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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	205435 and 205436
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Indication(s):	Acute Bacterial Skin and Skin Structure Infections
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Non-inferiority

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1 EXECUTIVE SUMMARY

Trius Therapeutics, a Cubist Company, hereafter referred to as Applicant, submits this NDA intended to support the approval of Sivextro (tedizolid phosphate) 200 mg tablet or injection once daily (qd) × 6 days for the treatment of acute bacterial skin and skin structure infection (ABSSSI).

This NDA contains the results of two Phase 3 studies, Study TR 701-112 and Study TR 701-113. Study TR 701-112 is a randomized, double-blind, double-dummy, multicenter non-inferiority (NI) study of oral (tablet) tedizolid phosphate 200 mg once daily for 6 days versus oral linezolid 600 mg every 12 hours for 10 days. Six-hundred sixty-seven adults with ABSSSI, including cellulitis/erysipelas, major cutaneous abscess, and wound infections, were randomized 1:1 to study treatment across 82 sites globally. Randomization was stratified by the presence/absence of fever at baseline, geographic region, and clinical syndrome (cellulitis/erysipelas, major cutaneous abscess [maximum of 30% of the study population], and wound infection). Study TR 701-113 is also a randomized, double-blind, double-dummy, multicenter, global non-inferiority study of intravenous (IV) to oral tedizolid phosphate 200 mg once daily for 6 days versus IV to oral linezolid 600 mg every 12 hours for 10 days. Six-hundred sixty-six adults with ABSSSI, including cellulitis/erysipelas, major cutaneous abscess, and wound infections, were randomized 1:1 to study treatment across approximately 130 sites globally. Randomization was stratified by geographic region and clinical syndrome (major cutaneous abscess [maximum of 30% of the study population], cellulitis/erysipelas, and wound infection).

The primary objective in both studies is to determine the NI in the early clinical response rate of 6-day tedizolid phosphate compared with that of 10-day linezolid treatment at the 48-72 Hour Visit in the all randomized, intent-to-treat (ITT) population. The non-inferiority margin is pre-specified at -10%. The secondary objectives are to compare the clinical response of the treatment arms at the End of Therapy (EOT) Visit (Day 11) in the ITT and Clinically Evaluable (CE)-EOT[1] populations as well as to compare the Investigator's assessment of clinical success at the Post-therapy Evaluation (PTE) Visit (7 to 14 days after the EOT Visit) in the ITT and CE-PTE[2] population.

In Study TR 701-112, the primary outcome measure is the early clinical response at the 48-72 Hour Visit in the ITT population. This outcome is determined programmatically based on data recorded on the electronic case report form (e-CRF) and the Investigator's assessment is not a component of the primary outcome measure. In particular, patients who meet the following criteria at the 48-72 Hour Visit are programmatically defined as a responder:

[1] Patients receiving minimal study therapy, completed 48-72 Hour and EOT assessments, no concomitant systemic antibiotic therapy through EOT, no confounding events or factors

[2] Patients receiving minimal study therapy, completed EOT and PTE assessments, no concomitant systemic antibiotic therapy through PTE, no confounding events or factors

- Cessation of spread of the primary ABSSSI lesion, compared with baseline (cessation of spread defined as no increase in lesion surface area [length × width] compared to baseline);
- Temperature measurement (assessed by the Investigator) is ≤37.6°C (oral) and the next measurement (taken within 24 hours of the 48-72 Hour Visit) is also ≤37.6°C (oral).

In Study TR 701-113, the primary outcome measure is also early clinical response at the 48-72 Hour Visit in the ITT population. However, a patient is programmatically defined as a responder, at 48 to 72 hours after the first infusion of study drug (Dose 1, Infusion A), if the following criteria are met:

- ≥20% reduction in area of erythema, edema and/or induration (length x width) compared with baseline.

The enrolled patients composing the study population were balanced between the two groups in terms of factors that could potentially affect the results, e.g. demographics and some important medical history, fever, type of infection and anatomical site of infection, prior medications or procedures that have potential impact on the efficacy results, baseline pathogen isolated at the infection site, and baseline signs and symptoms of the primary ABSSSI infection (see more details in Table 3-5, Table 3-6).

The early clinical response at the 48-72 Hour Visit in Study TR 701-112 was observed in 256/323(79.3%) of patients in the tedizolid phosphate group and 258/326(79.1%) of patients in the linezolid group in the ITT* Population, with a treatment difference 0.1% [adjusted 95% CI: -6.2%, 6.3%]. In Study TR 701-113, the early clinical response based on ≥ 20% decrease from baseline at 48-72 hour visit in lesion area was observed in 283/332(85.2%) of patients in the tedizolid phosphate group and 276/334(82.6%) of patients in the linezolid group, with a treatment difference of 2.6% [unadjusted 95% CI: -3.0%, 8.2%]. The lower limits of the 95% confidence intervals meet the pre-specified NI margin which required for it to be greater than -10%. Therefore, non-inferiority of tedizolid phosphate to linezolid is demonstrated in both Study TR 701-112 and Study TR 701-113. See further discussion in Section 3.2.7.1.

For a consistent measure of efficacy across trials, results for the outcome of Study TR 701-112 using the primary efficacy endpoint of Study TR 701-113 were calculated. In particular, the early clinical response based on ≥ 20% decrease from baseline at 48-72 hour visit in lesion area was observed in 252/323(78.0%) of patients in the tedizolid phosphate group and 246/326(75.5%) of patients in the linezolid group in Study TR 701-112 ITT* Population[3] with a treatment difference of 2.6% [unadjusted 95% CI: -4.0%, 9.1%]. Hence, if this had been the pre-specified primary outcome measure for Study TR 701-112, the study would still meet the non-inferiority requirement because the lower limit of the 95% confidence interval about the treatment difference exceeds -10%.

[3] The ITT* population excludes 18 patients from sites 120, 121, and 122. See discussion in Section 3.1.

There are two secondary efficacy outcome measures of interest: the clinical response at the end of therapy (EOT) Visit, performed 11-13 days after first infusion of study drug, in the ITT Population and the Investigator's assessment of clinical success at the post therapy evaluation (PTE) Visit (7 to 14 days after the EOT Visit) in the ITT. Their definitions are found in Appendix 6.1.1 and 6.1.2, respectively. Results show that the treatment response of tedizolid phosphate is similar to linezolid and supports the non-inferiority result obtained at the early clinical evaluation at 48-72 hours after first study drug infusion.

In Study TR 701-112, the sustained clinical response, i.e., all nonresponders at the 48-72 Hour Visit were carried forward as clinical failures in the assessment of clinical response at EOT, was observed in 235/326 (67.5%) of patients in the tedizolid phosphate group and 224/323(70.2%) of patients in the linezolid group. The treatment difference is -2.7% with a 95% CI of (-9.7, 4.4); see Table 3-19. If carry-over and pain component is removed, the clinical response at the EOT Visit was observed in 281/323(87.0%) subjects in the tedizolid phosphate group and 285/326 (87.4%) subjects in the linezolid group with treatment difference of -0.4 and an unadjusted 95% CI of (-6.2, 5.9). These response rates are similar to the observed response rates in both treatment groups in Study TR 701-113 (see Table 3-20), which uses this outcome measure as its pre-specified secondary endpoint. In particular, in Study TR-701-113, clinical success was 289/332 (87.0%) in the tedizolid phosphate group and 294/334 (88.0%) in the linezolid group, with a treatment difference of -1.0% [unadjusted 95% CI: -6.1%, 4.1%]. See further discussion in Section 3.2.7.2.

In terms of investigator's assessment of clinical response at the PTE Visit which was performed within 7 to 14 days after the EOT Visit, the proportion of patients considered a responder for this endpoint in the ITT* population of Study TR 701-112 is 85.8% and 85.6% for tedizolid phosphate and linezolid groups, respectively (treatment difference of 0.2% with an unadjusted 95% CI of -5.3% to 5.6%). In Study TR 701-113, the proportion was 88.0% for tedizolid phosphate and 87.7% for linezolid arms respectively (treatment difference of 0.3% with an unadjusted 95% CI of -4.8% to 5.3%; see Table 1-1). In this endpoint, the result obtained in Study TR 701-112 is also replicated in Study TR 701-113. See further discussion in Section 3.2.7.3.

The cure rate based on the investigator's assessment of clinical response defined as complete resolution of all signs and symptoms observed at baseline was observed in 218/323 (67.5%) of patients in tedizolid phosphate and 222/326 (68.1%) of patients in linezolid in Study TR 701-112, and the treatment difference is -0.6 (unadjusted 95% CI of -7.8 to 6.6). For Study TR 701-113, resolution based on the investigator's assessment of clinical response was observed in 224/332 (67.5%) of patients in the tedizolid phosphate group and 218/334 (65.3%) of patients in the linezolid group with a treatment difference of 2.2 (unadjusted 95% CI of -5.0 to 9.4). Similar to the original definition of investigator's assessment of clinical response at the PTE Visit, the result obtained based on complete resolution is replicated and the two treatments have comparable results.

These investigations suggest that tedizolid phosphate is therapeutically non-inferior to linezolid. There were other investigations made on factors that could potentially confound the treatment

response, e.g., NSAID/oral steroid use, incision and drainage performed, inclusion of major cutaneous abscess, inclusion of a significant number of patients from Europe (see Sections 3.2.7.1, 3.2.7.2, 3.2.7.3, and 3.2.7.5). The two treatment groups, however, are balanced with respect to these subgroups so that their combined effect is not manifested in the difference of the treatment response; hence, does not alter the conclusion of non-inferiority established in the primary efficacy endpoint and supported by the secondary endpoints.

2 INTRODUCTION

2.1 Overview

Tedizolid phosphate (TR-701) is a novel oxazolidinone prodrug antibiotic initiated by Dong-A Pharmaceutical Co. Ltd., Korea. Trius Therapeutics, a Cubist Company, licensed the drug for clinical development in the United States and Europe. The prodrug is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid (TR-700) which is a protein synthesis inhibitor that interacts with the bacterial 23S ribosome subunit. The interaction prevents the initiation of translation by inhibiting formation of the initiation complex.

Tedezolid phosphate is being developed for both oral and intravenous (IV) administration in the treatment of acute bacterial skin structure infections (ABSSSI) caused by Gram-positive bacteria including methicillin-resistant *S. aureus* (MRSA). ABSSSI consists of clinical syndromes such as cellulitis, infected burns, major abscesses, and wound infections. The availability of both IV and oral formulations of antibacterial agents allows for an IV-to-oral switch in treatment scheme that is common practice in the treatment of severe forms of ABSSSI. The switch from IV to oral outpatient therapy generally occurs as soon as clinically indicated, allowing continuation of therapy in either an in-patient or outpatient setting.

Table 2-1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population	Endpoint
TR 701-112	phase 3, randomized, double-blind, non-inferiority	Oral TR 701 FA QD × 6 days + placebo QD × 4 days Linezolid BID × 10 days	18-25 days after the EOT Visit (Day 11)	TR 701 FA: N=332 Linezolid: N=335	ABSSSI patients	Cessation of lesion spread and afebrile at 48 to 72 Hours
TR 701-113	phase 3, randomized, double-blind, non-inferiority	IV to Oral TR 701 FA QD × 6 days + placebo QD × 4 days Linezolid BID × 10 days	18-25 days after the EOT Visit (Day 11)	TR 701 FA: N=332 Linezolid: N=334	ABSSSI patients	≥20% reduction in lesion size at 48 to 72 Hours

A total of 19 tedizolid phosphate clinical studies have been completed: 15 Phase 1 studies, 2 Phase 2 studies (TR701-104 and TR701-126) in patients with complicated skin or skin structure

infections (cSSSI) or cellulitis or abscess, and 2 Phase 3 studies in patients with ABSSSI. TR701-104 was a multicenter, randomized, double-blind, dose-ranging, noncomparative study evaluating the clinical and microbiological response, safety, and population PK in adult patients with cSSSI. In this study, 188 cSSSI patients received 200, 300, or 400 mg oral tedizolid phosphate once daily for 5 to 7 days. Study TR701-126 was a Phase 2, open-label, multicenter study designed to further assess the safety of oral tedizolid phosphate 200mg once daily for 6 days for the treatment of major cutaneous abscess or cellulitis/erysipelas (200 patients). Various lesion area measurement methods were tested. The two Phase 3 studies conducted to support tedizolid phosphate for the treatment of ABSSSI are shown in Table 2-1.

2.2 Regulatory Milestones

On 09 June 2010, the FDA issued a Special Protocol-Agreement letter for Study TR 701-112. The primary efficacy endpoint was agreed to be:

- cessation of spread of the primary ABSSSI lesion, compared with baseline (cessation of spread was defined as no increase in lesion surface area [length × width] compared to baseline); and,
- temperature measurement (assessed by the Investigator) is ≤37.6°C (oral) and the next measurement (taken within 24 hours of the 48-72 Hour Visit) is also ≤37.6°C (oral).

In addition, the FDA recommended that:

- The qualifying fever at baseline should be ≥38ºC and resolution of fever should be defined as having a maximum daily temperature of ≤ 37.6ºC.
- Approximately 50% of patients with fever at baseline should be enrolled and randomized.
- Precise measurements for the length and width of lesion size should be carried out and other reliable measurement methods should be explored. Absolute and percent reduction in lesion size from baseline should be analyzed separately from baseline through 48-72 hours, EOT and follow-up visits.
- The analysis of the primary endpoint of cessation of spread should also be performed using risk ratio and odds ration metrics, considering high response rates.

The SPA was issued prior to the issuance of the FDA draft guidance "Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" in August 2010.

On 28 January 2011, a Type C Meeting was held to discuss the Phase 3 trial design for Study TR701-112 and Study TR701-113. In that meeting, the FDA and Sponsor agreed to the removal of febrile quota for TR701-112 and no minimum percentage of febrile patients required for Study TR701-113. However the primary outcome for Study TR701-112 remained intact. The FDA agreed with the change in the proportion of represented clinical syndromes, with the exception of a cap of 30% on skin abscesses, but added that a good mix of patients with infection types was desirable.

On 02 August 2011, the FDA issued a special protocol-agreement for TR701-113. In particular, the definition of primary outcome measure of responder was defined as

- cessation of spread of erythema, edema, and/or induration of the primary ABSSSI lesion or reduction in the size (length, width, and area) of erythema, edema, and/or induration, compared with baseline; and
- temperature measurement at the 48-72 hour visit (assessed by the investigator) is less than 37.7 degrees Celsius (oral or equivalent) at 3 consecutive recordings by the same methodology measured four times a day (i.e. qid, allowing for an 8 hour interval at night) between 48 and 72 hours.

On February 28, 2012, the applicant met with the Agency to discuss the results of Study TR 701-112. In that meeting, the applicant stated that there were challenges with the acquisition of temperature measurements and proposed to submit a modified statistical analysis plan that would exclude fever in the assessment of the primary endpoint. The Agency agreed to evaluate this result as a sensitivity analysis.

On June 2012, the Biomarkers Consortium of the Foundation for the National Institutes of Health recommended defining the early response in clinical trials for ABSSSI as a decrease from baseline of ≥20% in lesion area (longest head-to-toe length × longest perpendicular width) at 48 to 72 hours after randomization and added that absence of elevated body temperature (fever) should not be a component of the primary outcome measure. Frequent temperature measurements cannot be obtained reliably in many clinical trials setting (Talbot 2012).

On 07 December 2012, the FDA acknowledged the 09 November 2012 amendment to Study TR701-113 protocol (Protocol Amendment 6), amending the special protocol agreement. The amendment made the following modifications:

- Change the definition of a responder to the primary efficacy endpoint of a ≥20% reduction in lesion area from baseline.

2.3 Data Sources

The main submission, including the case study report and datasets, are located in \\Cdsesub1\evsprod\NDA205435\0000. Additional data are located in sequence \\Cdsesub1\...\0020.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data have adequate quality. However, the naming of the variables is not consistent among datasets in the two studies. For example, in some datasets the subject ID is concatenated with the Study ID and the Site ID to form the unique subject ID while in some the subject ID is the unique subject ID. This makes it difficult to replicate analysis from one study to another.

Over the course of reviewing monitoring reports and essential documents in the trial master file (TMF) for Study TR 701-112, the applicant identified issues at three sites (120, 121, 122) that raised concerns. The applicant conducted a focused data audit on these sites on October 7, 2013 and determined that source data did not fully meet Good Clinical Practices (GCP) ALCOA (attributable, legible, contemporaneous, original, accurate) standards to support electronic case report form (eCRF) data. These sites enrolled a total of 18 subjects, equally distributed between the two treatment arms. They are excluded in all analysis populations that are superscripted by an asterisk (see Table 3-1).

The final statistical analysis plan (SAP) for Study TR 701-112 was finalized on 01 December 2011 while for Study TR 701-113, it was finalized on 08 November 2012 (Version 4).

All tables and figures were created by the reviewer except when they are indicated to be lifted from the Sponsor's Case Study Report.

3.2 Evaluation of Efficacy

3.2.1 Study Design

The evaluation of efficacy is based on two trials, Study TR 701-112 and Study TR 701-113. Study TR 701-112 is a randomized, double-blind, double-dummy, multicenter Phase 3 non-inferiority study of oral tedizolid phosphate 200 mg once daily for 6 days versus oral linezolid 600 mg every 12 hours for 10 days. Six-hundred sixty-seven adults with ABSSSI, including cellulitis/erysipelas, major cutaneous abscess, and wound infections, were randomized 1:1 to study treatment across 82 sites globally. Randomization was stratified by the presence/absence of fever at baseline, geographic region, and clinical syndrome (cellulitis/erysipelas, major cutaneous abscess [maximum of 30% of the study population], and wound infection).

TR 701-113 is also a randomized, double-blind, double-dummy, multicenter, global Phase 3 non-inferiority study of IV to oral tedizolid phosphate 200 mg once daily for 6 days versus IV to oral linezolid 600 mg every 12 hours for 10 days. Six-hundred sixty-six adults with ABSSSI, including cellulitis/erysipelas, major cutaneous abscess, and wound infections, were randomized 1:1 to study treatment across approximately 130 sites globally. Randomization was stratified by geographic region and clinical syndrome (major cutaneous abscess [maximum of 30% of the

study population, of which not more than approximately half were to originate from the North American study population], cellulitis/erysipelas, and wound infection).

Patients start treatment with at least 2 IV doses (Dose 1 comprised Infusion A and Infusion B, and Dose 2 was a single infusion) of study drug; patients can receive IV therapy for the entire treatment duration. After Dose 1 and Dose 2, subjects can be switched from IV to oral study drug provided 2 of the 4 following criteria are met:

- Primary skin lesion has not increased in area, length, or width from baseline;
- Temperature is <37.7°C at last measurement;
- No local signs or symptoms of the primary ABSSSI site worsened since previous visit;
- Improvement of at least 1 local sign or symptom of the primary ABSSSI site since previous visit.

In both studies, adjunctive antibacterial therapy is prohibited in patients with cellulitis/erysipelas or major cutaneous abscess. Patients with these infections and with a culture or Gram stain that indicates or suggests the presence of a gram-negative pathogen causing the ABSSSI are excluded from enrollment. Patients randomized before the baseline culture results are available and later found to only have a gram-negative pathogen that requires antibiotic therapy are to discontinue study drug.

Patients with wound infections can be treated with adjunctive aztreonam and/or metronidazole if a gram-negative pathogen is suspected (e.g., Gram stain) or confirmed by culture. A patient with a wound infection found to only have a gram-negative pathogen after randomization, but no gram-positive pathogen, is to discontinue study drug.

Baseline assessments are performed within 24 hours before Dose 1 (Study Day 1). Patients are also assessed on Study Day 1, Day 2, 48 to 72 hours after first dose, Day 7, and Day 11 (EOT Visit) during the treatment period; at the PTE Visit (7 to 14 days after the EOT Visit); and at the Late Follow-up (LFU) Visit (18 to 25 days after the EOT Visit).

3.2.2 Analysis Population

Both studies have the same analysis populations and are defined as follows:

The Intent-to-Treat (ITT) population consists of all randomized patients regardless of whether or not the patient received study drug. A patient is considered randomized when the Investigator or Investigator's designee receives the IVRS-generated randomization number.

The Safety population consists of all randomized patients who receive any amount of study drug.

The micro-ITT (MITT) population consists of all ITT Population patients who had 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.

There are two Clinically Evaluable (CE) populations: CE at End-of-Therapy (CE-EOT) and CE at Post-Therapy-Evaluation (CE-PTE). All patients in the ITT population who complied with the protocol with no major violations, as defined in the Statistical Analysis Plan (SAP), and who met the following criteria:

- completed the clinical response outcome assessment at the EOT Visit;
- received concomitant systemic antibiotic therapy or topical antibiotic from the first infusion 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

are included in the CE-EOT population. On the other hand, all patients in the ITT population who complied with the protocol with no major violations and who meet the following criteria:

- completed the Investigator's assessment of clinical response at the PTE Visit (unless assessed as a clinical failure at the EOT Visit);
- receipt of concomitant systemic antibiotic therapy or topical antibiotic from the first dose of study drug through the PTE Visit that is potentially effective against the baseline pathogen except adjunctive aztreonam and/or metronidazole in patients with wound infections

are to be included in the Clinically Evaluable at PTE Population.

The micro-evaluable (ME) population consists of all patients in both the MITT and the CE-PTE populations.

