (0.0%)
Ear and labyrinth disorders	1 (3.3%)	0 (0.0%)	0 (0.0%)
Eye disorders	2 (6.7%)	2 (3.5%)	0 (0.0%)
Gastrointestinal disorders	10 (33.3%)	9 (15.5%)	18 (26.9%)
General disorders and administration site conditions	2 (6.7%)	5 (8.6%)	8 (11.9%)
Infections and infestations	9 (30.0%)	6 (10.3%)	8 (11.9%)
Injury, poisoning and procedural complications	2 (6.7%)	2 (3.5%)	1 (1.5%)
Investigations	2 (6.7%)	0 (0.0%)	1 (1.5%)
Metabolism and nutrition disorders	2 (6.7%)	6 (10.3%)	4 (6.0%)
Musculoskeletal and connective tissue disorders	1 (3.3%)	3 (5.2%)	3 (4.5%)
Nervous system disorders	4 (13.3%)	8 (13.8%)	9 (13.4%)
Psychiatric disorders	1 (3.3%)	1 (1.7%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	4 (13.3%)	2 (3.5%)	2 (3.00%)
Skin and subcutaneous tissue disorders	1 (3.3%)	4 (6.9%)	3 (4.5%)
Vascular disorders	0 (0.0%)	1 (1.7%)	0 (0.0%)

In summary, the number of patients with at least one TEAE was similar for patients treated with tedizolid phosphate and linezolid with respect to diabetes status in the Phase 3 studies. Definitive conclusions regarding unique safety signals which may occur in patient subgroups with diabetes cannot be made.

7.5.4.4 IV Drug Users (IVDU)

Almost one third of the patients in the Phase 2 and Phase 3 studies were self-reported current or recent IV drug users. In Phase 2 studies, 44.4% of IVDU and 62.4% of non-IVDU experienced TEAEs.

In the Phase 3 studies, among IVDU, 46.2% of patients in the TR-701 FA arm and 47.8% in the linezolid arm experienced at least 1 TEAE, compared with 41.5% and 41.2%, respectively, of patients were not IVDU. Infections and Infestations TEAEs were more common among IV drug users than nonusers. In the tedizolid phosphate group 8.2% of IV drug users and 4.2% of nonusers experienced abscesses while 4.4% and 1.9%, respectively, had cellulitis. In the linezolid group; 6.9% and 2.6% of IV drug users and nonusers, respectively, had abscess, and 3.4% and 1.5% had cellulitis.

7.5.5 Drug-Drug Interactions

The Applicant conducted preclinical and Phase 1 studies to examine potential drug interactions with tedizolid phosphate. Additional details can be found in section 7.3.5 Submission Specific Primary Safety Concerns, as well as discipline-specific reviews.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term carcinogenicity studies have not been conducted with tedizolid phosphate. Genotoxicity was not observed with tedizolid phosphate in all *in vitro* assays (bacterial reverse mutation (Ames), Chinese hamster lung (CHL) cell chromosomal aberration) and *in vivo* tests (mouse bone marrow micronucleus, rat liver unscheduled DNA synthesis). Tedizolid, the active metabolite of tedizolid phosphate (TR701 FA) was also tested for genotoxicity. The metabolite was found to be positive for genotoxicity in an *in vitro* CHL cell chromosomal aberration assay, but negative for genotoxicity in other *in vitro* assays (Ames, mouse lymphoma mutagenicity) and *in vivo* in a mouse bone- marrow micronucleus assay.

Anticipated short term use of the tedizolid phosphate precludes further evaluation of oncologic potential.

7.6.2 Human Reproduction and Pregnancy Data

There were 4 patients who had a positive pregnancy test during the Phase 3 studies. Two patients received tedizolid phosphate and two received linezolid. A listing of patients who had a positive pregnancy test, and associated TEAEs, are listed in the Table 7.6.2-1. All patients were

discontinued from the study when the study site was informed of a positive pregnancy test result. A brief narrative for patient **TR701-112-262-467** is provided earlier in section 7.3.2, Nonfatal Serious Adverse Events.

Table 7.6.2-1: Listing of treatment emergent adverse events in patients with positive pregnancy test results.

Analysis Unique Subject ID	Age	Sex	Country	Actual Treatment	Study Day of Start of Adverse Event	Body System or Organ Class	Dictionary-Derived Term	Outcome of Adverse Event	Causality
TR701-112-105-043*	30	F	USA	TR701 FA 200 mg	-	-	-	-	-
TR701-112-128-217	21	F	USA	Linezolid 1200mg	14	Gastrointestinal disorders	Vomiting	NOT RECOVERED/NOT RESOLVED	NOT RELATED
					3	Gastrointestinal disorders	Nausea	RECOVERED/RESOLVED	NOT RELATED
TR701-112-262-467	28	F	UKR	Linezolid 1200mg	23	Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	RECOVERED/RESOLVED	PROBABLE
TR701-113-143-647	38	F	USA	TR-701 FA 200mg	14	Renal and urinary disorders	Nephrolithiasis	RECOVERED/RESOLVED	NOT RELATED
					3	Infections and infestations	Vulvovaginal mycotic infection	RECOVERED/RESOLVED	PROBABLE

*No TEAEs were noted for this patient.

There is no information on drug exposure in lactating women during the drug development program.

In nonclinical embryo-fetal development studies, tedizolid phosphate was shown to produce maternal (rats and rabbits) and fetal developmental (rats, mice, and rabbits) toxicities at plasma exposures approximately equivalent to (rats and mice) or below (rabbits) the expected clinical exposure based on plasma AUC comparisons. Maternal toxicities included reduced body weights in rats and mortality, reduced body weights, and abortions in rabbits. Fetal developmental effects occurring in mice included reduced fetal weights and an increased incidence of costal-cartilage anomalies. In rats, decreased fetal weights and increased skeletal variations including reduced ossification of the sternabrae, vertebrae, and skull were observed.

In rabbits, reduced fetal weights but no malformations or variations at the administered doses were observed.

In a pre-postnatal study, there were no adverse maternal or offspring effects when female rats were treated during pregnancy and lactation with tedizolid phosphate at plasma AUC exposures that were approximately equivalent to the expected clinical exposure.

In a fertility study, oral tedizolid phosphate had no adverse effects on the fertility or reproductive performance in male or female rats at plasma AUC exposures approximately 4-5 fold greater than the plasma AUC exposure expected in humans at the oral therapeutic dose.

Tedizolid phosphate is classified as a Pregnancy Category C drug. Please see Pharmacology-Toxicology Review for additional details.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant conducted TR701-111, a Phase 1, open-label, multicenter, two-part, single-dose, parallel-design, safety, tolerance, and pharmacokinetic study of orally and intravenously administered tedizolid phosphate in 12- to 17-year-old adolescent patients. This study enrolled 10 subjects each in the oral and IV arms. The Applicant reports that results of this study indicated that tedizolid phosphate, administered as a single dose of an oral tablet or an IV infusion to adolescent patients, is safe and generally well-tolerated. There were no deaths or serious adverse events and treatment emergent adverse events (TEAEs) were mild. No patient discontinued treatment due to a TEAE. The Applicant reports that there were no clinically significant changes to laboratory measurements, vital sign measurements, physical examinations, and 12-lead ECGs.

Although the sample sizes are small, the number of children experiencing a TEAE was higher in the intravenous group (**Table 7.6.3-1**).