3.2.3 Endpoints

In Study TR 701-112, the primary outcome measure is the early clinical response at the 48-72 Hour Visit in the ITT population. This outcome is determined programmatically based on data recorded on the e-CRF, and the Investigator's assessment is not a component of the primary outcome measure. In particular, patients who meet the following criteria at the 48-72 Hour Visit are programmatically defined as a responder:

- cessation of spread of the primary ABSSSI lesion, compared with baseline (cessation of spread defined as no increase in lesion surface area [length × width] compared to baseline);
- temperature measurement (assessed by the Investigator) is ≤37.6°C (oral) and the next measurement (taken within 24 hours of the 48-72 Hour Visit) is also ≤37.6°C (oral).

On the other hand, patients who meet the following criteria at the 48-72 Hour Visit are programmatically defined as a nonresponder:

- spread of the primary ABSSSI lesion, compared with baseline (spread of the lesion is defined as an increase in lesion surface area [length × width] as compared to baseline);
- receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections;
- death of any cause;
- temperature measurement at the 48-72 Hour Visit (assessed by the Investigator) or the next measurement (taken within 24 hours of the 48-72 Hour Visit) is >37.6°C (oral).

In Study TR 701-113, the primary outcome measure is also early clinical response at the 48-72 Hour Visit in the ITT population. However, a patient is programmatically defined as a responder, at 48 to 72 hours after the first infusion of study drug (Dose 1, Infusion A), if the following criteria are met:

- ≥20% reduction in area of erythema, edema and/or induration (length x width) compared with baseline.

On the other hand, patients are programmatically defined as a nonresponder if any of the criteria outlined below are met:

- spread in the size (area, defined as length x width) of the primary ABSSSI lesion, compared with baseline;
- receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections, through 72 hours after the first infusion of study drug (Dose 1, Infusion A). If a patient did not have a pathogen isolated at baseline and the systemic concomitant antibiotic received has gram-positive activity, the patient was defined as a failure;
- death of any cause through 72 hours after the first infusion of study drug (Dose 1, Infusion A).

The change in the endpoint is based on FNIH recommendations to FDA released on August 2011 that supported a definition of ≥20% decrease in lesion area at 48-72 hours and no fever component. Accordingly, the change is reflected in Protocol Amendment 6 (dated 17 October 2012), defining a responder as having a ≥20% reduction in lesion area regardless of fever status. This amendment was reviewed by the agency and agreement that the SPA remained intact was received on 07 December 2012.

The secondary efficacy outcome measures in both trials include:

- Clinical response at the EOT Visit in the ITT and CE-EOT Populations

- Investigator's assessment of clinical success at the PTE Visit in the ITT and CE-PTE Populations
- Change from baseline in the pain scores at each timepoint
- Change from baseline in lesion size, assessment of local signs and symptoms, and systemic signs (lymphadenopathy, percentage immature neutrophils, and WBC count)

The definitions for Clinical response at the EOT and the Investigator's assessment of clinical response at the PTE are found in Appendix 1 and 2, respectively. Note that in Study TR 701-112, all nonresponders at the 48-72 hour time point are carried forward as clinical failures at EOT. Hence in the protocol, it is aptly called sustained Clinical response. In Study TR 701-113, nonresponders at the 48-72 hour time point can be considered clinical successes at EOT provided they did not meet the failure criteria that include receipt of other effective antibacterial therapy. Another key difference is that patient-reported presence of pain is not a criterion in the programmatic definition of clinical failure in Study TR 701-113 but is in Study TR 701-112 while persistent purulent drainage from a wound infection at the same or greater intensity as Screening is a criterion in the programmatic definition of clinical failure in Study TR 701-113 but is not in Study TR 701-112.

The definition Investigator's assessment of clinical success at the PTE Visit is similar in both trials.

3.2.4 Statistical Methodologies

3.2.4.1 Primary Efficacy Analysis

For both trials, the primary efficacy outcome is the percentage of patients who are responders based on the programmatic determination of the early clinical response at the 48-72 Hour Visit in the ITT population. In Study TR 701-112, a 2-sided 95% confidence interval (CI) adjusted for the stratification factor of presence/absence of fever at baseline, for the observed difference in primary efficacy outcome rates (tedizolid phosphate treatment group minus linezolid treatment group) is calculated using the method proposed by Miettinen and Nurminen (Miettinen, 1985). On the other hand, in Study TR 701-113, an undjusted 2-sided 95% CI is calculated using the same method. If the lower limit of the 95% CI is greater than the pre-specified margin of -10%, NI of tedizolid phosphate to linezolid is concluded. This is the margin agreed upon in the SPA for both trials and is also recommended in the FDA draft guidance "Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" issued in in August 2010 and in October 2013.

Several sensitivity analyses of the primary efficacy outcome are conducted to determine the consistency of the result of the primary efficacy outcome.

3.2.4.2 Secondary Efficacy Analysis

The number and percentage of patients in each treatment group with a clinical success, clinical failure, and indeterminate response based on sustained response at EOT are determined in the ITT and CE-EOT Populations (by definition CE-EOT patients cannot have an indeterminate response). In addition, the number and percentage of patients in each treatment group with a clinical success, clinical failure, and indeterminate response based on the Investigator's assessment are reported for the ITT and CE-PTE Populations (by definition CE-PTE patients cannot have an indeterminate response). Two-sided 95% CIs are constructed for the observed differences in the clinical success rate based on sustained response at EOT and the Investigator's assessment using the method of Miettinen and Nurminen.

To control for inflation of the overall type I error rate, the hierarchical testing procedure of Westfall and Krishen (Westfall 2001) is used. If NI of tedizolid phosphate is declared for the primary outcome of an early clinical response at the 48-72 Hour Visit in the ITT population, the difference between the treatment groups is tested for superiority. If the lower bound of the 95% confidence limit is greater than 0, superiority of tedizolid phosphate is concluded. Only in this case is testing to proceed to the next outcome measure.

Order of secondary outcomes:

- Clinical response at EOT in the ITT Population
- Clinical response at EOT in the CE-EOT Population
- The Investigator's assessment of clinical success in the ITT Population
- The Investigator's assessment of clinical success in the CE-PTE Population

3.2.4.3 Additional Outcomes

Additional efficacy analyses are conducted to support the efficacy findings of the primary and secondary outcome measures. These include the following:

- The number and percentage of patients in the CE-PTE Population who relapsed at the LFU Visit;
- The per-patient microbiological response at the PTE Visit in the MITT Population;
- The percent change from baseline defined as 0 to <5%, 5 to <10%, 10 to <15%, 15 to <20%, 20 to <30%, 30 to <40%, 40 to <50%, and ≥50%;
- Presence of signs and symptoms of infection by visit;
- Actual pain score and change from baseline pain score by visit.

3.2.5 Handling of Missing Data

Missing values are not imputed and only observed values are used in data analyses. For the primary outcome measure, if there is any missing data field needed to determine the response at the 48-72 Hour Visit, the patient is assigned an indeterminate response. For analyses of the primary outcome, patients with an indeterminate response are included in the denominator, and thus, are considered nonresponders.

For the secondary outcome measure of sustained clinical response, if any component of the outcome measure, for example, pain at the EOT Visit, is missing, the patient is assigned a response of indeterminate. For the analysis in the ITT Population, indeterminates are included in the denominator and thus considered clinical failures. By definition, patients with an indeterminate response are excluded from the CE-EOT Population.

3.2.6 Patient Disposition, Demographic and Baseline Characteristics

3.2.6.1 Populations

Table 3-1 shows the analysis population in both trials. In Study TR-701-112, a total of 667 patients were randomized in the study, including 332 in the tedizolid phosphate group and 335 in the linezolid group. One patient in the tedezolid phosphate group was not treated. In TR 701-113, 666 patients were randomized in the study, including 332 in the tedizolid phosphate group and 334 in the linezolid group. One patient in the tedizolid phosphate and 7 patients in the linezolid arm did not receive their allocated treatment.

Table 3-1: Analysis Populations

Analysis Populations	Study TR 701-112			Study TR 701-113		
	Tedizolid phosphate	Linezolid	Total	Tedizolid phosphate	Linezolid	Total
Randomized – not treated	1	0	1	1	7	8
Randomized – Treated (Safety)	331	335	666	331	327	658
ITT	332	335	667	332	334	666
ITT*	323	326	649	NA	NA	NA
MITT	209	209	418	197	202	339
CE-EOT	273	286	559	304	299	603
CE-PTE	279	280	559	290	280	570

3.2.6.2 Patient Disposition

Table 3-2 shows the subject disposition which is categorized into study drug and study discontinuation. In Study TR 701-112, study drug completion rates are 91.6% for patients in the tedizolid phosphate group and 88.7% of patients in the linezolid group completed study drug treatment. The most common reasons for study drug discontinuation in both groups are lost to

follow-up (3.6% and 3.9% in the tedizolid phosphate and linezolid groups, respectively) and patient withdrew consent (2.1% and 1.5% in the tedizolid phosphate and linezolid groups, respectively). One patient (0.3%) in the tedizolid phosphate group and 2 patients (0.6%) in the linezolid group discontinued study drug due to an AE. In Study TR 701-113, study drug completion rates are 92.5% of patients in the tedizolid phosphate group and 91.0% of patients in the linezolid group completed study drug treatment. The most common reasons for study drug discontinuation in both groups are lost to follow-up (1.5% and 2.7% in the tedizolid phosphate and linezolid groups, respectively) and treatment failure (2.7% and 0.6% in the tedizolid phosphate and linezolid groups, respectively). One patient (0.3%) in the tedizolid phosphate group and 4 patients (1.2%) in the linezolid group discontinued study drug due to an AE.

Table 3-2: Subject Disposition

Study Drug Termination	**Study TR 701-112**			**Study TR 701-113**		
	Tedizolid phosphate (N = 332)	**Linezolid (N = 335)**	**Total**	**Tedizolid phosphate (N = 332)**	**Linezolid (N = 334)**	**Total (N = 666)**
Randomized but did not receive study drug	**1 (0.3)**	**0**	**1 (0.1)**	**1 (0.3)**	**7 (2.1)**	**8 (1.2)**
Completed study drug	**304 (91.6)**	**297 (88.7)**	**601 (90.1)**	**307 (92.5)**	**304 (91.0)**	**611 (91.7)**
Prematurely discontinued study drug	**27(8.1)**	**38 (11.3)**	**65 (9.7)**	**24 (7.2)**	**23 (6.9)**	**47 (7.1)**
Adverse Events	1 (0.3)	2 (0.6)	3 (0.4)	1 (0.3)	4 (1.2)	5 (0.8)
Treatment failure	2 (0.6)	7 (2.1)	9 (1.3)	9 (2.7)	2 (0.6)	11 (1.7)
Lost to follow-up	12 (3.6)	13 (3.9)	25 (3.7)	5 (1.5)	9 (2.7)	14 (2.1)
Withdrew consent	7 (2.1)	5 (1.5)	12 (1.8)	4 (1.2)	5 (1.5)	9 (1.4)
At request of sponsor or investigator	2 (0.6)	4 (1.2)	6 (0.9)	2 (0.6)	1 (0.3)	3 (0.5)
Requires prohibited medication	0	1 (0.3)	1 (0.1)	0	2 (0.6)	2 (0.3)
Gram-negative infection	2 (0.6)	5 (1.5)	7 (1.0)	0	0	
Other	1 (0.3)	1 (0.3)	2 (0.3)	3 (0.9)	0	3 (0.5)
Completed Study	**299 (90.1)**	**307 (91.6)**	**606 (90.9)**	**313 (94.3)**	**306 (91.6)**	**619 (92.9)**
Prematurely discontinued from study	**33 (9.9)**	**28 (8.4)**	**61 (9.1)**	**19 (5.7)**	**28 (8.4)**	**47 (7.1)**
Randomized but did not receive study drug	1 (0.3)	0	1 (0.1)	1(0.3)	7 (2.1)	8 (1.2)
Withdrew consent	9 (2.7)	7 (2.1)	16 (2.4)	6 (1.8)	5 (1.5)	11 (1.7)
Lost to follow-up	22 (6.6)	21 (6.3)	43 (6.4)	11 (3.3)	14 (4.2)	25 (3.8)
At request of Sponsor/Investigator	0	0		0	1 (0.3)	1 (0.2)
Other	1 (0.3)	0	1 (0.1)	1 (0.3)	1 (0.3)	2 (0.3)

For study discontinuation in Study TR 701-112, the most common reason in both groups are lost to follow-up (6.6% and 6.3% in the tedizolid phosphate and linezolid groups, respectively) and patient withdrew consent (2.7% and 2.1% in the tedizolid phosphate and linezolid groups,

respectively). Study completion rates are 90.1% of patients in the tedizolid phosphate group and 91.6% of patients in the linezolid group. In Study TR 701-113, the most common reasons are also similar, i.e., lost to follow-up (3.3% and 4.2% in the tedizolid phosphate and linezolid groups, respectively) and patient withdrew consent (1.8% and 5.5% in the tedizolid phosphate and linezolid groups, respectively). One patient in the tedizolid phosphate and 7 patients in the linezolid arm did not receive their allocated treatment. Study completion rates are 94.3% of patients in the tedizolid phosphate group and 91.6% of patients in the linezolid group.

3.2.6.3 Demographics

Table 3-3: Demographics at Baseline

Characteristic	Study TR 701-112		Study TR 701-113	
	TR 701 FA (N = 332)	**Linezolid (N = 335)**	**TR 701 FA (N = 332)**	**Linezolid (N = 334)**
Sex				
Female, n(%)	128 (38.6)	137 (40.9)	107 (32.2)	120 (35.9)
Male, n(%)	204 (61.4)	198 (59.1)	225 (67.8)	214 (64.1)
Age (years)				
Mean (SD)	43.6 (14.96)	43.1 (15.06)	45.6 (15.79)	45.6 (15.57)
Min, Max	18, 86	18, 100	17, 86	15, 89
Age group				
< 65 years, n(%)	303 (91.3)	309 (92.2)	289 (87.0)	301 (90.1)
≥ 65 to ≤ 75 years, n(%)	19 (5.7)	19 (5.7)	32 (9.6)	19 (5.7)
> 75 years, n (%)	7 (3.0)	7 (2.1)	11 (3.3)	14 (4.2)
Ethnicity				
Hispanic or Latino, n(%)	115 (34.6)	108 (32.2)	67 (20.2)	63 (18.9)
Not Hispanic or Latino, n(%)	217 (65.4)	227 (67.8)	265 (79.8)	271 (81.1)
Race				
White, n(%)	280 (84.3)	275 (82.1)	285 (85.8)	282 (8.4)
Asian, n(%)	2 (0.6)	7 (2.1)	4 (1.2)	7 (2.1)
Black or African American, n(%)	39 (11.7)	38 (11.3)	38 (11.4)	37 (11.1)
Native Hawaiian or Pacific Islander, n(%)	0	2 (0.6)	2 (0.6)	1 (0.3)
American Indian or Alaskan Native, n(%)	4 (1.2)	5 (1.5)	3 (0.9)	4 (1.2)
Other	7 (2.1)	8 (2.4)	0	3 (0.9)
BMI (kg/m2)				
Mean (SD)	27.9 (5.33)	28 (5.34)	28.6 (7.89)	28.7 (6.90)
Min, Max	15.99, 39.97	16.76, 39.99	14.23, 69.88	14.75, 56.24
BMI group				
BMI < 25 kg/m2, n (%)	111 (33.4)	113 (33.7)	120 (36.1)	121(36.2)
25 ≤ BMI < 30 kg/m2, n (%)	122 (36.7)	108 (32.2)	111 (33.4)	95 (28.4)
BMI ≥ 30 kg/m2, n(%)	99 (29.8)	114 (50.1)	101 (30.4)	118 (35.3)

There are no noticeable imbalances in demographic characteristics in either trial in terms of sex, age, race, and BMI. In Study TR 701-112, of the 667 patients enrolled, 60.3% are male and the mean age is 43.3 years (range 18 to 100 years), 612 patients are less than 65 years of age, 38 patients (5.7%) are ≥65 and ≤75 years of age and 17 patients (2.5%) are >75 years of age. The majority of patients are White (83.2%), followed by Black or African American (11.5%), and most is not of Latino or Hispanic ethnicity (66.6%). The mean BMI is 28.0 kg/m^2. In Study TR 701-113, of the 666 patients enrolled, 65.9% are male and the mean age is 45.6 years (range 18 to 100 years), 590 patients are below 65 years of age, 51 patients (5.7%) are ≥65 and ≤75 years of age and 25 patients (2.5%) are >75 years of age. The majority of patients are White (85.1%), followed by Black or African American (11.3%), and most was not of Latino or Hispanic ethnicity (85.5%). The mean BMI was 28.6 kg/m^2.

Table 3-4: Relevant Baseline Medical Condition/History or Laboratory values

Medical condition/history or Laboratory value	**Study TR 701-112**		**Study TR 701-113**	
	Tedizolid phosphate N = 332	**Linezolid N = 335**	**Tedizolid phosphate N = 332**	**Linezolid N = 334**
Diabetes mellitus, n (%)	26 (3.9)	26 (3.9)	32 (9.6)	41 (12.3)
Renal Impairment, N1	332	335	329	324
Normal (CrCl >=90 mL/min), n (n/N1%)	272 (81.9)	283 (84.5)	263 (79.9)	266 (82.1)
Mild (CrCl 60-89 mL/min), n (n/N1%)	49 (14.8)	36 (10.8)	51 (15.5)	44 (13.6)
Moderate (CrCl 30-59 mL/min), n (n/N1%)	11 (3.3)	14 (4.2)	12 (3.7)	13 (4.0)
Severe (CrCl <30 mL/min), n (n/N1%)	0	2 (0.6)	3 (0.9)	1 (0.3)
Hepatitis B				
Positive, n(%)	3 (0.9)	5 (1.5)	3 (0.9)	6 (1.9)
Negative, n(%)	326 (99.1)	322 (98.5)	318 (99.1)	312 (98.1)
Hepatitis C				
Positive, n(%)	101 (30.7)	116 (35.5)	65 (20.2)	80 (24.9)
Negative, n(%)	228 (69.3)	211 (64.5)	257 (79.8)	241 (75.1)
Current or recent IV drug use, n(%)	117 (35.2)	132 (39.4)	66 (19.9)	74 (22.2)

In terms of baseline medical history (Table 3-4), there is also no imbalance that can be noted between the two treatment groups. About a third of the patients are current or recent IV drug users. There are more patients with underlying hepatic disease that were enrolled in Study TR 701-112 than in Study TR 701-113. Despite more than 30% of the patients with BMI of greater than 30, less than 10% are actually diabetic and more than 80% have normal renal function (see Table 3-4).

Table 3-5 below shows the composition of patients by region. In Study TR 701-112, most patients were enrolled in North America (538 patients), followed by Europe (108 patients), and Latin America (21 patients). In TR 701-113, most patients enrolled were still from North America (314) but a significant portion of Europeans were also enrolled (233). There is no imbalance between treatment groups in terms of enrollments by region.

Table 3-5: Patients by Region

Region	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
North America	270 (81.3)	268 (80.0)	156 (47.0)	158 (47.3)
Latin America	9 (2.7)	12 (3.6)	13 (3.9)	13 (3.9)
Europe	53 (16.0)	55 (16.4)	112 (33.7))	111 (33.2)
South Africa	0	0	48 (14.5)	46 (13.8)
New Zealand/Australia	0	0	3 (0.9)	6 (1.8)

3.2.6.4 Baseline Disease Characteristics

Most patients enrolled in the two trials had cellulitis/erysipelas: 40.7% tedizolid phosphate, 41.5% linezolid in Study TR 701-112 and 50.0% tedizolid phosphate, 50.3% linezolid in TR 701-113. There are more patients with major cutaneous abscess enrolled in Study TR 701-112 (30.1% tedizolid phosphate, 29.3% linezolid) than in Study TR 701-113 (20.5% tedizolid phosphate, 20.5% linezolid), while there are more wound infection enrollments in Study TR 701-113 (29.5% tedizolid phosphate, 29.3% linezolid) than in Study TR 701-112. The distribution of infection types between the two arms is balanced.

Table 3-6: Distribution of Infection by Clinical Syndrome

Infection Type	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Cellulitis/erysipelas, n(%)	135 (40.7)	139 (41.5)	166 (50.0)	168 (50.3)
Major Cutaneous Abscess, n(%)	100 (30.1)	98 (29.3)	68 (20.5)	68 (20.4)
Wound infection, n(%)	97 (29.2)	98 (29.3)	98 (29.5)	98 (29.3)
Superficial incisional surgical site infection, n(%)	3 (0.9)	3 (0.9)	5 (1.5)	3 (0.9)
Post-traumatic wound, n(%)	94 (28.3)	95 (28.4)	93 (28.0)	95 (28.4)

In both trials, most of the anatomical sites of infection are in the legs, arms, buttocks, and feet (see Table 6-1 in Appendix 6.3). There are also a significant number of infections occurring on the hands in Study TR 701-113. Moreover, there are 43 patients in Study TR 701-112 (21 in

tedizolid phosphate and 22 in linezolid) and 80 patients in Study TR 710-113 (43 in tedizolid phosphate and 37 in linezolid) that have multiple anatomical sites that may or may not be contiguous. If the primary infection is present on two bilateral anatomical sides (left and right) the infection site is counted only once. If the infection extends on two or more contiguous anatomical sites, the sites are counted separately. It is also important to note that there are infections that extend into anatomical areas which limit the ability for accurate measurement, e.g. fingers and toes. This is the case for 15 enrolled patients. In Study TR 701-112, this includes 10 patients in the linezolid and 15 in the tedizolid phosphate arm. In Study TR 701-113, 23 patients in the linezolid and 26 in the tedizolid phosphate arm had an infection extending to these areas.

Table 3-7: Baseline Infection Measurement by Infection Type

Infection Type and Geographic Region	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Overall	332	335	332	334
Mean (SD)	321.3 (457.62)	298.7 (370.37)	373.0 (377.28)	397.3 (482.34)
Min, Max	28.0, 5572.8	27.0, 2952.0	75.0, 2711.2	76.0, 5220.0
Cellulitis/erysipelas, N1	135	139	166	168
Mean (SD)	444.8 (476.76)	405.6 (489.48)	416.5 (412.45)	496.6 (606.50)
Min, Max	76.5, 2515.5	76.0, 2952.0	76.1, 2711.2	76.5, 5220.0
Major Cutaneous Abscess, N1	100	98	68	68
Mean (SD)	266.7 (578.85)	208.0 (177.25)	267.3 (358.55)	218.1 (145.53)
Min, Max	48.8, 5572.8	27.0, 1293.8	78.8, 2385.0	77.0, 864.0
Wound infection, N1	97	98	98	98
Mean (SD)	205.6 (145.36)	237.9 (267.6)	372.6 (310.60)	351.6 (330.28)
Min, Max	28.0, 924.0	72.0, 2397.0	75.0, 1566.0	76.0, 1640.0

In Study TR 701-112, the overall mean (for all infection types) surface area at baseline is 321.3 cm^2 in the tedizolid phosphate group and 298.7 cm^2 in the linezolid group for the ITT Population (Table 3-7). The baseline surface area ranges from 28.0 cm^2 to 5572.0 cm^2 in the tedizolid phosphate group and 27.0 cm^2 to 2952.0 cm^2 in the linezolid group. Note that there are some patients enrolled with infections whose surface area are less than the required 75 cm^2. Prior to Protocol Amendment 3 (22 February, 2011), abscess and wound size measurement required that erythema extend at least 5 cm from the peripheral margin of the abscess at its greatest distance for a patient to be enrolled. During initial data reviews, the Sponsor discovered that approximately 4% of patients in both groups were enrolled with an abscess or wound surface area of <75 cm^2, and the protocol was subsequently amended.

In Study TR 701-113, the overall mean (for all infection types) surface area at baseline is higher than Study TR 701-112 with 373.0 cm^2 in the tedizolid phosphate group and 397.3 cm^2 in the

linezolid group for the ITT Population (Table 3-7). The baseline surface area ranges from 76.0 cm^2 to 2711.0 cm^2 in the tedizolid phosphate group and 75.0 cm^2 to 5220.0 cm^2 in the linezolid group.

In both trials, the infection type with the largest mean surface area is cellulitis/erysipelas in both groups. In Study TR 701-112, the cellulitis/erysipelas patients enrolled in North America have the smallest mean surface area; while those enrolled in Europe have the highest mean area (see more details in Table 6-2 in Appendix 6.3). In Study TR 701-113, although the average surface area is greater, the cellulitis/erysipelas patients enrolled in North America still have the smallest mean surface area compared to Latin America and Europe. Meanwhile, the average surface area of cellulitis/erysipelas infection is smaller in Study TR 701-113. In wound infection, on the other hand, the average mean surface area in both groups in Study TR 701-112 is lower than the average mean surface area in Study TR 701-113. The increase can be observed markedly in patients from Europe (see more details in Table 6-2 in Appendix 6.3).

3.2.6.5 Local, Regional, and Systemic Signs and Symptoms

There are no clinically significant differences between treatment groups in baseline local, regional, and systemic signs and symptoms in the ITT, MITT, CE-EOT, or CE-PTE Populations.

In Study TR 701-112, most patients have moderate erythema (54.2% tedizolid phosphate and 53.1% linezolid) or severe erythema (39.5% tedizolid phosphate and 40.3% linezolid) at baseline (see Table 6-3 in Appendix 6.3). Other most common local signs and symptoms of infection include moderate or severe swelling, moderate localized warmth, moderate or severe tenderness on palpitation, pain (Investigator-assessment of patient-reported pain), and induration. The most common regional or systemic sign of infection is lymphadenopathy (87.0% tedizolid phosphate and 86.3% linezolid), followed by WBC count ≥10,000 cells/mm3 or <4000 cells/mm3 (42.2% tedizolid phosphate and 39.7% linezolid) (see Table 3-10).

Similar observations can be observed in Study TR 701-113 (see Table 6-3 in Appendix 6.3). Most patients have moderate erythema (47.6.2% tedizolid phosphate and 51.5% linezolid) or severe erythema (43.4% tedizolid phosphate and 43.4% linezolid) at baseline. Other most common local signs and symptoms of infection include moderate or severe swelling, moderate localized warmth, moderate or severe tenderness on palpitation, pain (Investigator-assessment of patient-reported pain), and induration. The most common regional or systemic sign of infection is lymphadenopathy (70.8% tedizolid phosphate and 70.4% linezolid) which is less than what is observed in Study TR 701-112 (see Table 6-4 Appendix 6.3). The incidence of lymphadenopathy adjacent to the lesion is higher in patients (>85%) in North America and South Africa compared with patients in Europe (approximately 35%). Conversely, the incidence of fever at baseline is lower in patients in North America and South Africa (<10% and <22%, respectively) compared with patients in Europe (<70%).

In both trials, the majority of patients have infection drainage and/or discharge and the most common type is purulent drainage and/or discharge (see Table 6-3 in Appendix 6.3). In Study TR 701-112, fever (≥38°C) is also noted in 16.9% and 18.8% of patients in the tedizolid

phosphate and linezolid groups, respectively. A higher percentage is observed in Study TR 701-113 which includes 31.0% in tedizolid phosphate and 29.0% in linezolid.

3.2.6.6 Baseline Microbiological Assessment

In Study TR 701-112, a gram-positive pathogen was isolated from the primary infection site at baseline in approximately 63% of patients in both groups and 59% of patients in Study TR 701-113. Most of the pathogens isolated are gram-positive aerobes (99.0% tedizolid phosphate and 98.1% linezolid in Study TR 701-112 and 97.5% tedizolid phosphate and 98.5% linezolid in Study TR 701-113). The most common pathogen isolated is *S. aureus* (81.8% tedizolid phosphate and 83.7% linezolid in Study TR 701-112 and 80.2% tedizolid phosphate and 82.7% linezolid in Study TR 701-113). In Study TR 701-112, MRSA accounts for 42.1% and 43.1% of infections in the in the tedizolid phosphate and linezolid groups, respectively and methicillin-*sensitive S. aureus* (MSSA) accounting for 39.7% and 41.6% of infections in the tedizolid phosphate and linezolid groups, respectively (Table 3-8). In Study TR 701-113, MRSA pathogens are less and it accounts for 26.9% and 27.7% of infections in the in the tedizolid phosphate and linezolid groups, respectively, while methicillin-sensitive *S. aureus* (MSSA) accounts for 53.3% and 55.0% of infections in the tedizolid phosphate and linezolid groups, respectively (Table 3-8).

Table 3-8: Common Pathogenic Organisms from Baseline Primary ABSSSI Site or Blood

Pathogen	Study TR701-112		Study TR701-113	
	Tedizolid phosphate N=209	Linezolid N=209	Tedizolid phosphate N =197	Linezolid N = 202
Gram-positive organisms (aerobes)	**207 (99.0)**	**205 (98.1)**	**192 (97.5)**	**199 (98.5)**
Staphylococcus aureus	171 (81.8)	175 (83.7)	170 (86.3)	181 (89.6)
MRSA	88 (42.1)	90 (43.1)	64 (32.5)	69 (34.1)
MSSA	83 (39.7)	87 (41.6)	106 (53.8)	112 (55.4)
Streptococcus pyogenes	8 (3.8)	4 (1.9)	25 (12.7)	16 (7.9)
Streptococcus anginosus-milleri group	15 (7.2)	15 (7.2)	15 (7.6)	12 (5.9)
Enterococcus faecalis	5 (2.4)	0	5 (2.5)	5 (2.5)
Enterococcus faecium	1 (0.5)	2 (1.0)	0	0
Enterococcus gallinarum	1 (0.5)	0	0	0
Staphylococcus haemolyticus	4 (1.9)	3 (1.4)	1 (0.5)	5 (2.5)
Staphylococcus lugdunensis	3 (1.4)	2 (1.0)	1 (0.5)	5 (2.5)
Streptococcus agalactiae	9 (4.3)	5 (2.4)	0	5 (2.5)

The Sponsor reported that IV drug use is associated with more diverse and frequent polymicrobial infections with organisms not traditionally associated with acute skin infections

(approximately 37% of patients enrolled in Study TR 701-112 reported current or recent IV drug use, while is approximately 20% in Study TR 701-113; see Table 3-4).

3.2.6.7 Receipt of Prior/Concomitant Medications/Procedures related to efficacy

Concomitant medications that may affect lesion size and temperature measurements are used in the trials. These include antibacterial medications, NSAIDs, oral steroids, antipyretics, and pain medication.

Table 3-9: Prior/Concomitant Medications/Procedures Related to Efficacy

Categories	Study TR701-112		Study TR701-113	
	TR 701 FA N = 332	Linezolid N = 335	TR 701 FA N = 332	Linezolid N = 334
Patients with at least one prior antibacterial medication, n(%)	12 (3.6)	15 (4.5)	10 (3.0)	6 (1.8)
Concomitant Antibiotics[1]				
At least one concomitant antibacterial medication through the 48-72 Hour Visit, n(%)	4 (1.2)	7 (2.1)	11 (3.3)	7 (2.1)
Concomitant Systemic/Topical Antibacterial Medications through the EOT Visit, n(%)	16 (4.8)	14 (4.2)	22 (6.6)	17 (5.1)
NSAID/Oral Steroid, Antipyretic, Pain Medications				
NSAID/Oral Steroid, Antipyretic, and Pain medications through the 48-72 Hour Visit, n(%)	139 (41.9)	138 (41.2)	137 (41.3)	135 (40.4)
NSAID/Oral Steroid, Antipyretic, and Pain medications through EOT Visit, n(%)	147 (44.3)	147 (43.9)	139 (41.9)	140 (41.9)
NSAID/Oral Steroid medications through the 48-72 Hour Visit, n(%)	18 (5.4)	18 (5.4)	12 (3.6)	21 (6.3)
NSAID/Oral Steroid medications through EOT Visit, n(%)	23 (6.9)	24 (7.2)	20 (6.0)	22 (6.6)
Antipyretic medications through the 48-72 Hour Visit, n(%)	116 (34.9)	111 (33.1)	44 (13.3)	52 (15.6)
Antipyretic medications through EOT Visit, n(%)	124 (37.3)	119 (35.5)	49 (14.8)	55 (16.5)
Incision and Drainage[2]				
Prior to Study Day 1 through the 48-72 Hour Visit	148 (44.6)	153 (45.7)	175 (52.7)	177 (53.0)
Prior to Study Day 1 through the EOT Visit	151 (45.5)	160 (47.8)	179 (53.90	181 (54.2)

[1]Excludes Aztreonam and Metronidazole
[2]Includes subjects captured under coding for "bedside incision and drainage" and "operative incision and drainage."

Antibacterial medications are prohibited through the LFU Visit, however, antibiotics associated with surgical dressing on a clean wound or with local activity such as norfloxacin, nalidixic acid, pipemedic acid, or oral vancomycin are allowed as they are not expected to interfere with the

clinical and microbiological response assessments of the primary lesion or for clinical failure of study drug. Subjects are considered failures if they require additional antibiotic therapy for treatment of the primary lesion at the EOT or PTE Visit.

Excluding aztreonam and metronidazole, few patients used concomitant systemic and topical antibacterial medications through the EOT Visit in Study TR 701-112 113 (22 [4.8%] tedizolid phosphate and 14 [4.2%] linezolid) and in Study TR 701-113 (22 [6.6%] tedizolid phosphate and 17 [5.1%] linezolid; Table 3-9). The most common concomitant antibacterial medications in both trials are sulfonamides and trimethoprim and other beta-lactam antibacterials.

Medications potentially affecting lesion size include NSAIDs and oral steroids are used as single agents or part of combination pharmaceutical presentations. As illustrated in the table, a similar percentage of patients used these medications through the 48-72 Hour Visit and through the EOT Visit across treatment groups and studies. The same can be said of the use of medications affecting temperature which include antipyretics (anti-inflammatory/antirheumatic products, nonsteroids alone or in combination with opioids; and other combinations of analgesics and antipyretics); although, more usage is noted in Study TR 701-112 than in Study TR 701-113. Moreover, since many anti-inflammatory medicines also have analgesic and antipyretics effects, all medications targeting these symptoms are combined together (see Table 3-9). A similar percentage of patients used all of these medications through the 48-72 Hour Visit and through the EOT Visit across treatment groups and studies.

Bedside or operative incision and drainage (I&D) were performed prior to Study Day 1 through the 48-72 Hour Visit in more than 40% of the patients in both treatment groups and across studies. The majority of these procedures were actually performed prior to first infusion of study drug. It is combined with procedures that were performed after first infusion through the ECE Visit because they all have an aggregate effect towards the responder outcome at ECE.

3.2.7 Analysis Results

3.2.7.1 Early Clinical Evaluation at 48-72 hours

As noted earlier, the primary efficacy endpoint in Study TR 701-112 is the clinical response (responder) at the 48-72 hour visit. In the ITT population, 79.5% of patients in the tedizolid phosphate group and 79.4% of patients in the linezolid group were responders. The treatment difference is 0.1% and the 95% CI around the point estimate of the difference adjusted for the stratification factor of the presence/absence of fever at baseline is (-6.1%, 6.2%). This meets the prespecified NI margin which required that the lower limit of the 95% CI interval to be greater than -10%. A comparison of the primary efficacy result between the ITT and ITT* populations, where subjects from three sites were removed, is also shown in Table 3-13. Because these sites enrolled a total of 18 patients, equally distributed between the two treatment arms, the change in efficacy results is negligible. The remaining efficacy analyses for Study TR 701-112 are presented for the ITT* population.

Table 3-10: ECE (Cessation and Afebrile) at 48-72 hours in Study TR 701-112 - ITT/ITT* populations

Response	ITT		ITT*	
	Tedizolid phosphate N = 332	Linezolid N = 335	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]		0.1 (-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

In Table 3-11, the early clinical response at the 48-72 Hour Visit based on cessation of spread of lesion defined as no increase from baseline in area with fever component, which is the protocol defined primary efficacy endpoint of Study TR 701-112, was observed in 79.3% of patients in the tedizolid phosphate group and 79.1% of patients in the linezolid group in Study TR 701-112 ITT* Population, with a treatment difference 0.1% [adjusted 95% CI: -6.2%, 6.3%] which is also illustrated in Table 3-10. Since this meets the prespecified NI margin which required the lower limit of the 95% CI interval to be greater than -10%, non-inferiority of tedizolid phosphate to linezolid is demonstrated in Study TR 701-112. In TR 701-113, the early clinical response at the 48-72 Hour in the same endpoint was observed in 86.1% of patients in the tedizolid phosphate group and 84.1% of patients in the linezolid group, with a treatment difference 2.0% [95% unjusted CI: -3.5%, 7.3%]. On the other hand, the early clinical response based on ≥ 20% decrease from baseline at 48-72 hour visit in lesion area with fever component was observed in 71.8% of patients in the tedizolid phosphate group and 70.5% of patients in the linezolid group in Study TR 701-112 ITT* Population with a treatment difference of 1.3% [adjusted 95% CI: -5.9%, 7.9%]. In Study TR 701-113, this outcome was observed in 79.2% of patients in the tedizolid phosphate group and 76.9% of patients in the linezolid group, with a treatment difference of 2.3% [adjusted 95% CI: -4.1%, 8.4%].

Table 3-11: Primary efficacy definitions of ECE at 48-72 hours with fever component - ITT/ITT* populations

Primary Efficacy Definitions	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323 n (%)	Linezolid N = 326 n (%)	Tedizolid phosphate (N = 332) n (%)	Linezolid (N = 334) n (%)
48-72 Hour Response (Cessation of Spread as no increase from baseline in area, with fever component)[1]				
Responder	256 (79.3)	258 (79.1)	286 (86.1)	281 (84.1)
Difference (CI)	0.1 (-6.2, 6.3)[2]		2.0 (-3.5, 7.3)[2]	
Nonresponder or indeterminate	67 (20.7)	68 (20.9)	46 (13.9)	53 (15.9)
Nonresponder	27 (8.3)	35 (10.7)	26 (7.8)	30 (9.0)
Indeterminate	40 (12.4)	33 (10.1)	20 (6.0)	23 (6.9))
≥20% decrease from baseline at 48-72 hour visit in lesion area (fever criteria; include primary outcome antibiotic/death criteria)				
Responder	232 (71.8)	230 (70.5)	263 (79.2)	257 (76.9)
Difference (CI)	1.3 (-5.9. 7.9)[2]		2.3 (-4.1, 8.4)[2]	
Nonresponder or indeterminate	93 (28.0)	97 (29.0)		
Nonresponder	59 (17.8)	67 (20.0)	52 (15.7)	55 (16.5)
Indeterminate	34 (10.2)	30 (9.0)	17 (5.1)	22 (6.6)

[1]Primary efficacy endpoint of Study TR 701-112
[2]95% CI for the treatment difference adjusted for the presence/absence of fever at baseline using Miettinen and Nurminen method

In Table 3-12, the early clinical response at the 48-72 Hour Visit based on cessation of spread of lesion defined as no increase from baseline in area and no fever component was observed in 86.7% of patients in the tedizolid phosphate group and 85.0% of patients in the linezolid group in Study TR 701-112 ITT* Population, with a treatment difference 1.7% [95% CI: -3.7%, 7.1%]. In TR 701-113, the early clinical response at the 48-72 Hour was observed in 93.4% of patients in the tedizolid phosphate group and 92.4% of patients in the linezolid group, with a treatment difference 3.0% [95% CI: -1.2%, 7.2%]. On the other hand, the early clinical response based on ≥ 20% decrease from baseline at 48-72 hour visit in lesion area was observed in 78.0% of patients in the tedizolid phosphate group and 75.5% of patients in the linezolid group in Study TR 701-112 ITT* Population with a treatment difference of 2.6% [unadjusted 95% CI: -4.0%, 9.1%]. In Study TR 701-113, this outcome, which is its protocol defined primary efficacy endpoint, was observed in 85.2% of patients in the tedizolid phosphate group and 82.6% of patients in the linezolid group, with a treatment difference of 2.6% [unadjusted 95% CI: -3.0%, 8.2%]. Since this meets the prespecified NI margin which required that the lower limit of the 95% CI interval to be greater than -10%, non-inferiority of tedizolid phosphate to linezolid is demonstrated in Study TR 701-113.

Table 3-12: Efficacy definitions of ECE at 48-72 hours without fever component - ITT/ITT* populations

Efficacy Definitions	Study TR 701-112 (ITT*) Tedizolid phosphate N = 323 n (%)	Study TR 701-112 (ITT*) Linezolid N = 326 n (%)	Study TR 701-113 (ITT) Tedizolid phosphate (N = 332) n (%)	Study TR 701-113 (ITT) Linezolid (N = 334) n (%)
48-72 Hour Response (Cessation of spread as no increase from baseline in area, without fever component)				
Responder	280 (86.7)	277 (85.0)	310 (93.4)	302 (90.4)
Difference (CI)	1.7 (-3.7, 7.1)[1]		3.0 (-1.2, 7.2)[1]	
Nonresponder or indeterminate	43 (13.3)	49 (15.0)	22 (6.6)	32 (9.6)
Nonresponder	20 (6.2)	25 (7.7)	17 (5.1)	18 (5.4)
Indeterminate	23 (7.1)	24 (7.4)	5 (1.5)	14 (4.2)
≥20% decrease from baseline at 48-72 hour visit in lesion area, no fever criteria[2]				
Responder	252 (78.0)	246 (75.5)	283 (85.2)	276 (82.6)
Difference (CI)	2.6 (-4.0, 9.1)[1]		2.6 (-3.0, 8.2)[1]	
Nonresponder or indeterminate	71 (47.0)	80 (24.5)	49 (14.8)	58 (17.4)
Nonresponder	48 (14.9)	56 (17.2)	44 (13.3)	44 (13.2)
Indeterminate	23 (7.1)	24 (7.4)	5 (1.5)	14 (4.2)

[1]95% unadjusted CI for the treatment difference using Miettinen and Nurminen method
[2]Primary efficacy endpoint for Study TR 701-113

As illustrated in these two tables (Table 3-11 and Table 3-12), the four endpoints have the same trend in Study TR 701-112 and Study TR 701-113 and all the lower limits of the 95% CI whether they are adjusted for the presence/absence of fever at baseline or not are greater than -10%. However, the proportion of patients who were responders in the four endpoints in both arms of Study TR 701-112 is lower than in Study TR 701-113.

Based on the endpoint defined as ≥20% decrease from baseline at the 48-72 hour visit in lesion area, no fever criteria, the primary reasons for classification of early outcome as a nonresponder or indeterminate in Study TR 701-112 are <20% reduction in area of the primary ABSSSI lesion (13.9% of tedizolid phosphate patients and 15.3% of linezolid patients) and missing lesion measurement (6.6% of tedizolid phosphate patients and 7.2% of linezolid patients) (see Table 3-13). In Study TR 701-113, the primary reasons for early clinical outcomes of nonresponder or indeterminate response are <20% reduction in area of the primary ABSSSI lesion (11.1% of tedizolid phosphate patients and 11.4% of linezolid patients) and missing lesion measurement (1.5% of tedizolid phosphate patients and 4.2% of linezolid patients). The imbalance in the frequency of missing lesion measurement data between tedizolid phosphate and linezolid in Study TR 701-113 is because seven patients in the linezolid arm did not receive their allocated treatment. On the other hand, the greater percentage of patients who did not achieve a ≥20% reduction in area of the primary ABSSSI lesion or who had missing lesion measurement in Study TR 701-112 partly explains why its response rate is lower than in Study TR 701-113 in the four endpoints mentioned previously.