Table 7.6.3-1: Summary of Treatment Emergent Adverse Events in Study TR701-111

	Number of Events (Number of Distinct Patients, %)	
	Part A N=10	Part B N=10
Any TEAE	1 (1, 10.0%)	6 (5, 50.0%)
Mild	1 (1, 10.0%)	6 (5, 50.0%)
Moderate	0	0
Severe	0	0
Possibly, Probably, or Definitely Related TEAE	1 (1, 10.0%)	3 (3, 30.0%)
Possible	1 (1, 10.0%)	2 (2, 20.0%)
Probable	0	0
Definite	0	1 (1, 10.0%)
Not related	0	3 (3, 30.0%)
TEAE Leading to Study Discontinuation	0	0
Serious Adverse Event	0	0

Source: Tables 14.3.1-1a and 14.3.1-1b
Abbreviations: TEAE=treatment emergent adverse event; N=number of patients
Note: Part A: TR-701 FA Tablets, 200 mg (oral administration); Part B: TR-701 FA for Injection, 200 mg/vial (IV infusion); For patients who experienced the same TEAE more than once, only the most severe of the adverse event or the most related adverse event was used. Percentages are based on number of patients receiving specific treatment.

Source: Clinical Study Report for TR701-111, Figure 12-1.

A summary of patients with adverse events by system organ class and dictionary-derived term is listed below (Table 7.6.3-2).

Table 7.6.3-2: Adverse Events for TR701-111

System Organ Class Preferred Term	Number of Distinct Patients (%)		
	Part A N=10	Part B N=10	Overall N=20
Gastrointestinal Disorders	1 (10.0%)	1 (10.0%)	2 (10.0%)
Abdominal Pain	1 (10.0%)	0	1 (5.0%)
Constipation	0	1 (10.0%)	1 (5.0%)
General Disorders and Administration Site Conditions	0	1 (10.0%)	1 (5.0%)
Infusion Site Extravasation	0	1 (10.0%)	1 (5.0%)
Injury, Poisoning and Procedural Complications	0	1 (10.0%)	1 (5.0%)
Procedural Pain	0	1 (10.0%)	1 (5.0%)
Investigations	0	1 (10.0%)	1 (5.0%)
Hepatic Enzyme Increased	0	1 (10.0%)	1 (5.0%)
Nervous System Disorders	0	1 (10.0%)	1 (5.0%)
Dizziness	0	1 (10.0%)	1 (5.0%)
Skin and Subcutaneous Tissue Disorders	0	1 (10.0%)	1 (5.0%)
Rash	0	1 (10.0%)	1 (5.0%)

Source: Tables 14.3.1-2a and 14.3.1-2b
Abbreviations: N=number of patients receiving specific treatment
Note: Part A: TR-701 FA Tablets, 200mg (oral administration); Part B: TR-701 FA for Injection, 200mg/vial (IV infusion); System organ class is sorted in descending order based on data in Overall column. Preferred Term is sorted in descending order within system organ class.

Source: Clinical Study Report for TR701-111, Figure 12-2.

Phase 3 trials enrolled only 2 patients < 18 years old (1 in the tedizolid phosphate arm and 1 in the linezolid arm).

Additional data are required regarding the safety and efficacy of tedizolid phosphate in the pediatric population.

An assessment on the effect of the drug on pediatric growth cannot be conducted given the limited number of pediatric patients enrolled, the short duration of treatment for tedizolid phosphate (typically 5 to 7 days) and the relatively short length of study follow up (18 – 25 days after EOT visit).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.6.4.1 Overdosage

In the clinical development program, the highest dose of tedizolid phosphate healthy subjects received was 1200 mg (five times the therapeutic dose) in two studies. No new safety signals were identified, but the incidence of common TEAEs, including nausea, diarrhea, and headache, appears to be greater than observed with the therapeutic dose of 200 mg TR-701

FA. In addition, administration of tedizolid phosphate at higher doses (≥400 mg) for longer than 7 days may require closer scrutiny of hematologic parameters.