Table 3-13 Reasons for Early Clinical Nonresponse or Indeterminate (≥20% decrease from baseline at 48-72 hour visit in lesion area, no fever criteria) - ITT/ITT* populations

Reasons	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Spread of primary ABSSSI lesion[1], n(5)	45 (13.9)	50 (15.3)	37 (11.1)	38 (11.4)
Missing lesion measurement data, n(%)	22 (6.6)	24 (7.2)	5 (1.5)	14 (4.2)
Systemic concomitant antibiotics potentially effective against baseline pathogen, n(%)	4 (1.2)	4 (1.2)	4 (1.2)	3 (0.9)
Spread of primary ABSSSI lesion and received Systemic concomitant antibiotics potentially effective against baseline pathogen, n(%)	0	2 (0.6)	3 (0.9)	3 (0.9)

[1]<20% decrease in lesion area compared to baseline

In the following tables (Table 3-17, Table 3-18, Table 3-19, Table 3-20, Table 3-21, and Table 3-22), the responder rate based on stratification factors and by prior/concomitant medication/procedure are explored.

Table 3-14: Early Clinical Response at 48-72 Hour Visit by Region - ITT/ITT* populations

Region	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
North America, N1	261	259	156	158
Responder, n (n/N1%)	205 (78.5)	208 (80.3)	128 (82.1)	131 (82.9)
Europe, N1	53	55	112	111
Responder, n (n/N1%)	45 (84.9)	41 (74.5)	104 (92.9)	99 (89.2)
Rest of the World, N1	9	12	64	65
Responder, n (n/N1%)	6 (66.7)	9 (75.0)	51 (79.7)	46 (70.8)

In Study TR 701-112, early clinical response is seen in a higher percentage of patients treated with tedizolid phosphate in Europe (84.9% tedizolid phosphate vs 74.5% linezolid); there is little difference between groups in early clinical response in North America (78.5% tedizolid phosphate and 80.3% linezolid). Similar results can be observed in Study TR 701-113 (see Table 3-17).

Table 3-15: Early Clinical Response at 48-72 Hour Visit by Type of Infection - ITT/ITT* populations

Infection Type	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Cellulitis/erysipelas, N1(%)	131 (40.6)	135 (41.4)	169 (50.9)	171 (51.2)
Responder, n (n/N1%)	98 (30.3)	96 (29.4)	137 (41.3)	138 (41.3)
Infected Wound, N1(%)	96 (29.7)	96 (29.4)	90 (27.1)	90 (26.9)
Responder, n (n/N1 %)	82 (25.4)	81 (24.8)	82 (24.7)	72 (21.6)
Major cutaneous abscess, N1(%)	96 (29.7)	95 (29.1)	73 (22.0)	73 (21.9)
Responder, n (n/N1%)	76 (23.5)	81 (24.8)	64 (19.3)	66 (19.8)

Early clinical response by infection type is generally similar in tedizolid phosphate and linezolid groups in the ITT/ITT* population in both trials (see Table 3-18). Responder rate among subjects with cellulitis is consistently lower across treatment arms and studies, though the magnitude of its difference from the overall rate in each treatment arm is lower in Study 112 than in Study 113. If abscess isremoved from the ITT/ITT* population, the responder rate is 79.3% for tedizolid phosphate and 76.6% for linezolid in Study TR 701-112 and the responder rate is 89.0% for tedizolid phosphate and 84.2% for linezolid in Study TR 701-113. The treatment difference is 4.8 and the 95% unadjusted CI for the treatment difference is (-1.0, 10.7). Tedizolid phosphate is numerically better than linezolid particularly in cellulitis/erysipelas and wound infections.

Table 3-16: Early Clinical Response at 48-72 Hour Visit by Anatomical Site - ITT/ITT* populations

Anatomical Location	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Extremity	231	250	260	255
Responder, n (n/N1%)	176 (76.2)	191 (76.4)	224 (86.1)	210 (82.3)
Non-extremity	92	76	72	79
Responder, n (n/N1%)	77 (83.7)	62 (81.6)	59 (81.9)	66 (83.5)

In baseline lesion area of less than 300cm^2, early clinical response (responder) is achieved in a similar percentage of patients between the treatment groups. In infections with baseline surface area exceeding 300 cm^2, 71.4% are responders in the tedizolid phosphate group and 83.1% are responders in the linezolid group in Study TR 701-112 (see Table 6-5 in Appendix 6.3). In Study

TR 701-113, the two groups have similar responder rates 86.1% (124/144) and 86.1% (118/137) for the tedizolid phosphate and linezolid groups, respectively.

Table 3-17: Early Clinical Response at 48-72 Hour Visit by Presence or Absence of Fever at Baseline - ITT/ITT* populations

Presence/Absence of Fever at Baseline	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Fever at baseline, N1	52	59	103	97
Responder, n (n/N1%)	40 (76.9)	43 (72.9)	96 (93.2)	89 (91.7)
No fever at baseline, N1	271	267	229	237
Responder, n (n/N1%)	216 (79.7)	215 (80.5)	187 (81.7)	187 (78.9)

There is no notable imbalance in the responder rate between treatment groups across studies in terms of anatomical site (extremity or non-extremity) of infection at baseline (see Table 3-16).

Cessation/reduction of lesion spread at 48-72 hours by baseline fever status is similar in both treatment groups (see Table 3-17). In Study TR 701-112, response rates are lower in the febrile group than in the afebrile group. In Study TR 701-113, response rates have the opposite pattern, i.e., response rates are lower in the afebrile group than in the febrile group.

Table 3-18: Early Clinical Response at 48-72 Hour Visit by Prior/Concomitant Medication/Procedure. - ITT/ITT* populations

Subgroup Categories	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Patients with at least one prior antibacterial medication, N1	11	15	10	6
Responder, n (n/N1%)	9 (81.8)	13 (86.7)	7 (70.0)	5 (83.3)
Patients with no prior antibacterial medication , N1	312	311	322	328
Responder, n (n/N1%)	247 (79.2)	245 (78.9)	276 (85.7)	271 (82.6)
At least one concomitant antibacterial[1] medication through the 48-72 Hour Visit, N1	4	7	11	7
Responder, n (n/N1%)	0	0	3 (27.0)	0
No concomitant antibacterial[1]	319	319	321	327

medication through the 48-72 Hour Visit, N1				
Responder, n (n/N1%)	256 (80.3)	258 (80.9)	280 (87.2)	276 (84.4)
NSAID/Oral steroid medications through the 48-72 Hour Visit, N1	18	18	12	21
Responder, n (n/N1%)	11 (61.1)	14 (77.9)	10 (83.3)	14 (66.7)
No NSAID, Oral steroid medications through the 48-72 Hour Visit, N1	305	308	320	313
Responder, n (n/N1%)	245 (80.3)	244 (79.2)	273 (85.3)	262 (83.7)
Antipyretic medications through the 48-72 Hour Visit, N1	116	111	44	52
Responder, n (n/N1%)	88 (75.9)	83 (74.8)	34 (77.3)	36 (69.2)
No Antipyretic medications through the 48-72 Hour Visit, N1	207	215	288	282
Responder, n (n/N1%)	168 (81.2)	175 (81.4)	249 (86.5)	240 (85.1)
NSAID/Oral steroid, Antipyretic, and Pain medications through the 48-72 Hour Visit, N1	139	138	137	135
Responder, n (n/N1%)	106 (76.2)	101 (73.2)	108 (78.8)	105 (77.8)
No NSAID/Oral steroid, Antipyretic, and Pain medications through the 48-72 Hour Visit, N1	184	188	195	199
Responder, n (n/N1%)	150 (81.5)	157 (83.5)	175 (89.7)	171 (85.9)
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)	(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

Few patients used prior or concomitant systemic and topical antibacterial medications through the ECE Visit in both studies. Hence, any differential effect observed between treatment groups is most likely spurious and is due to small patient numbers, e.g. 70% for tedizolid phosphate versus 83.3% in linezolid in Study TR 701-113. As for concomitant antibacterial medication,

they are generally prohibited through the LFU Visit and subjects are considered failures if they require additional antibiotic therapy for treatment of the primary lesion at the EOT or PTE Visit. In Table 3-22, all, except 3 patients (103-042, 286-148, 358-250), who received concomitant antibacterials were failures or indeterminates at ECE. These three patients each received mupirocin, cefazolin and levomecol. The most commonly used are other beta-lactam antibacterials and sulfonamides and trimethoprim.

Only a few patients in each treatment group and across studies took medications that can potentially affect lesion size, e.g., NSAIDs and oral steroids (< 6% of the total population in the two trials). Subjects who received NSAIDS/oral steroid medications through the 48-72 Hour Visit have a lower early clinical response rate (61.1% tedizolid phosphate and 77.9% linezolid in Study TR 701-112 and 83.3% tedizolid phosphate and 83.7% linezolid in Study TR 701-113) than those subjects who did not receive such medications (see Table 3-18).

More than a third of the patients in Study TR 701-112 took antipyretic medications through the 48-72 Hour Visit (34.9% tedizolid phosphate and 33.1% linezolid) while approximately 15% of the patients in Study TR 701-113 took them (13.3% tedizolid phosphate and 15.6% linezolid). Unlike the responder trend in patients with fever at baseline, subjects who received antipyretic medications through the 48-72 Hour Visit have a lower early clinical response rate (75.9% tedizolid phosphate and 74.8% linezolid in Study TR 701-112 and 77.3% tedizolid phosphate and 69.2% linezolid in Study TR 701-113) than those subjects who did not receive such medications (see Table 3-18). Note that in both studies, more than 80% of the patients who took antipyretic medications did not have fever at baseline.

Since many anti-inflammatory medicines (e.g. ibuprofen) also have analgesic and antipyretics effects (or vice versa, e.g. aspirin), all medications targeting these symptoms are combined together. As illustrated in the table, a similar percentage of patients used these medications through the 48-72 Hour Visit across treatment groups and studies. Subjects who received NSAIDS/oral steroids, antipyretics, and pain medications through the 48-72 Hour Visit have a lower early clinical response rate (76.2 tedizolid and 73.2 linezolid in Study TR 701-112 and 78.8 tedizolid and 77.8 linezolid in Study TR 701-113) than those subjects who did not receive such medications.

Lastly, for bedside or operative I&D performed prior to Study Day 1 through the 48-72 Hour Visit, patients who received the procedure have a higher early clinical response rate (89.7% tedizolid phosphate and 85.3% linezolid than those who did not (80.3% tedizolid and 79.6% linezolid). This observation is particularly evident in Study TR 701-113.

3.2.7.2 Clinical Response at EOT

In Study TR 701-112, all nonresponders during the ECE at the 48-72 Hour Visit are carried forward as clinical failures at EOT. Hence, this protocol defined secondary endpoint is aptly called sustained clinical response and the results of this endpoint are shown in Table 3-19. In this table, linezolid have a numerically better sustained clinical response than tedizolid phosphate;

70.2% in linezolid and 67.5% in tedizolid phosphate. The treatment difference is -2.7% with a 95% CI of (-9.7, 4.4). This observation is also supported by the results in the CE-EOT population.

Table 3-19: Sustained Response at EOT (Non-responders at the 48-72 Hour Visit Carried Over) in Study TR 701-112 - ITT* and CEEOT* populations

	TR 701-112		
Response	**Tedizolid phosphate**		**Linezolid**
ITT*	323		326
Clinical success	224 (67.5)		235 (70.2)
Difference (CI)		-2.7 (-9.7, 4.4)	
Clinical failure or Indeterminate	60 (18.1)		61 (18.2)
Clinical failure	48 (14.5)		39 (11.6)
Indeterminate			
CE-EOT*	273		286
Clinical success	214 (78.4)		229 (80.1)
Difference (CI)		-1.7 (-8.5, 5.1)	
Clinical failure	59 (50.9)		57 (49.1)

In Study TR 701-113, on the other hand, nonresponders during the ECE at the 48-72 hour time point can be considered clinical successes at EOT provided they do not meet the failure criteria that includes receipt of other effective antibacterial therapy. For a consistent measure, the endpoint with no carry overs is investigated in both the trials (see Table 3-20). In Study TR 701-112, clinical response at the EOT Visit was observed in a similar percentage of subjects in the tedizolid phosphate group and in the linezolid group (81.1% and 81.2%, respectively; treatment difference -0.2% [unadjusted 95% CI: -6.2%, 5.9%]. Note that patient reported pain is a criterion for the assessment of clinical response at the EOT Visit in this study. If pain is removed, the clinical response at the EOT Visit was observed in 87.0% subjects in the tedizolid phosphate group and 87.4% subjects in the linezolid group. These response rates are similar to the observed response rates in both treatment groups in Study TR 701-113. In particular, clinical success is 87.0% in the tedizolid phosphate group and 88.0% in the linezolid group, with a treatment difference of -1.0% [unadjusted 95% CI: -6.1%, 4.1%]. The results of the analysis of clinical response in the CE-EOT population in both trials exhibit the same observation, although findings based on CE population can be biased as it is a subgroup analysis defined based on post-randomization exclusion (See Table 3-21).

Table 3-20: Clinical Response at EOT- ITT/ITT* populations

Response	Study TR 701-112 (ITT*) Tedizolid phosphate N = 323	Study TR 701-112 (ITT*) Linezolid N = 326	Study TR 701-113 (ITT) Tedizolid phosphate N = 332	Study TR 701-113 (ITT) Linezolid N = 334
Clinical response at EOT, no carry over, with pain criteria				
Clinical success	262 (81.1)	265 (81.2)	NA	NA
Difference (CI)	-0.2 (-6.2, 5.9)		NA	
Clinical failure or Indeterminate	61 (18.9)	61 (18.7)	NA	NA
Clinical failure	37 (11.5)	40 (12.3)	NA	NA
Indeterminate	24 (7.4)	21 (6.4)		
Clinical response at EOT, no carry over, no pain criteria[1]				
Clinical success	281 (87.0)	285 (87.4)	289 (87.0)	294 (88.0)
Difference (CI)	-0.4 (-5.6, 4.8)		-1.0 (-6.1, 4.1)	
Clinical failure or Indeterminate	42 (13.0)	41 (12.6)	43 (13.0)	40 (12.0)
Clinical failure	18 (5.6)	20 (6.1)	33 (9.9)	24 (7.2)
Indeterminate	24 (7.4)	21 (6.4)	10 (3.0)	16 (4.8)

[1]Secondary endpoint for Study TR 701-113

Table 3-21: Clinical Response at EOT- CE-EOT/CE-EOT* populations

Response	Study TR 701-112 (CE-EOT*) Tedizolid phosphate N = 265	Study TR 701-112 (CE-EOT*) Linezolid N = 280	Study TR 701-113 (CE-EOT) Tedizolid phosphate N = 304	Study TR 701-113 (CE-EOT) Linezolid N = 299
Clinical response at EOT, no carry over, with pain criteria				
Clinical success	234 (88.3)	246 (87.9)	NA	NA
Difference (CI)	0.4 (-5.1, 6.0)		NA	
Clinical failure or Indeterminate	31 (11.7)	34 (12.1)	NA	NA
Clinical response at EOT, no carry over, no pain criteria[1]				
Clinical success	252 (94.7)	266 (95.0)	272 (89.5)	280 (93.6)
Difference (CI)	-0.3 (-4.2, 3.6)		-4.1 (-8.8, 0.3)	
Clinical failure	14 (5.3)	14 (5.0)	32 (10.5)	19 (6.4)

[1]Secondary endpoint for Study TR 701-113

The primary reasons for clinical failure in the Study TR 701-112 are investigator assessment of patient pain (9.6% of tedizolid phosphate patients and 11.3% of linezolid patients) and nonresponder at the 48-72 hour visit (8.1% of tedizolid phosphate patients and 10.1% of linezolid patients). In Study TR 701-113, the primary reasons for clinical failure are tenderness

worse than mild (4.8% of tedizolid phosphate patients and 2.1% of linezolid patients) and additional antibacterial therapy for the primary lesion (3.9% of tedizolid phosphate patients and 1.8% of linezolid patients). As noted above, the sustained clinical response definition in Study Study TR 701-112 does not carried forward from the 48-72 hour visit, while this is not the case in Study TR 701-113, (i.e. a patient who is a nonresponder at the 48-72 hour visit can still be considered a clinical success for sustained clinical response at EOT). Furthermore, as noted earlier, there are slight differences between the two trials in the programmatic assessment of sustained response at EOT. For example, patient-reported presence of pain is not a criterion in the programmatic definition of clinical failure in Study TR 701-113 but is in Study TR 701-112. Table 3-22 illustrates the reasons for clinical failure at EOT.

Table 3-22: Primary reasons for clinical failure at EOT – ITT/ITT* populations

Reasons	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 323 n (%)	Linezolid N = 326 n (%)	Tedizolid phosphate N = 332 n (%)	Linezolid N = 334 n (%)
Temperature at EOT >37.6 °C	0	2 (0.6)	1 (0.3)	0
No decrease from baseline in primary ABSSSI lesion size	1 (0.3)	8 (2.5)	10 (3.0)	6 (1.8)
Clinical assessment of tenderness worse than mild	3 (0.9)	11 (3.7)	16 (4.8)	7 (2.1)
Investigator assessment of patient pain	30 (9.3)	35 (10.7)	NA	NA
Persistent purulent drainage from wound infection at same or greater intensity than baseline	NA	NA	0	0
Systemic concomitant antibiotics potentially effective against baseline pathogen	3 (0.9)	1 (0.3)	5 (1.5)	8 (2.4)
TEAE leading to study drug discontinuation and additional antibiotic therapy to treat ABSSSI	1 (0.3)	2 (0.6)	1 (0.3)	4 (1.2)
Additional antibiotic therapy for primary lesion	9 (2.8)	10 (3.1)	13 (3.9)	6 (1.8)
Unplanned major surgical intervention due to study drug failure	3 (0.9)	3 (0.9)	7 (2.1)	3 (0.9)
Osteomyelitis after baseline	0	0	0	0
Incision and drainage of ABSSSI site	7 (2.2)	5 (1.5)	11 (3.3)	6 (1.8)
Death within 28 days of first study drug dose	0	0	1 (0.3)	1 (0.3)

Most of the patients who are responders at the 48-72 hours also responded favorably at the EOT. Concordance between the early clinical response (at the 48-72 hour visit) and the response at EOT by programmatic determination, where pain is not included and the outcome at 48-72 hours is not carried forward, is 79.0% in Study TR 701-112 (see Table 3-27). Early clinical response is based on the original definition of ECE in Study TR 701-112, i.e., cessation of spread of lesion plus afebrile and concordance is calculated where both efficacy outcome measures indicate the

same result (clinical success responder + clinical failure/nonresponders + indeterminate/ indeterminate). On the other hand, concordance between early clinical response (≥20% reduction in lesion area at the 48-72 hour visit) and the clinical response at EOT is 83.6% in Study TR 701-113.

In Study TR 701-112, most early responders were determined failures at EOT due to pain (19 in tedizolid phosphate, 12 in linezolid) and receipt of additional antibiotics (3 in tedizolid phosphate, 3 in linezolid). In Study TR 701-113, most early responders were determined failures at EOT due to tenderness worse than mild (8 in tedizolid phosphate, 1 in linezolid), I&D (6 in tedizolid phosphate, 1 in linezolid), treatment emergent adverse event (TEAE) leading to drug discontinuation and receipt of additional antibacterial therapy (5 in tedizolid phosphate, 1 in linezolid). Patients can have multiple reasons for failure.

Note that in both trials, there are more patients who responded early but failed at EOT in the tedizolid phosphate group than in the linezolid group.

Table 3-23: Concordance between ECE at 48-72 hours and Clinical Response at EOT – ITT/ITT* population

Early Clinical Response at 48-72 Hours	Programmatic Determination of Sustained Clinical response at EOT	STUDY TR 701-112 (ITT*) Tedizolid phosphate N=323 n (%)	STUDY TR 701-112 (ITT*) Linezolid N=326 n (%)	Study TR 701-113 (ITT) Tedizolid phosphate N=332 n (%)	Study TR 701-113 (ITT) Linezolid N=334 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)

Another useful investigation is to relate the Clinical Response at EOT and the Investigator's Assessment of Clinical response at EOT. Both of these endpoints measure patient response to treatment at EOT but the former is based on programmatic determination while the latter uses Investigator's judgment based on resolution or near resolution of signs and symptoms of infection. Results of the Investigator Assessment of Clinical Response are shown in Table 6-6 in Appendix 6.3. The clinical success rate is similar to the Clinical response rate in the ITT/ITT* populations in Study TR 701-112 (87.0% tedizolid phosphate and 87.4% linezolid; see Table 3-20). Comparable numbers can also be seen in the CE-EOT/CE-EOT* populations (94.7% for tedizolid phosphate and 95.0% for linezolid; see Table 3-21). On the other hand, the

Investigator's assessment of Clinical Response (Clinical success) in Study TR 701-113 is higher than the Clinical success rate based on programmatic determination (87.0% tedizolid phosphate and 88.0% linezolid; see Table 3-20). The same can be observed in the CE-EOT population (89.5% tedizolid phosphate and 93.6% linezolid; see Table 3-21).