TR701-101 was a double-blind, placebo- and active-controlled, single and multiple rising dose, safety, tolerance, and pharmacokinetic study of TR-701 in normal healthy adults. In the single ascending dose portion of the study, there were 6 patients each in the 200 mg, 400 mg, 600 mg, 800 mg and 1200 mg tedizolid phosphate arms. At least 1 treatment-emergent adverse event (TEAE) was reported in thirteen (43.3%) of the 30 subjects receiving TR-701. Ten of the 30 subjects receiving TR-701 experienced TEAEs judged to be treatment-related. There was no apparent dose-related trend in the number of subjects reporting TEAEs. No SAEs were reported with single- or multiple-dose exposures. None of the 10 subjects receiving placebo in the study reported any TEAE. In the multiple dose portion of the study, healthy subjects received 200, 300, or 400 mg of tedizolid phosphate for 21 days. tedizolid phosphate was well tolerated at 200 and 300 mg; however, there was a higher incidence of mild to moderate TEAEs with multiple doses of 400 mg TR-701 for 21 days. In patients receiving 400 mg daily, a more pronounced decrease in platelets and ANCs appeared 7 days after dosing which stabilized after approximately 2 weeks.

TR701-115 was a Phase 1 blinded, placebo-controlled crossover study to evaluate the effects of oral TR-701 free acid on the electrocardiogram. Health subjects received a single therapeutic (200 mg, n=44) and supratherapeutic (1200 mg, n=46) dose of oral TR-701 FA. TEAEs were more frequent following 1200 mg TR-701 FA (41.3%) than 200 mg TR-701 FA (22.7%) or placebo (27.3%) administrations. The CSR indicates that gastrointestinal related TEAEs were more common following 1200 mg TR-701 FA (23.9% of subjects) than 200 mg (4.5% of subjects), including diarrhea (13.0% versus 2.3%) and nausea (6.5% versus 2.3%). In addition, headache was more common at the supratherapeutic dose (10.9% of subjects) than the therapeutic dose (4.5%). There were no serious adverse events or deaths. One subject was withdrawn from the study drug due to vomiting following 1200 mg TR-701 FA). Two other subjects withdrew from the study (upper respiratory infection for 1 subject following moxifloxacin and vaginitis bacterial for 1 subject following placebo). There were no clinically meaningful changes in blood pressure or heart rate with 1200 mg TR-701 FA administration.

In the clinical development program, there were no reports of subjects/patients accidentally receiving more than the therapeutic dose in a single administration or on a single day.

A Phase 1 study (TR701-123) in patients with advanced renal impairment on and off dialysis showed that tedizolid phosphate is not expected to effectively remove TR-700 from blood or tissues. Hence, supportive measures would be required.

It should be noted that this is in contrast to linezolid, the only approved oxazolidinone, where hemodialysis may facilitate more rapid elimination of linezolid. Per the linezolid label revised 05/2013, a Phase 1 clinical trial showed that approximately 30% of a dose of linezolid

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was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered

7.6.4.2 Drug Abuse Potential

The potential for abuse of TR-701 or TR-701 FA was not formally studied in the drug development program. TR-701 and TR-701 FA, as well as its active metabolite TR-700, are structurally and pharmacologically different to known drugs of abuse. Phase 2 and Phase 3 studies did not reveal adverse events suggestive of acute psychoactive effects.

7.6.4.3 Withdrawal and Rebound

TR701 is an antibacterial drug for short-term therapy (5 – 7 days) of ABSSSI. Withdrawal or rebound effects are not anticipated.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-Day Safety Update on February 11, 2014. This update communicated that no IND safety reports from any ongoing tedizolid phosphate studies were submitted to IND 077872 or IND 160307 during the NDA review. No additional information from the ABSSSI studies in the NDA was submitted as these were completed prior to NDA submission.

Two clinical studies were initiated since the NDA application as submitted. Protocol TR701-132, a Phase 3 randomized double-blind trial comparing tedizolid phosphate and linezolid in ventilated Gram-positive nosocomial pneumonia, was initiated at two clinical study sites on January 31, 2014; however no patients had been enrolled.