This result can be investigated further using measures of agreement between the two endpoints. Concordance between the programmatic definition of clinical success – no pain criteria and no carry-over of non-responders from the 48-72 Hour Visit with the investigator's assessment of clinical success is 94.5% in Study TR 701-112 and 91.1% in Study TR 701-113. For patients who are determined to be clinical successes based on programmatic determination, the investigator also assesses the same patient as a success more than 95% of the time. However, for patients who were determined programmatically as clinical failure, indeterminate or improving, the investigator assessment tends to vary (see Table 6-7) from being conservative in Study TR 701-112 to being not conservative in Study TR 701-113. Nevertheless, the agreement between the two endpoints is high.

Table 3-24: Investigator's Assessment of Clinical Response at EOT (Complete resolution) - ITT/ITT* populations

Response	Study TR 701-112 *		Study TR 701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Clinical response at EOT in the ITT/ITT* population				
Clinical success	116 (35.9)	115 (35.3)	146 (43.0)	160 (47.9)
Difference (CI)	0.6 (-6.7, 8.0)		-3.9 (-11.5, 3.6)	
Clinical failure/Indeterminate	207 (64.1)	211 (64.7)	186 (56.0)	174 (52.1)
Clinical response at EOT in the CE-EOT/CE-EOT* population				
Clinical success	109 (38.3)	111 (37.9)	141 (46.4)	153 (51.2)
Difference (CI)	0.4 (-7.5, 8.3)		-4.8 (-12.7, 3.2)	
Clinical failure/Indeterminate or Improving	176 (61.8)	182 (62.1)	163 (53.6)	146 (47.3)

*Excludes patients from Sites 120, 121, and 122.

Another measure that is important to evaluate at the EOT Visit is the assessment of clinical response based on complete resolution of baseline signs and symptoms of infection. As illustrated in Table 3-24, there are no differences between treatment groups in this endpoint in Study TR 701-112 (35.9% tedizolid phosphate vs 35.3% linezolid). However, the clinical success rates are very low compared to either the Clinical Response (Success) rate at EOT or the Investigator's assessment of clinical response at EOT. In Study TR 701-113, the clinical success rate in tedizolid phosphate is 43.0% and 47.9% in linezolid; the treatment difference (tedizolid phosphate – linezolid) is -3.9% with a 95% CI of (-11.5, 3.6).

In the following tables (Table 3-25, Table 3-26, Table 3-27, Table 3-28, and Table 3-29) the clinical success rate based on stratification factors and by prior/concomitant medication/procedure are explored. Clinical success is based on the definition in Study TR 701-113, i.e., no pain criteria and no carry-overs of non-responders from the 48-72 Hour Visit.

Table 3-25: Clinical Response at EOT by Region - ITT/ITT* populations

Region	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
North America, N1	261	259	156	158
Clinical Success, n (n/N1%)	223 (85.4)	222 (85.7)	124 (79.5)	131 (82.9)
Europe, N1	53	55	112	111
Clinical Success, n (n/N1%)	50 (94.3)	53 (96.4)	108 (96.4)	107 (96.4)
Rest of the World, N1	9	12	64	65
Clinical Success, n (n/N1%)	8 (88.9)	10 (83.3)	57 (89.1)	56 (86.2)

Similar results between treatment groups were observed by geographic region. Compared with the overall results for clinical response, higher clinical success rates are seen in Europe; 94.3% in tedizolid phosphate and 96.4% in linezolid while the overall clinical success rate 87.0%-87.4% (see Table 3-20).

Table 3-26: Clinical Response at EOT Visit by Type of Infection - ITT/ITT* populations

Infection Type	Study TR 701-112 (ITT*)		TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Cellulitis, N1	131	135	166	168
Clinical success, n (n/N1%)	115 (87.9)	114 (84.4)	144 (86.7)	145 (86.3)
Infected Wound, N1	96	96	98	98
Clinical success, n (n/N1%)	83 (86.5)	88 (91.7)	87 (88.8)	88 (89.8)
Major cutaneous abscess, N1	96	95	68	68
Clinical success, n (n/N1%)	83 (86.5)	83 (87.4)	58 (85.3)	61 (89.7)

Minor numerical differences can be observed by infection type between treatment groups. For infected wound, clinical success was observed in 86.5% of tedizolid phosphate patients and 91.7% in linezolid. In major cutaneous abscess, 85.3% of tedizolid patients achieved clinical

success while 89.7% of linezolid patients had the same response. Clinical success rates in patients with cellulitis are similar between treatment groups in both studies (see Table 3-26).

Table 3-27: Clinical Response at EOT Visit by Anatomical Site of Infection- ITT/ITT* populations

Anatomical Location	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Extremity, N1	231	250	260	255
Clinical success, n (n/N1%)	201 (87.0)	217 (86.8)	226 (86.9)	220 (86.3)
Non-extremity, N1	92	76	72	79
Clinical success, n (n/N1%)	80 (87.0)	68 (89.5)	63 (87.5)	74 (93.7)

Table 3-28: Clinical Response at EOT Visit by Presence/Absence of Fever at Baseline - ITT/ITT* populations

Presence/Absence of Fever at Baseline	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Fever, N1	52	59	103	97
Clinical success, n (n/N1%)	46(88.5)	53 (89.8)	100 (97.1)	94 (96.9)
No Fever, N1	271	267	229	237
Clinical success, n (n/N1%)	235 (86.7)	232 (86.9)	189 (82.5)	200 (84.4)

Both treatment groups have comparable clinical success rates in terms of anatomical site of infection; except for Study TR 701-113 infections that are not located on an extremity (see Table 3-27). In the exception, 87.5% of tedizolid phosphate patients achieved clinical success while 93.7% of linezolid patients did.

In terms of presence/absence of fever at baseline, both treatment groups have comparable clinical success rates in the two studies. However, unlike in the early clinical response rate at the 48-72 Hour Visit (see Table 3-17), patients with baseline fever in both studies have a higher clinical success rate than patients without fever at baseline. Furthermore, the magnitude of the difference in the overall clinical response rate between patients with fever at baseline and those patients who do not have fever is larger in Study TR 701-113 than in Study TR 701-112 (from ~2% to ~13%).

Table 3-29: Clinical Response at EOT by Prior/Concomitant Medication/Procedure. - ITT/ITT* populations

	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
At least one concomitant antibacterial [1]medication through the EOT Visit, N1	15	14	10	7
Clinical success, n (n/N1%)	3 (20.0)	0	3 (30.0)	0
No concomitant antibacterial[1] medication through the EOT Visit, N1	308	312	313	319
Clinical success, n (n/N1%)	278 (90.3)	285 (91.4)	286 (91.4)	294 (92.2)
NSAID/Oral steroid medications through the EOT Visit, N1	23	24	20	22
Clinical success, n (n/N1%)	20 (87.0)	23 (95.8)	16 (80.0)	18 (81.8)
No NSAID, Oral steroid medications through the EOT Visit, N1	300	302	312	312
Clinical success, n (n/N1%)	261 (87.0)	262 (86.8)	273 (87.5)	276 (88.5)
Antipyretic medications through the EOT Visit, N1	124	119	49	55
Clinical success, n (n/N1%)	105 (84.7)	100 (84.0)	38 (77.6)	43 (78.2)
No Antipyretic medications through the EOT Visit, N1	199	207	283	279
Clinical success, n (n/N1%)	176 (88.4)	185 (89.4)	251 (88.7)	251 (90.0)
NSAID/Oral steroid, Antipyretic, and Pain medications through the EOT Visit, N1	147	147	139	140
Clinical success, n (n/N1%)	124 (84.4)	122 (83.0)	111 (79.9)	114 (81.4)
No NSAID/Oral steroid, Antipyretic, and Pain medications through the EOT Visit, N1	176	179	193	194
Clinical success, n (n/N1%)	157 (89.2)	163 (91.1)	178 (92.2)	180 (92.8)
I&D[2] performed prior to Study Day 1 through the EOT Visit	150	157	179	181
Clinical success, n (n/N1%)	125 (83.3)	133 (84.7)	155 (86.6)	159 (87.9)
No I&D[2] performed prior to Study Day 1 through EOT Visit	173	169	153	153
Clinical success, n (n/N1%)	156 (90.2)	152 (89.9)	134 (87.6)	135 (88.2)

[1] Except aztreonam and metronidazole
[2] Bedside and operative incision and drainage

There were 3 patients (116-174, 128-159, 173-414) in the tedizolid phosphate arm who were considered clinical successes despite the use of concomitant antibacterials from Study Day 1 through the 48-72 Hour Visit in Study TR 701-112 (see Table 3-35). These patients received one of the following: mupirocin, cephalexin, or ciprofloxacin. The patients who took either mupirocin or ciprofloxacin received the medication after the 48-72 Hour Visit. Similarly, there were 3 patients (103-042, 286-148, 358-250) also in the tedizolid arm who were considered clinical successes despite the use of concomitant antibacterials from Study Day 1 through the 48-72 Hour Visit in Study TR 701-113. These patients either took mupirocin, levomecol, or ciprofloxacin and they were received through the 48-72 Hour Visit.

Less than 10% in each treatment group and across studies took NSAIDs and oral steroids (~ 7% in Study TR 701-112 and ~6% in Study TR 701-113) through the EOT Visit. In Study TR 701-113, subjects who received NSAIDS/oral steroid medications have a lower early clinical response rate (80.0%% tedizolid phosphate and 81.8% linezolid than those subjects who did not receive such medications (see Table 3-35). In Study TR 701-112, this is observation is not evident; 87.0% of patients in the tedizolid phosphate arm and 95.8% in the linezolid arm who took NSAIDS or oral steroids achieved clinical success. However, the numbers are small to provide meaning for the observed differential treatment effect.

There is no notable imbalance between treatment groups in terms of receipt of concomitant antipyretic medications through the EOT Visit. However, patients who received these medications have a lower early clinical response rate (84.7% tedizolid phosphate and 84.0% linezolid in Study TR 701-112 and 77.6% tedizolid phosphate and 78.2% linezolid in Study TR 701-113) than those subjects who did not receive such medications (see Table 3-35).

For the combined use of anti-inflammatory, analgesic and antipyretics effects, there is no notable difference between the two groups. Similar to the clinical response at the 48-72 Hour Visit, subjects who received NSAIDS/oral steroids, antipyretics, and pain medications through EOT have a lower early clinical response rate (84.4% tedizolid phosphate and 83.0% linezolid in Study TRR 701-112 and 79.9% tedizolid phosphate and 81.4% linezolid in Study 113) than those subjects who did not receive such medications.

Lastly, for bedside or operative I&D performed prior to Study Day 1 through the EOT Visit, patients in Study TR 701-112 who received the procedure have a lower clinical success rate (83.3% tedizolid phosphate and 84.7% linezolid than those who did not (90.2% tedizolid phosphate and 89.9% linezolid; see Table 3-35) which is contrary to what was observed in Table 3-22. But, there is no difference between treatment arms. More than 80% of the patients who had major cutaneous abscess had bedside or operative I&D whereas only about 20% of patients with cellulitis/erysipelas or infected wound had bedside or operative I&D performed. In Study TR 701-113, similar clinical success rates can be observed regardless of any bedside or operative

I&D performed through the EOT visit. This suggests that I&D only affects the early clinical response but not the long term clinical response.

3.2.7.3 Investigator Assessment of Clinical Response at the PTE Visit

The investigator assessment of clinical response at the PTE Visit is the protocol defined primary endpoint designed to address the European Medicines Agency regulatory requirement. It was performed within 7 to 14 days after the EOT Visit. The proportion of patients considered a responder for this endpoint in the ITT population for Study TR 701-112 is 85.5% and 86.0% for tedizolid phosphate and linezolid groups, respectively (treatment difference of -0.2% with an unadjusted 95% CI of -5.3% to 5.6%). In Study TR 701-113, the proportion was 88.0% for tedizolid phosphate and 87.7% for linezolid arms respectively (treatment difference of 0.3% with an unadjusted 95% CI of -4.8% to 5.3%; see Table 3-30).

Table 3-30: Investigator Assessment of Clinical Response at PTE[1]

Clinical Response at PTE	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate	Linezolid	Tedizolid phosphate	Linezolid
ITT* or ITT	323	326	332	334
Clinical success	277 (85.8)	279 (85.6)	292 (88.0)	293 (87.7)
Difference	0.2 (-5.3, 5.6)		0.3 (-4.8, 5.3)	
Clinical failure or indeterminate	46 (14.2)	47 (14.4)	40 (12.0)	41 (12.3)
CE-PTE* or CE-PTE	270	273	290	280
Clinical success	257 (95.2)	260 (95.2)	268 (92.4)	269 (96.1)
Difference	-0.0 (-3.9, 3.7)		-3.7 (-7.7, 0.2)	
Clinical failure or indeterminate	13 (4.8)	13 (4.8)	22 (7.6)	11 (3.9) 12

[1]Near resolution (not complete) of all symptoms

Note that this endpoint is based on resolution or near resolution of most disease specific signs and symptoms and absence or near absence of systemic signs of infection (see Appendix 6.2). A closer look at this endpoint and the amount of residual shows that at less than or equal to 10% residual lesion, the proportion of patients considered a clinical success for this endpoint in the ITT population for Study TR 701-112 was 85.8% and 85.9% for tedizolid phosphate and linezolid groups, respectively, (treatment difference of -0.1% with an unadjusted 95% CI of -5.6% to 5.3%; see Table 3-32). This is similar to what was observed in the original secondary endpoint (see Table 3-30). In Study 113, the proportion was 82.8% for tedizolid phosphate and 82.0% for linezolid arms (treatment difference of 0.8% with an unadjusted 95% CI of -5.0% to 6.6%). These rates are more than what was observed in the original definition of the secondary endpoint (see Table 3-30). Hence, it can be concluded that most patients considered clinical successes at the PTE visit likely has some residual lesion.

Table 3-31: Investigator Assessment of Clinical Response at PTE1 by Residual Lesion

Clinical Response at PTE	Study TR 701-112 (ITT*)		Study TR 701-113(ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Residual lesion ≤ 5 %				
Clinical success	270 (83.6)	278 (85.3)	266 (80.1)	264 (79.0)
Difference	-1.7 (-7.3, 3.9)		1.1 (-5.1, 7.2)	
Clinical failure or indeterminate	53 (16.4)	48 (14.7)	66 (19.9)	70 (21.0)
Residual lesion size ≤ 10 %				
Clinical success	277 (85.8)	280 (85.9)	275 (82.8)	274 (82.0)
Difference	-0.1 (-5.6, 5.3)		0.8 (-5.0, 6.6)	
Clinical failure or indeterminate	46 (14.2)	46 (14.1)	57 (17.2)	60 (18.0)

Using complete resolution of all signs and symptoms observed at baseline, the proportion of patients considered a clinical success for the Investigator assessment of clinical response in the ITT population is within 65.3% to 68.1% in Study TR 701-112 and Study TR 701-113. This is about 20 percentage points lower than the original definition of the endpoint (see Table 3-32).

Table 3-32: Investigator Assessment of Clinical Response at PTE1 (Complete resolution)

Clinical Response at PTE	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate	Linezolid	Tedizolid phosphate	Linezolid
ITT* or ITT	323	326	332	334
Clinical success	218 (67.5)	222 (68.1)	224 (67.5)	218 (65.3)
Difference	-0.6 (-7.8, 6.6)		2.2 (-5.0, 9.4)	
Clinical failure or indeterminate	105 (32.5)	104 (31.9)	16 (4.8)	29 (8.7)

In the following tables (Table 3-33 and Table 3-34) the clinical success rate based on some stratification factors are explored (see also Table 6-9 in Appendix 6.3).

Table 3-33: Investigator Assessment of Clinical Response at PTE by Region - ITT/ITT* populations

Region	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
North America, N1	261	259	156	158
Clinical Success, n (n/N1%)	219 (83.9)	219 (84.6)	127 (81.4)	129 (81.7)
Europe, N1	53	55	112	111
Clinical Success, n (n/N1%)	51 (96.2)	51 (92.7)	108 (96.4)	105 (95.6)
Rest of the World, N1	9	12	64	65
Clinical Success, n (n/N1%)	7 (77.8)	9 (75.0)	57 (89.1)	59 (90.7)

Results in this endpoint in terms of geographic region are similar to what was observed at EOT. Comparable rates between treatment groups are observed by geographic region. Compared with the overall results for clinical response, higher clinical success rates are seen in Europe (see Table 3-33).

Table 3-34: Investigator Assessment of Clinical Response at PTE Visit by Type of Infection - ITT/ITT* populations

Infection Type	Study TR 701-112 (ITT*)		TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Cellulitis, N1	131	135	166	168
Clinical success, n (n/N1%)	116 (88.7)	110 (81.5)	146 (88.0)	149 (88.7)
Infected Wound, N1	96	96	98	98
Clinical success, n (n/N1%)	81 (84.4)	86 (89.6)	86 (87.8)	87 (88.8)
Major cutaneous abscess, N1	96	95	68	68
Clinical success, n (n/N1%)	80 (83.3)	83 (87.4)	60 (88.2)	57 (83.8)

As with the EOT result, minor numerical differences can be observed by infection type between treatment groups. For infected wound, clinical success rate is numerically higher in linezolid than in tedizolid phosphate in Study TR 701-112, while in major cutaneous abscess, tedizolid phosphate has numerically higher clinical success rate than linezolid in Study TR 701-113. Clinical success rate in patients with cellulitis are similar between treatment groups in both studies (see Table 3-34).

Lastly, patients with fever at baseline have a higher clinical success rate than patients without fever in Study TR 701-113. Comparable clinical success rates can be observed between treatment groups.

3.2.7.4 Investigator Assessment of Clinical Response at LFU Visit

The investigator assessment of clinical response at the LFU Visit was performed within 18 to 25 days after the EOT Visit. The proportion of patients considered a clinical success for this endpoint population for Study TR 701-112 is 93.3% and 96.0% for tedizolid phosphate and linezolid groups, respectively. In Study TR 701-113, the proportion is 90.3% for tedizolid phosphate and 95.0% for linezolid arms. Note that linezolid has numerically higher response rate than tedizolid phosphate in this endpoint. In Study TR 701-112, there are 5 patients in tedizolid phosphate who failed or relapsed. In Study 113, there are 6 patients in tedizolid phosphate and 3 in linezolid who either failed or relapsed. Missing observations are observed at greater frequency in Study TR 701-112.

Table 3-35: Investigator Assessment of Clinical Response at LFU – CE-PTE/CE-PTE* population

	Study TR 701-112		Study TR 701-113	
Clinical Response	**Tedizolid phosphate N= 270**	**Linezolid N= 273**	**Tedizolid phosphate N= 290**	**Linezolid N= 280**
Sustained Clinical response	252 (93.3)	262 (96.0)	262 (90.3)	266 (95.0)
Failure/Relapse or Indeterminate	5 (1.9)	0	6 (2.1)	3 (1.1)
Failure/Relapse	3 (1.1)	0	4 (1.4)	1 (0.4)
Indeterminate	2 (0.7)	0	2 (0.7)	2 (0.7)
Missing	13 (4.8)	11 (4.0)	22 (7.6)	11 (3.9)

3.2.7.5 Change from Baseline in Infection Surface Area Measurements by Study Day

Overall, the percent change from baseline in lesion size measurements is similar across the tedizolid phosphate and linezolid treatment groups (Table 6-8 in Appendix 6.3) in Study TR 701-112 and Study TR 701-113.

By Day 2, approximately 90% of patients in both groups had a decrease in lesion size measurements in Study TR 701-112 (see Figure 1) and more than 90% of patients in both groups had a decrease in lesion size measurements in Study TR 701-113 (see Figure 2). Improvements continued and by 48-72 hours, in Study TR 701-112, 94.3% of patients in the tedizolid phosphate group and 93.0% of patients in the linezolid group had decreases in lesion size measurements while more than half of the patients in both treatment groups had more than 50% decrease in surface area of lesion from baseline. Similarly, 96.3% of patients in the tedizolid phosphate group and 95.9% of patients in the linezolid group had decreases in lesion size measurements

while more than half of the patients in both treatment groups also had more than 50% decrease in surface area of lesion from baseline in Study TR 701-113.