Protocol 16099, a randomized, open-label, active-controlled, multicenter study in Japanese patients with methicillin-resistant *Staphylococcus aureus* infections, enrolled 4 patients beginning on November 23, 2013. All 4 patients completed the treatment period with no serious adverse events reported.

An oral neurotoxicity nonclinical study (TOX-11-0701-028) evaluated the potential effects of tedizolid phosphate in Long Evans Rats at 1, 3, 6, and 9 months by select neurobehavioral, gross neuropathologic, and microscopic histopathologic assessments. In addition, the study evaluated the recovery, persistence, or progression of any effects following a minimum 3 month recovery following six months of administration. The original NDA submission included functional observational data for the 1- 3-, 6-, and 3-month recovery groups from the 6-month treated rats and 9-month groups. The update provided histopathology results from the 9-month group. The update reports that there were no gross or microscopic histopathologic test-

article related alterations at the 1, 3, 6, or 9 month necroscopies or at the recovery necroscopy. The complete report was submitted to IND 077872 and IND 106307.

8 Postmarket Experience

Tedizolid phosphate is a new molecular entity which has not been approved in the United States or other countries. There is no information on postmarket experience.

9 Appendices

None.

9.1 Literature Review/References

Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

9.2 Labeling Recommendations

Final labeling recommendations are under review. Suggestions for changes to the label submitted by the Applicant included the need to highlight the fact that safety issues have only been studied for treatment duration of 6 days. Potential oxazolidinone class specific toxicities noted with linezolid such as myelosuppression, as well as peripheral and optic neuropathy, may become apparent with potential off-label use at higher doses or longer durations. Furthermore, data in certain sub-populations, such as adolescents and children, elderly, obese, renally impaired, hepatically impaired, neutropenic, and non-White individuals, are not adequate to make definitive conclusions regarding safety.

Suggested modifications to the Applicant's submitted label follow.

Efficacy: The modified label forwarded to the Applicant for review had a revised section 14 Clinical Studies. In particular, rather than using a pooled analysis for efficacy, both studies were described and analyzed independently. One table highlighted study results using the primary endpoints for both studies in the ITT population. A second table presented the study results for the investigator assessment at PTE for both the ITT and CE-PTE populations. Two separate tables displayed pooled clinical outcomes for mITT subjects who had "indicated" pathogens.

Safety:

Section 5 Warnings and Precautions

1. Add section 5.1 warning about usage in neutropenic subjects

Section 6.1 Adverse Reactions in Clinical Trials.

1. Table 2: The table describing treatment emergent adverse events occurring at ≥2% incidence should include dizziness in the nervous system disorders SOC.

2. Pertinent adverse reactions occurring at <2% should be highlighted.

3. Table 3: The table describing potentially significant laboratory abnormalities for select hematology parameters should be modified to reflect the appropriate number of patients in the subset used for the analyses. Only the columns illustrating potentially clinically significant laboratory values should be included in the label. Furthermore, the Sponsor is requested to provide the actual value of the clinically significant hematology parameter for the column.

4. A statement should be added that emphasizes the fact that safety issues have only been studied for treatment durations of 6 days. Definitive safety conclusions cannot be made for longer duration of treatment particularly with regards to peripheral and optic neuropathy myelosuppression. (b) (4)

5. A statement should be added that addresses the fact that definitive safety conclusions cannot be made in sub-populations including adolescents and children, elderly, obese, renally impaired, hepatically impaired, neutropenic and non-White individuals.

9.3 Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on March 31, 2014. A verbatim transcript is posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm385739.htm

The members and temporary voting members were provided the background materials from FDA and Cubist Pharmaceuticals, which had acquired Trius Pharmaceuticals prior to the meeting. There were approximately 175 people in attendance and six Open Public Hearing speakers.

The following questions were posed to the committee for deliberation.

1. Has the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed?

All committee members voted “Yes”, indicating that the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms.

Emerging themes in the discussion by the committee members included the following:

1.) Lack of diverse patient population, particularly in the pivotal trials. Further study is required in patient subgroups and clarification should be provided in the label.
2.) Reluctance to approve tedizolid phosphate for use in adolescent patients based on the data at hand. Clarification should be provided in the label.
3.) Pediatric studies should be conducted.
4.) Safety issues with tedizolid phosphate for treatment course beyond 6 days require further study. Clarification should be provided in the label.
5.) Reluctance to approve tedizolid phosphate for use in neutropenic patients based on the data at hand. Clarification should be provided in the label.
6.) Consider a warning to address the potential for cross-resistance of tedizolid phosphate with linezolid.
7.) Ensure that there is enough microbiologic data to support indicated organisms in the label.
8.) Further data is needed for drug-drug interactions.
9.) Results of the MITT analyses should be included in label.
10.) Differences for dosing, safety and efficacy for obese patient, if any, should be clarified in the label.

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/s/

SHRIMANT MISHRA
06/10/2014

SHERAL S PATEL
06/10/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205435/ 205436	**Applicant:** Trius Therapeutics	**Stamp Date:** October 21, 2013
Drug Name: Tedizolid phosphate (TR-701/ TR-701 FA)	**NDA/BLA Type:** Priority Review Qualified Infectious Diseases Product Designation	

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
FORMAT/ORGANIZATION/LEGIBILITY						
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD Submitted 10/18/2013 Received 10/21/2013	eCTD Submitted 10/18/2013 Received 10/21/2013
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			Section 5: Clinical Study Reports 5.3.1 Reports of biopharmaceutic studies 5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials 5.3.3 Reports of human pharmacokinetic (PK) studies 5.3.4 Reports of efficacy and safety studies [Indication]	Original Module 5 located in NDA 205435. Cross dossier links provided in NDA 205436.
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x				
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x				
5.	Are all documents submitted in English or are English translations provided when necessary?	x			English	English
6.	Is the clinical section legible so that substantive review can begin?	x			Electronic submission	Electronic submission
LABELING						
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			1.14.1 Draft Labeling 1.14.1.1 Draft carton and container labels (Blister carton, blister label, bottle label) 1.14.1.2 Annotated draft labeling text 1.14.1.3 Proposed labeling text (Word, PDF, and SPL)	1.14.1 Draft Labeling 1.14.1.1 Draft carton and container labels (Vial carton, vial label) 1.14.1.2 Cross-reference 205435. 1.14.1.3 Cross-reference 205435.
SUMMARIES						
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			2.2 Introduction 2.3 Quality Overview	Sections 2.3.P and 2.3.R, unique for

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
					Summary 2.4 Nonclinical Summary 2.5 Clinical Overview 2.6 Nonclinical written and tabulated summaries 2.7 Clinical Summary 2.7.1 Summary of biopharmaceutic studies and associated analytical methods 2.7.2 Summary of clinical pharmacology studies including special studies in microbiology 2.7.3 Summary of clinical efficacy for ABSSSI 2.7.4 Summary of clinical safety 2.7.5 Literature references 2.7.6 Synopses of individual studies	tedizolid phosphate for injection All other sections of Module 2: cross-dossier link to NDA 205435.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			5.3.5.3 ISS (STF) Integrated summary of safety	Module 5: cross-dossier link to NDA 205435.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			5.3.5.3ISE (STF) Integrated summary of effectiveness 5.3.5.3 ISM (STF) Integrated summary of microbiology data (analysis data only)	Module 5: cross-dossier link to NDA 205435.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			2.5 Clinical Overview (Section 6 in document)	Module 2: cross-dossier link to NDA 205435.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	1.1.2 Form 356h: 505(b)(1) 1.7.1 Fast track designation request: QIDP (3 Jan 13)	1.1.2 Form 356h: 505(b)(1) 1.7.1 Cross-dossier link to NDA 205435.
DOSE						
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	x			2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods (Human) Study Number: TR701-103, 107, 108	Module 2: cross-dossier link to NDA 205435.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
					2.7.2 Summary of Clinical Pharmacology Studies	
EFFICACY						
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			2.5 Clinical Overview 2.7.6 Synopses of individual studies 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication TR701-112: Efficacy, safety, popPK in the treatment of ABSSSI TR701-113: Efficacy and safety in the treatment of ABSSSI	Modules 2 and 5: cross-dossier link to NDA 205435.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x				
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			In the original submission, the Sponsor did not state the rationale for assuming the applicability of foreign data to the US population and practice of medicine in a single EDR location. The Sponsor provided clarification (SD 3) on 11/20/2013.	In the original submission, the Sponsor did not state the rationale for assuming the applicability of foreign data to the US population and practice of medicine in a single EDR location. The Sponsor provided clarification (SD 3) on 11/20/2013.
SAFETY						
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x				
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval	x			5.3.5.4 TR701-115 (STF) Ph1 Oral tQT (Other study reports)	Module 5: cross-dossier link to NDA 205435.