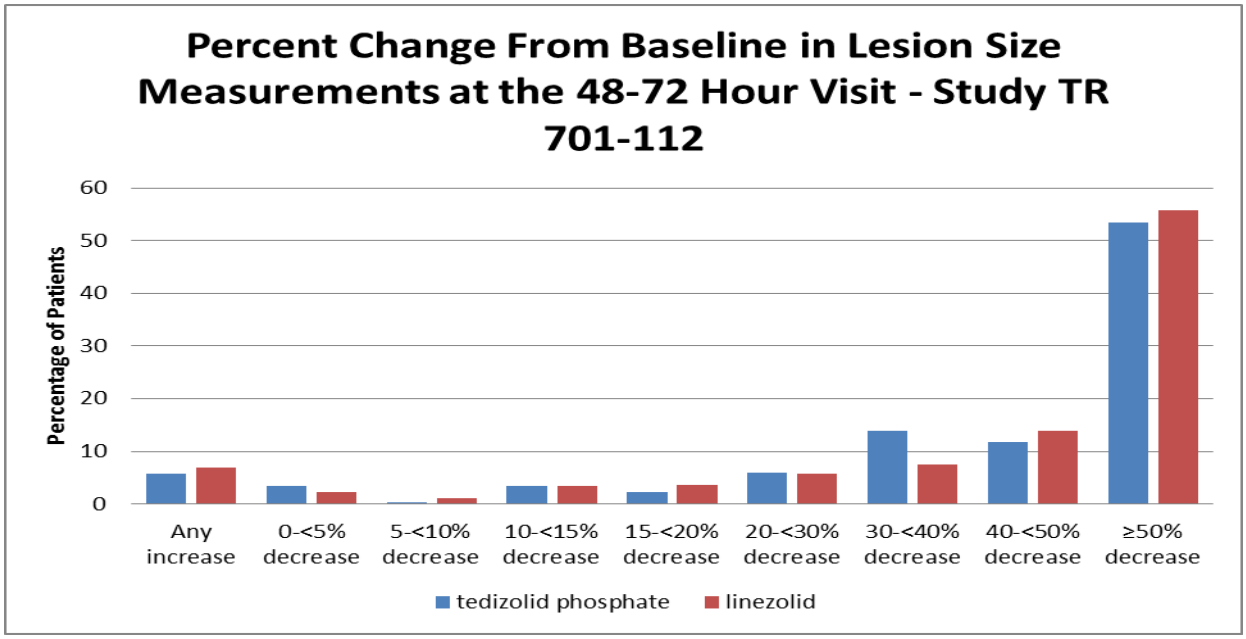

Figure 1: Percent Change from Baseline in Lesion Size Measurement at the 48-72 Hour Visit - Study TR 701-112

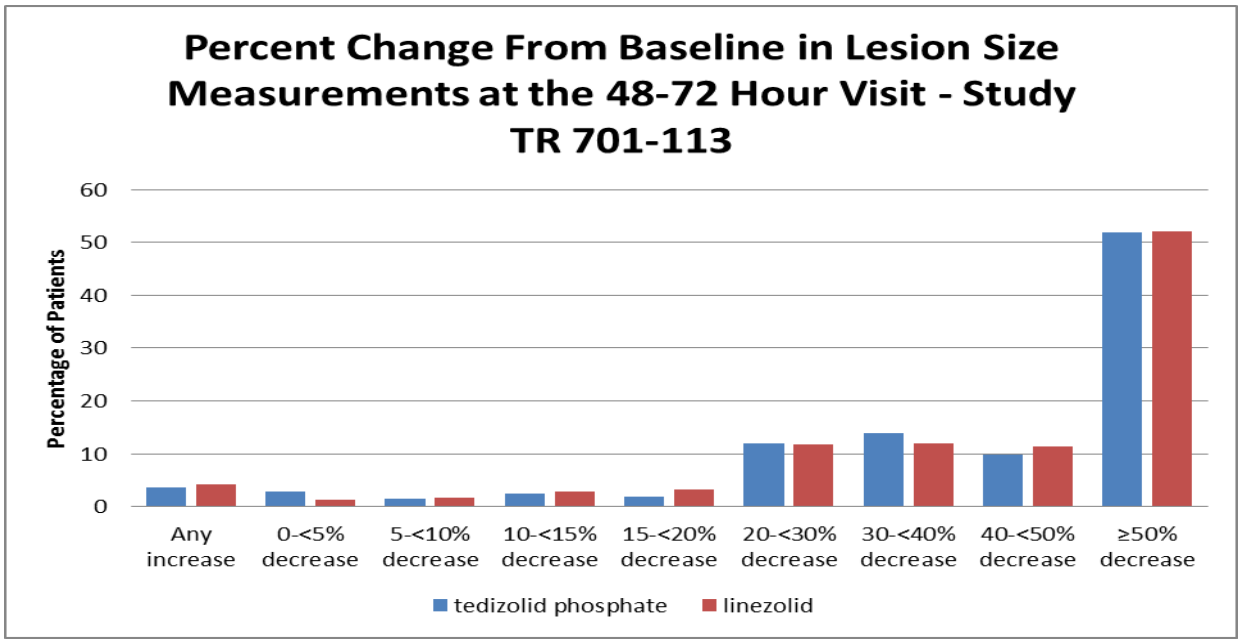

Figure 2: Percent Change from Baseline in Lesion Size Measurement at the 48-72 Hour Visit - Study TR 701-113

All patients were experiencing decreases in lesion size measurements by Day ≥14, with almost all patients experiencing a ≥50% decrease (100% in the tedizolid phosphate group vs. 99.7% in the linezolid group) in Study TR 701-112 and Study TR 701-113 (98.0% in the tedizolid phosphate group vs. 98.3% in the linezolid group).

Of the 325 patients who had more than 50% decrease in lesion surface area at baseline by the 48-72 Hour Visit in Study TR 701-112, 121 had major cutaneous abscess, 89 had infected wound, and 115 had cellulitis/erysipelas. This means that about 63.3% of the total patients with major cutaneous abscess responded rapidly while only 46.8% of the patients with infected wound and 43.2% of the patients with cellulitis/erysipelas responded rapidly (see Table 3-45). On the other hand, 57.8% of the patients who had bedside or operative I&D performed prior to Study Day 1 through the 48-72 Hour Visit responded rapidly compared to 43.4% for patients who did not have I&D performed (see Table 6-11 in Appendix 6.3).

In Study TR 701-113, 91 had major cutaneous abscess, 101 had infected wound, and 138 had cellulitis/erysipelas. This means that about 66.9% of the total patients with major cutaneous abscess responded rapidly while only 51.5% of the patients with infected wound and 41.3% of the patients with cellulitis/erysipelas responded rapidly (see Table 6-10 in Appendix 6.3). Moreover, there the treatment effect of tedizolid phosphate in patients with wound infection is higher than linezolid (59.2% tedizolid phosphate vs 43.9 linezolid) while the treatment effect of linezolid is numerically higher than tedizolid phosphate in patients with major cutaneous abscess (73.5 linezolid and 60.3 tedizolid phosphate). On the other hand, 51.7% of the patients who had bedside or operative I&D performed prior to Study Day 1 through the 48-72 Hour Visit responded rapidly compared to 47.1% for patients who did not have I&D performed (see Table 6-11 in Appendix 6.3).

From these numbers, both performing I&D and inclusion of major cutaneous abscess contribute significantly to the rapid response rate at the 48-72 hours. However, the inclusion of the latter provides a more significant contribution than I&D.

These results show that an argument can be made for excluding patients with abscess in the analysis population. Table 3-36 shows the result for early clinical response at the 48-72 Hour Visit in the ITT population composed only of patients with cellulitis/erysipelas and infected wound.

Table 3-36: Efficacy definitions of ECE at 48-72 Hours – ITT/ITT*Population Excluding Patients with Major Cutaneous Abscess

Efficacy Definitions	STUDY TR 701-112 (MITT*)		TR 701-113 (MITT)	
	Tedizolid phosphate N = 227 n (%)	Linezolid N = 231 n (%)	Tedizolid phosphate N = 264 n (%)	Linezolid N = 266 n (%)
48-72 Hour Response (Cessation of spread as no increase from baseline in area, with fever component)				
Responder	180 (79.3)	177 (76.6)	235 (89.0)	224 (84.2)
Difference	2.7 (-5.0, 10.3)		4.8 (-1.0, 10.7)	
Nonresponder or indeterminate	47 (20.7)	54 (23.4)	29 (11.0)	42 (15.8)
Nonresponder	25 (11.0)	34 (14.7)	16 (6.1)	26 (9.8)
Indeterminate	22 (9.7)	20 (8.7)	13 (4.9)	16 (6.0)
≥20% decrease from baseline at 48-72 hour visit in lesion area, no fever criteria				
Responder	170 (74.9)	166 (71.9)	224 (84.9)	215 (80.8)
Difference	3.0 (-5.1, 11.1)		4.0 (-2.4, 10.5)	
Nonresponder or indeterminate	57 (25.1)	65 (28.1)	40 (15.2)	51 (19.2)
Nonresponder	45 (19.8)	51 (22.1)	37 (14.0)	41(15.4)
Indeterminate	12 (5.3)	14 (6.1)	3 (1.1)	10 (3.8)

95% unadjusted CI for the treatment difference

Based on cessation of spread of lesion defined as no increase from baseline in area with fever component, 79.3% of patients in the tedizolid phosphate group and 76.6% of patients in the linezolid group in Study TR 701-112 ITT* Population (excluding abscess), with a treatment difference 2.7% [95% CI: -5.0%, 10.3%]. In Study TR 701-113, the early clinical response at the 48-72 Hour was observed in 89.0% of patients in the tedizolid phosphate group and 84.2% of patients in the linezolid group, with a treatment difference 4.8% [95% CI: -1.0%, 10.7%]. On the other hand, the early clinical response based on ≥ 20% decrease from baseline at 48-72 hour visit in lesion area was observed in 74.9% of patients in the tedizolid phosphate group and 71.9% of patients in the linezolid group in Study TR 701-112 ITT* Population (excluding abscess) with a treatment difference of 3.0% [95% CI: -5.1%, 11..1%]. In Study TR 701-113, this outcome was observed in 84.9% of patients in the tedizolid phosphate group and 80.8% of patients in the linezolid group, with a treatment difference of 4.0% [95% CI: -2.4%, 10.5%]. This meets the prespecified NI margin which required the lower limit of the 95% CI interval to be greater than -10%.Signs and Symptoms of Primary ABSSSI Site by Study Day

In general, a similar percentage of patients in both treatment groups showed an improvement in local signs and symptoms of infection beginning on Day 2. There were some differences between the treatment groups, e.g. Erythema on Day 7, Swelling on Day 7 and EOT, Localized warmth at the 48-72 Hour Visit, Presence of Pain on at the 48-72 Hour Visit, etc. (see categories highlighted in Table 6-12 and Table 6-13 in Appendix 6.3). However, the number of these local signs and symptoms present at baseline are not the same and precludes making conclusions. Nevertheless, patients in both arms improve progressively through all the post baseline visits

with almost all patients in both groups showing an improvement by Day 10 in all local signs and symptoms.

3.2.7.6 Patient Reported Pain by Study Day

Patient-reported level of pain is similar across the tedizolid phosphate and linezolid treatment groups in both studies as assessed by the Visual Analog Scale (VAS) (Table 6-14 and Table 6-15 in Appendix 6.3). From Day 2, an improvement in pain from baseline was seen in both treatment groups. In addition, pain scores continued to improve over time for both treatment groups. Similar observations can also be seen using the Face Rating Scale (FRS); results are redundant and will not be shown.

3.2.7.7 Microbiological Response

Table 3-37 shows the clinical response (responder) at 48-72 Hours per pathogen. In general, the two treatments are well-balanced except for MSSA in Study TR 701-113. In this category, the responder rate is 92.5% for tedizolid phosphate versus 84.8% for linezolid. Most of the pathogen counts are small and prohibits making inferences about deferential treatment response between groups.

Table 3-37: : 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 = 334 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)		
Enterococcus gallinarum	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)

Table 3-38 shows the clinical response at the PTE Visit per pathogen. No notable difference can be observed between treatment groups.

Table 3-38: : 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 = 334 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)

3.3 Evaluation of Safety

The objective in this section is to evaluate tolerability and safety of tedizolid phosphate 200 mg once daily for 6 days. The reader is invited to refer to the Medical Officer's Review for more detailed safety and tolerability analysis.

3.3.1 Summary of All Adverse Events

In Study TR 701-112, of the 332 patients in the tedizolid phosphate group, 331 patients were included in the Safety Analysis Set; and of the 335 patients in the linezolid group, all 335 patients were included in the Safety Analysis Set. In Study TR 701-113, of the 332 patients in the tedizolid phosphate group, 331 patients were included in the Safety Analysis Set. On the other hand, of the 334 patients in the linezolid group, 327 patients were included in the Safety Analysis Set (see Table 3-2).

An overall summary of adverse events (AEs) is presented in Table 3-56. The incidence of AEs by category (i.e., all AEs, treatment emergent adverse events (TEAEs) and related TEAEs, serious adverse events (SAEs) and related SAEs, deaths) was similar between treatment groups. Related AEs were defined as those with a possible, probable, or definite relationship to study drug based on the Investigator's assessment.

In Study TR 701-112, the overall incidence of TEAEs was 40.8% of patients in the tedizolid phosphate group and 43.3% of patients in the linezolid group (see Table 3-39). Treatment-emergent AEs considered by the Investigator to be drug-related were experienced by 24.2% of patients in the tedizolid phosphate group and 31.0% of patients in the linezolid group. Only 1.5% of patients in the tedizolid phosphate group and 1.2% of patients in the linezolid group experienced an SAE. There was a single death in the study (in the tedizolid phosphate group, septic shock) that was considered unrelated to study treatment. Two patients in each treatment group (0.6% in each group) discontinued study drug due to an AE. There were no study discontinuations due to an SAE.

In Study TR 701-113, the overall incidence of TEAEs was 44.7% of patients in the tedizolid phosphate group and 43.1% of patients in the linezolid group. Treatment-emergent AEs considered by the Investigator to be drug-related were experienced by 20.5% of patients in the tedizolid phosphate group and 24.8% of patients in the linezolid group. Only 0.3% of patients in each treatment group experienced an SAE leading to death. There were 2 deaths in the study (1 in each treatment group). One subject in the tedizolid phosphate group experienced a myocardial infarction and one subject (linezolid) experienced meningitis tuberculous. Both of these events were considered not related to study drug. Discontinuation of study drug due to an AE occurred in 0.3% of patients in the tedizolid phosphate group and 1.2% of patients in the linezolid group. There was 1 study drug discontinuation due to an SAE in the linezolid group.

Table 3-39: Summary of Adverse Events (Safety Analysis Set)

Category	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 331	Linezolid N = 335	Tedizolid phosphate N = 331	Linezolid N = 327
Patients with any AE	137 (41.4)	145 (43.3)	152 (45.9)	143 (43.7)
Patients with any TEAE	135 (40.8)	145 (43.3)	148 (44.7)	141 (43.1)
Patients with any drug-related TEAE (possibly, probably, or definitely related)	80 (24.2)	104 (31.0)	68 (20.5)	81 (24.8)
Patients with any TEAE leading to premature discontinuation of study drug	2 (0.6)	2 (0.6)	1 (0.3)	4 (1.2)
Patients with any serious TEAE	5 (1.5)	4 (1.2)	7 (2.1)	9 (2.8)
Patients with any drug-related serious TEAE	0	1 (0.3)	0	1 (0.3)
Patients with any serious TEAE leading to death	1 (0.3)	0	1 (0.3)	1 (0.3)
Patients with any serious TEAE leading to premature discontinuation of study drug	0	0	0	1 (0.3)

Source: Table 12-3 on p. 343 of Study TR 701-112 CSR and Table 12-3 on p 164 of Study TR 701-113 CSR

3.3.2 Treatment-emergent AEs Occurring in ≥2% of Patients

The most commonly reported treatment-emergent AEs in each study (≥10% of patients in any treatment group) occur in the system organ classes (SOCs) of Gastrointestinal Disorders Study TR 701-112: 16.3% tedizolid phosphate and 25.4% linezolid; Study TR 701-113: 15.7% tedizolid phosphate and 20.5% linezolid), Infections and Infestations (Study TR 701-112: 15.1% tedizolid phosphate and 11.0% linezolid; Study TR 701-113: 12.1% tedizolid phosphate and 12.2% linezolid), and Nervous System Disorders (10.9% tedizolid phosphate and 9.6% linezolid in Study TR 701-112).

Treatment-emergent AEs occurring in ≥2% of patients in either treatment group are presented in Table 3-40. The commonly reported TEAEs (≥2% of patients in either group) were nausea (8.5% tedizolid phosphate and 13.4% linezolid), headache (6.3% tedizolid phosphate and 5.1% linezolid) and diarrhea (4.5% tedizolid phosphate and 5.4% linezolid) in Study TR 701-112; while in Study TR 701-113, they are were nausea (7.9% tedizolid phosphate and 11.0% linezolid), headache (6.0% tedizolid phosphate and 6.7% linezolid), and abscess (4.2% tedizolid phosphate and 3.1% linezolid). The incidence of commonly reported TEAEs was similar between the treatment groups in Study TR 701-112, except for nausea, vomiting, dyspepsia, and pruritus where the incidence was lower in the tedizolid phosphate group compared with the linezolid group. Similarly, the incidence of commonly reported TEAEs was similar between the treatment groups in Study TR 701-113, except for nausea, diarrhea, vomiting, dizziness, and vulvovaginal mycotic infection where the incidence was lower in the tedizolid phosphate group compared with the linezolid group.

Table 3-40: Incidence of Treatment-Emergent Adverse Events Occurring in

Preferred Term	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 331	Linezolid N = 335	Tedizolid phosphate N = 331	Linezolid N = 327
Patients with at least one TEAE	135 (40.8)	145 (43.3)	148 (44.7)	141 (43.1)
Nausea	28 (8.5)	45 (13.4)	26 (7.9)	36 (11.0)
Headache	21 (6.3)	17 (5.1)	20 (6.0)	22 (6.7)
Diarrhoea	15 (4.5)	18 (5.4)	11 (3.3)	17 (5.2)
Abscess	14 (4.2)	8 (2.4)	14 (4.2)	10 (3.1)
Abscess limb	12(3.6)	10 (3.0)		
Vomiting	9 (2.7)	20 (6.0)	10 (3.0)	17 (5.2)
Cellulitis	8 (2.4)	8 (2.4)	9 (2.7)	6 (1.8)
Dizziness	8 (2.4)	7 (2.1)	4 (1.2)	7 (2.1)
Pruritus	3 (0.9)	8 (2.4)		
Dyspepsia	2 (0.6)	7 (2.1)		
Fatigue			8 (2.4)	7 (2.1)
Vulvovaginal mycotic infection			2 (0.6)	7 (2.1)

Source: Table 12-4 on p 344 of Study TR 701-112 CSR and Table 12-4 on p 165 of Study TR 701-113 CSR

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 4-1 ECE at 48-72 hours by Subgroup – ITT/ITT* population

	Study TR 701-112 (MITT*)		**Study TR 701-113 (MITT)**	
	Tedizolid phosphate N = 323 n(%)	**Linezolid N = 326 n(%)**	**Tedizolid phosphate N = 332 n(%)**	**Linezolid N = 334 n(%)**
Age				
< 65years	294	302	289	301
Responder	232 (78.9)	236 (78.1)	250 (86.5)	250 (83.1)
≥ 65 years	29	24	43	33
Responder	**24 (82.8)**	**22 (91.7)**	**36 (83.7)**	**31 (93.9)**
Sex				
Male	198	195	225	214
Responder	155 (78.3)	155 (79.5)	196 (87.1)	180 (84.1)
Female	125	131	107	120
Responder	101 (80.8)	103 (78.6)	90 (84.1)	101 (84.2)
Race				
White	274	268	285	282
Responder	223 (81.4)	211 (78.7)	244 (85.6)	240 (85.1)
Black or African American	36	36	38	37
Responder	25 (69.4)	29 (80.6)	**35 (92.1)**	**28 (75.7)**
Asian	2	7	4	7
Responder	2 (100.0)	6 (85.7)	4 (100.0)	6 (85.7)
Other	11	15	5	8
Responder	**6 (54.5)**	**12 (80.0)**	**3 (60.0)**	**7 (87.5)**
Region				
North America	261	259	156	158
Responder	205 (78.5)	208 (80.3)	128 (82.1)	131 (82.9)
Europe	53	55	112	111
Responder	**45(84.9)**	**41 (74.5)**	104 (92.9)	99 (89.2)
Rest of the World	9	12	64	65
Responder	**6 (66.7)**	**9 (75.0)**	**51 (79.7)**	**46 (70.8)**

Early clinical response rates at the 48-72 Hour Visit are displayed by demographic characteristics in Table 4-1 for the ITT/ITT* population. Early clinical response in Study TR 701-112 is based on its original definition, i.e., cessation of lesion spread + afebrile; while Study TR 701-113 uses ≥20% reduction in lesion from baseline without fever component. As illustrated in the table, no notable differences in in the responder rates can be observed between tedizolid phosphate and linezolid groups across a spectrum of subgroups (sex, race, and region). For patients aged 65 years and older, tedizolid phosphate has numerically lower response rate than linezolid in each of the studies. There are other categories that show numerical difference in treatment responses, e.g. treatment response in Europe in Study TR 701-112, Black or African-Americans in Study TR 701-113, but either the results are inconsistent in both studies, small numbers, and multiplicity issues prohibit making further claims.

The clinical success rates at EOT by subgroup are shown in Table 6-16 (Appendix 6.3). The clinical success rate is based on the definition in Study TR 701-113, i.e., without pain criteria and no carry forward of non-responders at the 48-72 Hour Visit. In this table, the differential treatment effect in patients more than 65 years or older is not apparent.

4.2 Harder to Treat Subgroup Populations

There are only a handful of patients with bacteremia; hence no conclusion can be inferred despite differential treatment response observed in each of the studies. There is notable difference between treatment groups in terms of patients with BMI ≥ 35 kg/m2 in Study TR 701-113 but cannot be corroborated by the result in Study TR 701-112. In addition, there is some notable difference in terms of diabetic patients in Study TR 701-112 but cannot be observed in Study TR 701-113. There are also some notable differences in terms of renal impairment, e.g. mild or moderate renal impairment in Study TR 701-112 but they do not support each other (opposite trend) and may just be due to chance because of low patient numbers in each category. No notable difference can be seen in terms of patients who are current or recent IV drug users and patients who are flagged for Systemic Inflammatory Response (SIRS).