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	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
	studies, if needed)?					
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			Drug not approved or marketed in any country.	Drug not approved or marketed in any country.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x		
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			Pivotal trials; number receiving study drug TR701-112: *n*=331 TR701-113; *n*=331 2.7.4 Summary of Clinical Safety: Overall: 1048 (1050?) unique patients + 437 (438?) unique volunteers 2.7.6 Synopses of individual studies	Module 2: cross-dossier link to NDA 205435.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			1.2 Reviewer's Guide: page 13, Table 4: List of differences in MedRA preferred terms for all studies. CSC JumpStart Data Fitness Session 11/8/2013	Module 2: cross-dossier link to NDA 205435.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			5.3.5.3 ISS – (STF) Integrated Summary of Safety Listing 1.4.1 Abnormal neurologic exam Listing 1.5.1 AE for study drug and prior or concomitant medications with potential serotonergic activity (Phase 2 and 3 studies)	Module 5: cross-dossier link to NDA 205435.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
					Listing 1.5.1.2 AE for study drug and prior or concomitant medications with potential serotonergic activity (Phase 1 study) Listing 1.5.2.1 AE for prior or concomitant efflux transporter substrates (Phase 2 and 3) Listing 1.5.2.2 AE for prior or concomitant efflux transporter substrates (Phase 2 and 3) Also tables for pertinent laboratory parameters as well as Snellen exam were included.	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			2.7.4 Summary of Clinical Safety Section 2.6 Narratives (for 2 deaths) Table 17: Table 17 Listing of Subjects/Patients with Serious Adverse Events Table 19: Listing of Subjects/Patients Discontinuing Study Drug due to an Adverse Event 5.3.5.3 ISS – (STF) Integrated Summary of Safety Listing 1.2.1 SAE All studies combined Listing 1.2.2 Deaths All studies combined Listing 1.2.3 AEs leading to permanent discontinuation from study drug – all studies combined Listing 1.2.4 AEs leading to permanent discontinuation from study– all studies	Module 2: cross-dossier link to NDA 205435.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
					combined	
OTHER STUDIES						
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x		
PEDIATRIC USE						
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			1.9.2 Request for deferral of pediatric studies 1.9.6 Pediatric Study Plan	Cross-dossier link to NDA 205435.
ABUSE LIABILITY						
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			2.7.4 Summary of Clinical Safety (Section 5.6 Drug abuse)	Module 2: cross-dossier link to NDA 205435.
FOREIGN STUDIES						
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			In the original submission, the Sponsor did not state the rationale for assuming the applicability of foreign data to the US population and practice of medicine in a single location. The Sponsor provided clarification (SD 3) on 11/20/2013.	In the original submission, the Sponsor did not state the rationale for assuming the applicability of foreign data to the US population and practice of medicine in a single location. The Sponsor provided clarification (SD 3) on 11/20/2013.
DATASETS						
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Original submission: For Study 112, Unique Subject ID differs in analysis and tabulation datasets. Sponsor resubmitted on 2013-11-18 (SD 3), readjusting the study TR701-112 nomenclature for unique subject identifier so that it is the same for both the analysis and tabulation datasets and can be pooled with study 113.	Original submission: For Study 112, Unique Subject ID differs in analysis and tabulation datasets. Sponsor resubmitted on 2013-11-18 (SD 3), readjusting the study TR701-112 nomenclature for unique subject identifier so that it is the same for both the analysis and tabulation datasets and can be pooled with study 113.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment - 205435	Comment - 205436
					Pending further investigation if data can be uploaded and integrated.	Pending further investigation if data can be uploaded and integrated.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			JumpStart Data Fitness Session 11/8/2013	JumpStart Data Fitness Session 11/8/2013
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			JumpStart Data Fitness Session 11/8/2013	JumpStart Data Fitness Session 11/8/2013
34.	Are all datasets to support the critical safety analyses available and complete?	x			JumpStart Data Fitness Session 11/8/2013	JumpStart Data Fitness Session 11/8/2013
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			JumpStart Data Fitness Session 11/8/2013	JumpStart Data Fitness Session 11/8/2013
CASE REPORT FORMS						
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			5.3.5.1 TR701-112 Sample eCRF 5.3.5.1 TR701-112 eCRF 5.3.5.1 TR701-113 Sample eCRF 5.3.5.1 TR701-113 eCRF	Module 5: cross-dossier link to NDA 205435.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			Previously submitted CRF for Ophtho consult under IND 77872.	Previously submitted CRF for Ophtho consult under IND 77872.
FINANCIAL DISCLOSURE						
38.	Has the applicant submitted the required Financial Disclosure information?	x			1.3.4 Financial Disclosures *Form FDA 3454* – Box 1 marked *Form FDA 3455* – contracted (b) (6) clinical investigator, (b) (6) $276,951 ($1500 honoraria directly to investigator, rest to (b) (6))	Cross-dossier link to NDA 205435.
GOOD CLINICAL PRACTICE						
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication TR701-112 TR701-113	Module 5: cross-dossier link to NDA 205435.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? *YES*