Table 4-2: ECE at 48-72 hours by Harder to Treat Subgroups – ITT/ITT* population

	Study TR 701-112 (ITT*)		**Study TR 701-113 (ITT)**	
	Tedizolid phosphate N = 323 n(%)	**Linezolid N = 326 n(%)**	**Tedizolid phosphate N = 332 n(%)**	**Linezolid N = 334 n(%)**
Bacteremia = Y	4	3	7	12
Responder	4 (100.0)	1 (33.3)	7 (100.0)	9 (75.0)
BMI				
< 35 kg/m^2	287	288	280	288
Responder	227 (79.1)	227 (78.8)	246 (87.9)	238 (82.6)
≥ 35 kg/m^2	36	38	52	46
Responder	29 (80.6)	31 (81.6)	**37 (71.2)**	**38 (82.6)**

Diabetes Mellitus				
Diabetic	21	25	32	41
Responder	**17 (81.0)**	**23 (92.0)**	25 (78.1)	34 (82.9)
Not diabetic	302	301	300	293
Responder	239 (79.1)	235 (78.1)	258 (86.0)	242 (82.6)
IV Drug Use				
Current or recent IV drug User	117	132	66	74
Responder	95 (81.2)	111 (84.1)	54 (81.8)	60 (81.1)
Not a current or recent IV drug user	206	194	266	260
Responder	161 (78.2)	147 (75.8)	229 (86.1)	216 (83.1)
Renal Impairment				
Normal (CrCl >=90 mL/min)	264	277	263	266
Responder	211 (79.9)	218 (78.7)	226 (85.9)	221 (83.1)
Mild (CrCl 60-89 mL/min)	48	34	51	44
Responder	38 (79.2)	28 (82.4)	**40 (78.4)**	**37 (84.1)**
Moderate (CrCl 30-59 mL/min)	11	13	12	13
Responder	7 (63.6)	11 (84.6)	**11 (91.7)**	**10 (76.9)**
Severe (CrCl <30 mL/min)	0	2	3	1
Responder		1 (50.0)	3 (100.0)	1 (100.0)
SIRS				
SIRS Flag = Y	151	156	206	200
Responder	115 (76.2)	118 (75.6)	177 (85.9)	163 (81.5)
SIRS Flag = N	172	170	126	134
Responder	141 (82.0)	140 (82.4)	106 (84.1)	113 (84.3)

For Clinical response at the EOT Visit, there is notable difference between treatment groups in terms of patients with BMI $\geq$ 35 kg/m^2 in either studies. However, it is surprising to see the treatment response between the $\geq$ 35 kg/m^2 BMI group and the <35 kg/m^2 BMI group. In Study TR 701-112, the $\geq$ 35 kg/m2 BMI group has higher treatment response than the <35 kg/m2 BMI group. In Study TR 701-113, the trend is reversed (see Table 6-18 in Appendix 6.3). There is also some notable difference in terms of diabetic patients in both studies. Linezolid has a higher clinical success rate than tedizolid phosphate in diabetic patients. There are some imbalances in clinical success rate in terms of renal impairment but the numbers do not support each other and may just be due to chance. Lastly, no notable difference can be seen in terms of patients who are current or recent IV drug users and patients who are flagged for Systemic Inflammatory Response (SIRS).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The methods of analysis are acceptable and no statistical issues were found. The non-inferiority margin was agreed upon in two SPAs and is the recommended margin in both FDA drafts of the ABSSSI guidance. The method to calculate the confidence intervals, i.e., Miettinen and Nurminen, is also acceptable.

Missing data does not appear to have an impact on the results and the method for handling missing data is conservative.

There are no multiplicity issues since the testing of the endpoints are performed using a hierarchical strategy.

5.2 Collective Evidence

Figure 3 and Figure 4 illustrate the risk difference or the difference in the percentage of responders based on the 4 ECE definitions (see Table 3-14 and Table 3-15) and its associated 95% CI in the ITT/ITT* population as discussed in Section 3.2.7.1. The ECE definitions are the following:

- ECE1: cessation of spread of lesion defined as no increase from baseline in area with fever component
- ECE2: cessation of spread of lesion defined as no increase from baseline in area without fever component
- ECE3: ≥20% decrease from baseline at 48-72 hour visit in lesion area with fever component
- ECE4: ≥20% decrease from baseline at 48-72 hour visit in lesion area without fever component

ECE1 is the primary endpoint of Study TR 701-112 and ECE4 is the primary endpoint of Study TR 701-113. Note that in general, the four endpoints have the same trend, i.e., the points estimate of the risk differences favor tedizolid phosphate. In addition, all the lower limits of the 95% CI are greater than -10%. Since this meets the prespecified NI margin which required that the lower limit of the 95% CI interval to be greater than -10%, non-inferiority of tedizolid phosphate to linezolid is demonstrated in both Study TR 701-112 and Study TR 701-113.

The primary reasons for classification of early outcome as a nonresponder or indeterminate based on the ECE4 endpoint were investigated to determine whether the results were driven by factors other than failure of the study drugs. Results show that the most common reason is <20% reduction in area of the primary ABSSSI lesion in each study (see Table 3-26). The percentage

of patients classified into various categories of reasons for failure or indeterminate appeared balanced between groups except for missing lesion measurement in Study TR 701-113. This imbalance was caused by seven patients in the linezolid arm who did not receive their allocated treatment. This number, however, is minimal to drastically change the overall conclusion.

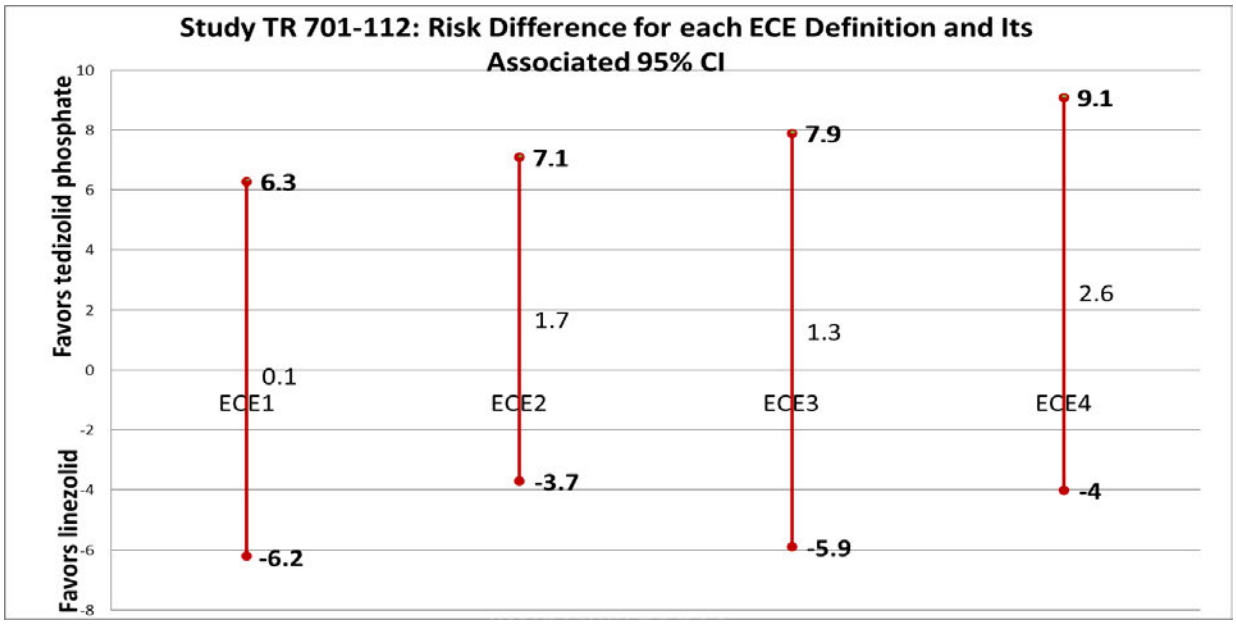

Figure 3: Point Estimate of the Risk Difference and Its Associated 95% CI Based on the Different Definitions of a Responder during ECE at the 48-72 hours in the ITT* Population– Study TR 701-112

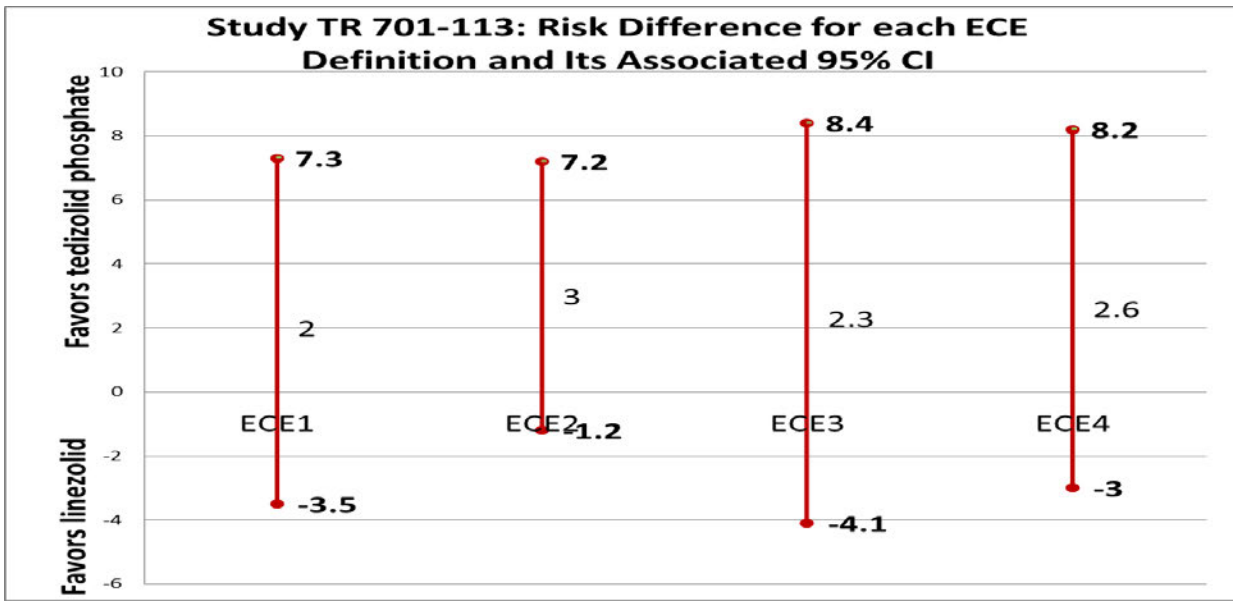

Figure 4: Point Estimate of the Risk Difference and Its Associated 95% CI Based on the Different Definitions of a Responder during ECE at the 48-72 hours – Study TR 701-113

Investigations were also made on the factors/difference in study population that could potentially affect the results, e.g. demographics and some important medical history, stratification factors, type of infection and anatomical site of infection, prior medications or procedures that have potential impact on the efficacy results, baseline pathogen isolated at the infection site, and baseline signs and symptoms of the primary ABSSSI infection. Results show no notable imbalance in the study population between the two groups (see Table 3-3, Table 3-4, Table 3-5, Table 3-6, Table 3-7, Table 3-8, Table 3-9, and Table 3-10). However, there is notable information about the composition of patients enumerated in the following:

- About 40% of the patients enrolled in Study TR 701-112 had cellulitis/erysipelas; about 30% had infected wound and another 30% had major cutaneous abscess. In Study TR 701-113, about 50% had cellulitis/erysipelas, 30% had infected wound and 20% had major cutaneous abscess;
- Less than 20% of patients in Study TR 701-112 had fever (≥38°C) at baseline (16.9% and 18.8% of patients in the tedizolid phosphate and linezolid groups, respectively). A higher percentage is observed in Study TR 701-113 which includes 31.0% in tedizolid phosphate and 29.0% in linezolid.
- Most patients in Study TR 701-112 were enrolled in North America (538 patients), followed by Europe (108 patients), and Latin America (21 patients). In TR 701-113, most patients enrolled were still from North America (314) but a significant portion of Europeans were also enrolled (233).
- More than 40% of the patients had bedside or operative incision and drainage prior to Study Day 1 through the 48-72 Hour Visit and more than a third of the patients in Study TR 701-112 took antipyretic medications through the 48-72 Hour Visit (34.9% tedizolid phosphate and 33.1% linezolid) while approximately 15% of the patients in Study TR 701-113 took them (13.3% tedizolid phosphate and 15.6% linezolid).

Further explorations were also conducted to look at how the treatment response varies across these subgroups and to check whether there are subgroups that confound treatment response. Findings show that early clinical response by infection type was generally similar in tedizolid phosphate and linezolid groups in the ITT/ITT* population in both trials (see Table 3-15). Responder rates among subjects with cellulitis are consistently lower across treatment arms and studies. For subjects with baseline surface area of infection exceeding 300 cm^2, 71.4% (60/84) are responders in the tedizolid phosphate group and 83.1% (69/83) are responders in the linezolid group in Study TR 701-112 (see Table 6-5 in Appendix 6.3). However, in Study TR 701-113, the two groups have similar responder rates. Furthermore, there is no imbalance in the responder rate between treatment groups across studies in terms of anatomical site (extremity or non-extremity) of infection at baseline (see Table 3-16). Cessation/reduction of lesion spread at 48-72 hours by baseline fever status was similar in both treatment groups (see Table 3-17). However, in Study TR 701-112, response rates were lower in the febrile group than in the afebrile group while the opposite trend is observed in Study TR 701-113. Early clinical response was also seen in a higher percentage of patients treated with tedizolid phosphate in Europe (84.9% tedizolid phosphate vs 74.5% linezolid); there was little difference between groups in early clinical

response in North America (78.5% tedizolid phosphate and 80.3% linezolid). Similar results can be observed in Study TR 701-113 (see Table 3-14).

Few patients used prior or concomitant systemic and topical antibacterial medications through the ECE Visit in both studies. Hence, any differential effect observed between treatment groups is most likely spurious and is due to small patient numbers. Subjects who received NSAIDS/oral steroid medications through the 48-72 Hour Visit have a lower early clinical response rate (61.1% tedizolid phosphate and 77.9% linezolid in Study TR 701-112 and 83.3% tedizolid phosphate and 83.7% linezolid in Study TR 701-113) than those subjects who did not receive such medications (see Table 3-18). Subjects who received antipyretic medications through the 48-72 Hour Visit have a lower early clinical response rate (75.9% tedizolid phosphate and 74.8% linezolid in Study TR 701-112 and 77.3% tedizolid phosphate and 69.2% linezolid in Study TR 701-113) than those subjects who did not receive such medications (see Table 3-18). Subjects who received NSAIDS/oral steroids, antipyretics, and pain medications through the 48-72 Hour Visit have a lower early clinical response rate (76.2 tedizolid and 73.2 linezolid in Study TR 701-112 and 78.8 tedizolid and 77.8 linezolid in Study TR 701-113) than those subjects who did not receive such medications (see Table 3-18). Lastly, for subjects who had bedside or operative I&D performed prior to Study Day 1 through the 48-72 Hour Visit have a higher early clinical response rate (89.7% tedizolid phosphate and 85.3% linezolid than those who did not (80.3% tedizolid and 79.6% linezolid) (see Table 3-18).

From these observations, it can be concluded that (1) the inclusion of major cutaneous abscess (see also Table 6-10 in Appendix 6.3), (2) administration of concomitant NSAIDS/oral steroid, antipyretic or pain medication, (3) performance of incision and drainage whether during therapy or prior to therapy (see also Table 6-11 in Appendix 6.3), and (4) inclusion of a significant number of patients from Europe can alter treatment response. However, since the two treatment groups are well balanced with respect to these subgroups, its effect is not manifested in the difference of the treatment response.

The results observed during the ECE at 48-72 Hour Visit were also supported by the results at the EOT Visit in the ITT/ITT* and CE-EOT/CE-EOT* populations and the results of the investigator assessment of clinical response at PTE in the ITT/ITT* and CE-PTE/CE-PTE* populations (see Sections 3.2.7.2and 3.2.7.3). In fact, concordance between the early clinical response (at the 48-72 hour visit) and the response at EOT by programmatic determination where pain was not included and the outcome at 48-72 hours was not carried forward is high in both trials (79.0% in Study TR 701-112 83.6% in Study TR 701-113) (see Table 3-27). Since these three endpoints (ECE at 48-72 Hours, Clinical Response at EOT, and Investigator assessment of clinical response at PTE) are not defined exactly the same and were measured at different time points, the totality of results, which has high agreement among each other, provide range and robustness of measurements that show therapeutic non-inferiority of tedizolid phosphate to linezolid (see also lesion measurements in Table 3-44, signs and symptoms of infection in Table 3-48 and Table 3-49, and pain scores in Table 3-50 and Table 3-51).

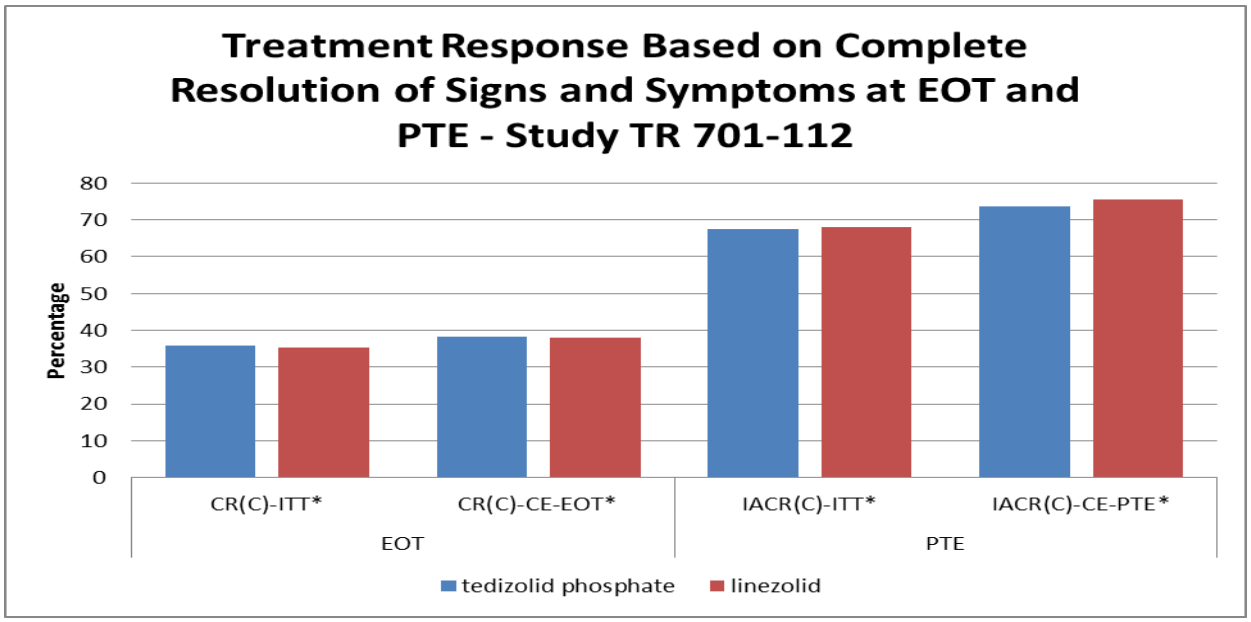

Figure 5: Treatment Response based on Complete Resolution (C) of Signs and Symptoms Present at Baseline at the EOT and the PTE Visit - Study TR 701-112

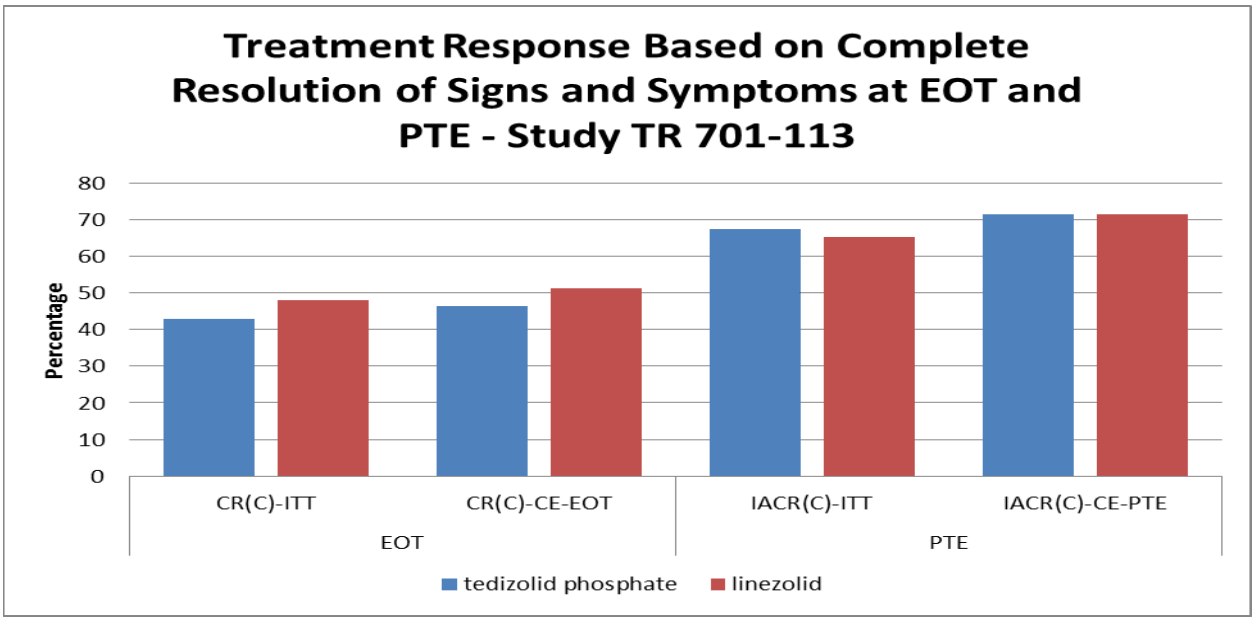

Figure 6: Treatment Response based on Complete Resolution (C) of Signs and Symptoms Present at Baseline at the EOT and the PTE Visit - Study TR 701-113

Investigations were conducted to look at complete resolution of signs and symptoms of the primary ABSSSI (see Table 3-30 and Table 3-39). The two endpoints (clinical response and investigator assessment of clinical response) are based on an aggregate of different criteria which is either programmatically carried out or by investigator assessment. Figure 5 and Figure 6 show

the clinical success rate based on complete resolution (CR(C)) in the ITT* and CE-EOT* populations in Study TR 701-112 as well as the ITT and CE-EOT populations in Study TR 701-113. The figures illustrate progressive response at EOT through PTE (30-40% cure at EOT and 60-70% cure at PTE) and the two treatment groups are comparable at all times.