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Preliminary review issues to be communicated to the Sponsor have been addressed. In the original submission, Unique Subject ID differs in analysis and tabulation datasets for Study 112. The Sponsor resubmitted on 2013-11-18 (SD 3), readjusting the study TR701-112 nomenclature for unique subject identifier so that it is the same for both the analysis and tabulation datasets and can be pooled with study 113. Clinical is working with JReview team to confirm that data can be uploaded and integrated.

Sheral S. Patel, M.D.	November 26, 2013
Reviewing Medical Officer	Date
Shrimant Mishra, M.D.	November 26, 2013
Clinical Team Leader	Date

Reference ID: 3426416

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERAL S PATEL
12/20/2013

SHRIMANT MISHRA
01/02/2014

CLINICAL Microbiology: 45-Day Meeting NDA Checklist for Filing NDA 205435/205436 Tedizolid Phosphate for Complicated Skin and Skin Structure Infections.

Reviewer: Avery Goodwin, Ph.D
Date Completed: 11/25/2013

On **initial** overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant submitted draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓		
6	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	✓		
8	Has the applicant submitted the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant submitted a clinical microbiology dataset in a format which intents to determine resistance development by correlating changes in the	✓		

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	phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?			
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.**	✓		

Any Additional Clinical Microbiology Comments: There are no additional comments

Avery Goodwin, Ph.D.
Reviewing Clinical Microbiologist
DAIP

Kerry Snow, MS.
Team Leader Clinical Microbiology
DAIP
FIN 11-25-13

Reference ID: 3413669

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AVERY C GOODWIN
11/26/2013

KERRY SNOW
11/26/2013