There are three other investigations worthy of a discussion.

1. Whether the cessation in lesion spread or the 20% reduction in surface area are marginal, i.e., either there is only minimal reduction in lesion surface area in the case of Study TR 701-112 or the reductions in surface area barely made it to the 20% threshold.

The data shows (see Figure 1 and Figure 2) that in both trials, the majority of the patients had more than 50% reduction from baseline in lesion area at the 48-72 Hour Visit. Further explorations were conducted on who these patients were.

There were 325 patients who had more than 50% decrease in lesion surface area at baseline by the 48-72 Hour Visit in Study TR 701-112, including 121 patients with major cutaneous abscess, 89 with infected wound, and 115 with cellulitis/erysipelas. This means that about 63.3% of the total patients with major cutaneous abscess responded rapidly based on reduction of lesion size while only 46.8% of the patients with infected wound and 43.2% of the patients with cellulitis/erysipelas responded rapidly. On the other hand, 57.8% of the patients who had bedside or operative incision and drainage (I&D) performed prior to Study Day 1 through the 48-72 Hour Visit responded rapidly compared to 43.4% for patients who did not have I&D performed (see further details in Section 3.2.7.5).

In Study TR 701-113, 91 patients had major cutaneous abscess, 101 had infected wound, and 138 had cellulitis/erysipelas. This means that about 66.9% of the total patients with major cutaneous abscess responded rapidly based on reduction of lesion size while only 51.5% of the patients with infected wound and 41.3% of the patients with cellulitis/erysipelas responded rapidly. On the other hand, 51.7% of the patients who had bedside or operative I&D performed prior to Study Day 1 through the 48-72 Hour Visit responded rapidly compared to 47.1% for patients who did not have I&D.

These results suggest that the inclusion of major cutaneous abscess and performance of incision and drainage whether during therapy or prior to therapy can confound treatment response. In NI trials, such procedures or patient populations deemed to have mild infections can obscure the true treatment differences; thus making the drugs appear similar. Hence, the use of I&D should be limited and if it cannot be eliminated, such procedures should be pre-planned based on baseline disease characteristics.

2. What is the treatment response of the study drug in all patients in the ITT Population who had a baseline gram-positive bacterial pathogen known to cause ABSSSI (MITT population)?

With respect to patients in the MITT population, the early clinical response results at the 48-72 Hour Visit based on cessation of spread of lesion defined as no increase from baseline in area with fever component, was observed in 159/203 (78.3%) of patients in the tedizolid phosphate group and 164/206 (79.6%) of patients in the linezolid group in Study TR 701-112 ITT* Population, with a treatment difference -1.3% [95% CI: -8.9%, 6.9%]. On the other hand, the early clinical response (responder) based only on ≥ 20% decrease from baseline at 48-72 hour visit in lesion area was observed in 162/203 (79.8%) of patients in the tedizolid phosphate group and 162/206 (78.6%) of patients in the linezolid group in Study TR 701-112 ITT* Population with a treatment difference of 1.2% [95% CI: -6.8%, 9.1%]. In Study TR 701-113, this outcome was observed in 174/197 (88.3%) of patients in the tedizolid phosphate group and 166/202 (82.2%) of patients in the linezolid group, with a treatment difference of 6.2% [95% CI: -0.9%, 12.2%]. Again, the lower limits of the 95% confidence intervals are all greater than -10%.

At the PTE Visit, the investigator's assessment of clinical response (clinical success) of patients whose primary ABSSSI was caused by methicillin susceptible *Staphylococcus Aureus* was observed in 71/81 (87.7%) patients in the tedizolid phosphate group and 81/86 (94.2%) patients in the linezolid group in Study TR 701-112, while in Study TR 701-113, it was observed in 101/106 (95.3%) patients in the tedizolid phosphate group and 104/112 (92.9%) patients in the linezolid group. Although there is some notable difference in the treatment response in Study TR 701-112, that difference cannot be corroborated by results in Study TR 701-113. Also, these clinical success rates are comparable to the overall rate. As for methicillin resistant *Staphylococcus Aureus*, clinical success was observed in 74/86 (86.0%) patients in the tedizolid phosphate group and 74/87 (85.1%) patients in the linezolid group in Study TR 701-112, while in Study TR 701-113, it was observed in 53/64 (82.8%) patients in the tedizolid phosphate groupand 55/69 (79.7%) patients in the linezolid group. Note that the clinical success rate of patients with methicillin resistant *Staphylococcus Aureus* in Study TR 701-113 is lower than the overall rate.

As a word of caution, it is important to note that the pathogen(s) isolated could be colonizers of the human skin microbiome and not necessarily a causative pathogen of the infection. Furthermore, pathogens causing cellulitis maybe underrepresented especially if the infection does not have an accompanying abscess.

3. What is the treatment response of the study drug in harder to treat subgroups?

The majority of the patients enrolled in both studies were young (approximately 90% were less than 65 years old), white (greater than 80%), healthy males (approximately 60%) i.e., majority had less than 30 kg/m2 in body mass index (BMI), had no diagnosis of diabetes mellitus (more than 90%) and had normal renal function (approximately 80%). These patients are believed to respond favorably to either study drugs. For selected subgroups of interest, e.g. elderly, harder to treat patients due to some related medical history, minorities or status of IV drug use, the following table (Table 1-2) shows their response rates at the 48-72 Hour visit based on ≥ 20% decrease from baseline. See more discussion in Section 4.

Table 1-1: Early Clinical Response (Responder) based on ≥ 20% decrease from baseline at the 48-72 Hour Visit by Selected Subgroup

	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate	**Linezolid**	**Tedizolid phosphate**	**Linezolid**
Age ≥ 75 years old, N	10	7	14	17
Responder, n(%)	6 (60.0)	3 (42.9)	11 (78.6)	14 (82.3)
Black or African American, N	36	36	38	37
Responder, n (%)	27 (75.0)	28 (77.8)	35 (92.1)	28 (75.7)
BMI ≥ 35 kg/m^2, N	36	38	52	46
Responder, n (%)	27 (75.0)	33 (86.8)	37 (71.2)	38 (82.6)
Diabetes Mellitus, N	21	25	32	41
Responder, n (%)	13 (61.9)	20 (80.0)	25 (78.1)	34 (82.9)
Current or recent IV drug User, N	117	132	66	74
Responder, n(%)	97 (82.9)	104 (78.8)	54 (81.8)	60 (81.1)
Moderate to Severe Renal Impairment (CrCl <60 mL/min), N	11	15	15	14
Responder, n(%)	6 (54.6)	11 (73.3)	14 (93.3)	11 (78.6)

5.3 Conclusions and Recommendations

The early clinical response at the 48-72 Hour Visit based on cessation of spread of lesion defined as no increase from baseline in area with fever component, which is the protocol defined primary efficacy endpoint of Study TR 701-112, was observed in (256/323) 79.3% of patients in the tedizolid phosphate group and (258/326) 79.1% of patients in the linezolid group in Study TR 701-112 ITT* Population, with a treatment difference 0.1% [adjusted 95% CI: -6.2%, 6.3%]. For Study TR 701-113, on the other hand, the early clinical response at the 48-72 Hour Visit based on cessation of spread of lesion defined as no increase from baseline in area and no fever component was observed in 283/332 (85.2%) of patients in the tedizolid phosphate group and 276/334 (82.6%) of patients in the linezolid group, with a treatment difference 2.6% [95% CI: -3.0%, 8.2%]. These endpoints meet the prespecified NI margin which required the lower limit of the 95% CI interval to be greater than -10%, non-inferiority of tedizolid phosphate to linezolid is demonstrated in both Study TR 701-112 and Study TR 701-113.

The secondary endpoints, clinical response at EOT in the ITT/ITT* populations and investigator assessment of clinical response at PTE in the ITT/ITT* populations also support the result at the 48-72 Hour Visit. In addition, the endpoints based on complete resolution of signs and symptoms show similar response between tedizolid phosphate and linezolid and that the cure rate is progressively increasing over time.

No notable imbalance between treatments groups were observed in most subgroups that show consistent trend. In subgroups that can potentially confound treatment response, the analyses populations were well balanced (e.g. incision and drainage, use of NSAIDS/oral steroids) and minimized (e.g. major cutaneous abscess, inclusion of subjects from Europe) between the treatment groups.

All the investigations suggest that tedizolid phosphate is therapeutically non-inferior to linezolid.

5.4 Labeling Recommendations

The following are some relevant information that can be conveyed in the product label. Note that Study TR 701-112 and Study TR 701-113 are called Study 112 and Study 113, respectively, in the label.

Acute Bacterial Skin and Skin Structure Infections

A total of 1315 adults with acute bacterial skin and skin structure infections (ABSSSI) were randomized in 2 multicenter, multinational, double-blind, non-inferiority trials (Study 112 and Study 113). Both trials compared SIVEXTRO (tedizolid phosphate) 200 mg once daily for 6 days versus linezolid 600 mg every 12 hours for 10 days. In Study 112, patients were treated with oral therapy, while in Study 113; patients could receive oral therapy after a minimum of 1 day of IV therapy. Patients with cellulitis/erysipelas, major cutaneous abscess, or wound infection were enrolled in the studies. Patients with wound infections could receive aztreonam and/or metronidazole as adjunctive therapy for gram-negative bacterial coverage, if needed. The intent-to-treat (ITT) patient population included all randomized patients.

Of the 1315 adults with ABSSSI, 323 patients were randomized to SIVEXTRO and 326 patients were randomized to linezolid in Study 112; 332 patients were randomized to SIVEXTRO and 334 patients to linezolid in Study 113. Majority (61%) of the patients treated with SIVEXTRO in Study 112 are less than 65 years old with a median age of 43 years old (range: 18 to 86 years) and mean body mass index (BMI) of 28kg/m^2. Patients treated with SIVEXTRO were also predominantly male (61%), White (85%) and coming from North America (81.3%). The types of ABSSSI infections treated were cellulitis/erysipelas (40%), wound infection (30%), and major cutaneous abscess (30%) with an overall median surface area of 190 cm^2. In Study 113, majority (67%) of the patients treated with SIVEXTRO are also less than 65 years old with a median age of 46 years old (range: 17 to 86 years) and mean BMI of 2928kg/m2. Patients treated with SIVEXTRO were predominantly male (68%), White (86%) and coming from North America (47%) and Europe (34%). The types of ABSSSI infections treated were cellulitis/erysipelas (50%), wound infection (30%), and major cutaneous abscess (20%) with an overall median surface area of 231cm^2.

The primary analysis in Study 112 evaluated early clinical responder rates based on achieving no increase from baseline lesion area at 48-72 hours after the first dose in the ITT patient population and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours, while the primary analysis in Study 113 evaluated early clinical responder rates based on achieving at least a 20% decrease from baseline lesion area at 48-72 hours after the first dose in the ITT patient population (Table 5-1). For consistency, an analysis evaluating early clinical responder rates based on achieving at least a 20% decrease from baseline lesion area at 48-72 hours after the first dose in the ITT patient population is also shown for Study 112.

Table 5-2: Early Clinical Response in the ITT Patient Population

	SIVEXTRO (200 mg)	Linezolid (1200 mg)	Treatment Difference (2 sided 95% CI)
No increase in lesion surface area from baseline and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours at 48-72 Hours			
Study 112, N	323	326	
Responder, n (%)	264 (79.5)	266 (79.4)	0.1 (-6.1, 6.2)
At least a 20% decrease from baseline in lesion area			
Study 112, N	323	326	
Responder, n (%)	252 (78.0)	246 (75.5)	2.6 (-4.0, 9.1)
Study 113, N	332	334	
Responder, n (%)	283 (85.2)	276 (82.6)	2.6 (-3.0, 8.2)

Early clinical response is similar for SIVEXTRO and linezolid groups across subgroups determined by sex, age, race, body mass index. Table 5-2 shows the response rates for some selected subgroups of potential interest.

Table 5-3: Early Clinical Response at 48-72 hours by Selected Subgroups in the ITT population

	Study 112 (No increase in lesion surface area from baseline and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours at 48-72 Hours)		Study 113 (At least a 20% decrease from baseline in lesion area)	
	SIVEXTRO (200 mg)	**Linezolid (1200 mg)**	**SIVEXTRO (200 mg)**	**Linezolid (1200 mg)**
Black or African American, N	36	36	38	37
Responder, n (%)	25 (69.4)	29 (80.6)	35 (92.1)	28 (75.7)
BMI ≥ 35 kg/m^2, N	36	38	52	46
Responder, n (%)	29 (80.6)	31 (81.6)	37 (71.2)	38 (82.6)
Diabetes Mellitus, N	21	25	32	41
Responder, n (%)	17 (81.0)	23 (92.0)	25 (78.1)	34 (82.9)
Current or recent IV drug User, N	117	132	66	74
Responder, n(%)	95 (81.2)	111 (84.1)	54 (81.8)	60 (81.1)
Moderate to Severe Renal Impairment (CrCl <60 mL/min), N	11	15	15	14
Responder, n(%)	7 (63.6)	12 (80.0)	14 (93.3)	11 (78.6)

The protocol specified analyses also included programmatic clinical response at the end of therapy (EOT) and Investigator-assessed clinical response at the post-therapy evaluation (7 –

14 days after the end of therapy) in the ITT patient population (Table 5-3). In the programmatic clinical response at EOT , patients were considered a clinical success if they were afebrile, had a decrease from baseline in size of primary ABSSSI lesion, had a clinical assessment of tenderness as mild or absent, had no purulent drainage, and took no other antibiotics. On the other hand, the Investigator Assessed Clinical Response at post-therapy evaluation considers a patient to be a clinical success if most disease-specific signs and symptoms, as well as systemic signs of infection, present at baseline are resolved or nearly resolved and requires no further antibiotic therapy.

Table 5-4: Clinical Response at End of Therapy and Investigator Assessed Clinical Response at Post-therapy Evaluation in ITT Patient Population from Two Phase 3 ABSSSI Trials

	SIVEXTRO (200 mg) n/N (%)	**Linezolid (1200 mg) n/N (%)**	**Treatment Difference (2 sided 95% CI)**
Clinical Response at End of Therapy			
Study 112	281/323 (87.0)	285/326 (87.4)	-0.4 (-5.6, 4.8)
Study 113	289/332 (87.0)	294/334 (88.0)	-1.0 (-6.1, 4.1)
Investigator Assessed Clinical Response at Post-therapy Evaluation			
Study 112	277/323 (85.8)	279/326 (85.6)	0.2 (-5.3, 5.6)
Study 113	279/332 (85.6)	293/334 (87.7)	0.3 (-4.8, 5.3)

6 APPENDICES

6.1 Definition of Clinical Response at EOT

6.1.1 Sustained Clinical Response for Study TR 701-112

Patients assessed as a nonresponder at the 48-72 Hour Visit are considered a clinical failure at the EOT Visit. Patients will be programmatically defined as **clinical failures** as outlined below:

- At the EOT Visit (Day 11) the patient meets any of the following:
    - Presence of fever > 37.6°C (oral; investigator reported) with no cause other than the primary skin infection
    - No decrease from baseline in the size of the primary ABSSSI lesion
    - Clinician assessment of tenderness worse than mild
    - Patient-reported presence of pain

- At any time from the first dose of study drug through the EOT Visit (Day 11), the patient meets any of the following:
    - Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
    - Treatment-emergent AE 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 **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 clinical failures or indeterminates will be considered a **clinical successes**.

For the secondary outcome measure of sustained response at the EOT Visit, patients assessed as a nonresponder at the 48-72 Hour Visit were considered a clinical failure at the EOT Visit.

6.1.2 Clinical Response for Study TR701-113

Patients will be programmatically defined as **clinical successes** as outlined below:

- At the EOT Visit (Day 11) the patient meets any of the following:
    - Patient is afebrile (<37.7°C oral; investigator reported) or the fever ≥37.7°C is attributable to a cause other than the primary skin infection
    - Decrease from baseline in the size (area, length, and width) of the primary ABSSSI lesion
    - Clinician assessment of tenderness of mild or absent
    - No purulent drainage from a wound infection or the purulent drainage is of a lesser intensity than at Screening

- The patient meets any of the following from the first infusion of study drug through the EOT Visit (Day 11):
    - Did not receive any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
    - Did not have a TEAE leading to discontinuation of study drug and required additional antibiotic therapy to treat the ABSSSI
    - No additional antibiotic therapy for treatment of the primary lesion is required
    - No unplanned major surgical intervention to the primary lesion
    - Did not develop osteomyelitis after baseline
    - For wounds and abscess: no incision and drainage of the ABSSSI site was performed after Day 1 unless it was planned before randomization
    - For cellulitis/erysipelas: no incision and drainage of the ABSSSI site after the 48-72 Hour Visit

Patients will be programmatically defined as **clinical failures** as outlined below:

- At the EOT Visit (Day 11) the patient meets any of the following:
    - Presence of fever ≥37.7°C (oral; investigator reported) with no cause other than the primary skin infection
    - No decrease from baseline in the size of the primary ABSSSI lesion (area, length, or width)
    - Clinician assessment of tenderness worse than mild
    - Persistent purulent drainage from a wound infection at the same or greater intensity as Screening

- At any time from the first infusion of study drug through the EOT Visit (Day 11), the patient meets any of the following:
    - Receipt of any systemic concomitant antibiotic therapy that is potentially effective against the baseline pathogen with the exception of adjunctive aztreonam and/or metronidazole in patients with wound infections
    - Treatment-emergent AE leading to discontinuation of study drug and patient required additional antibiotic therapy to treat the ABSSSI
    - Requires additional antibiotic therapy for treatment of the primary lesion
    - Unplanned major surgical intervention required due to failure of study drug (ie. amputation)
    - Developed osteomyelitis after baseline
    - For wounds and abscess: incision and drainage of the ABSSSI site not planned before randomization and performed after Day 1
    - For cellulitis/erysipelas: incision and drainage of the ABSSSI site after the 48-72 Hour Visit
    - Death (all-cause mortality) within 28 days of the first infusion of study drug

Patients will be programmatically defined as **indeterminates** 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

6.2 Definition of Investigator's Assessment of Clinical Response

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

6.3 Supplementary Tables

Table 6-1: Primary Site of Infection

Anatomical Site	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Head	15 (4.5)	11 (3.3)	15 (4.5)	15 (4.5)
Neck	6 (1.8)	6 (1.8)	2 (0.6)	5 (1.5)
Chest	4 (1.2)	10 (3.0)	9 (2.7)	8 (2.4)
Abdomen	21 (6.3)	8 (2.4)	12 (3.6)	7 (2.1)
Back	7 (2.1)	6 (1.8)	4 (1.2)	5 (1.5)
Groin	13 (3.9)	9 (2.7)	11 (3.3)	12 (3.6)
Buttock	36 (10.8)	33 (9.9)	22 (6.6)	28 (8.4)
Shoulder	3 (0.9)	4 (1.2)	8 (2.4)	5 (1.5)
Axillary	6 (1.8)	6 (1.8)	14 (4.2)	10 (3.0)
Hand	16 (4.8)	11 (3.3)	31 (9.3)	20 (6.0)
Arm	77 (23.2)	92 (27.5)	103 (31.0)	105 (31.4)
Leg	132 (39.8)	137 (40.9)	124 (37.3)	131 (39.2)
Foot	19 (5.7)	24 (7.2)	22 (6.6)	21 (6.3)

Table 6-2: Baseline Infection Measurement by Infection Type and Geographic Measurement

Infection Type and Geographic Region	Study TR 701-112 Tedizolid phosphate N = 332	Study TR 701-112 Linezolid N = 335	Study TR 701-113 Tedizolid phosphate N = 332	Study TR 701-113 Linezolid N = 334
Overall	332	335	332	334
Mean (SD)	321.3 (457.62)	298.7 (370.37)	373.0 (377.28)	397.3 (482.34)
Min, Max	28.0, 5572.8	27.0, 2952.0	75.0, 2711.2	76.0, 5220.0
Cellulitis/erysipelas	135	139	166	168
Mean (SD)	444.8 (476.76)	405.6 (489.48)	416.5 (412.45)	496.6 (606.50)
Min, Max	76.5, 2515.5	76.0, 2952.0	76.1, 2711.2	76.5, 5220.0
North America, n(%)	81	83	64	64
Mean (SD)	310.4 (338.99)	286.5 (.344.53)	392.8 (414.90)	421.1 (700.14)
Min, Max	76.5, 2030.0	76.0, 2490.0	77.4, 1811.2	76.5, 5220.0
Latin America, n(%)	9	10	12	12
Mean (SD)	488.8 (420.59)	539.2 (420.44)	502.5 (382.70)	528.9 (493.88)
Min, Max	180.0, 1537.5	161.0, 1591.0	102.8, 1110.0	102, 1840.0
Europe, n(%)	45	46	63	67
Mean (SD)	678.0 (601.57)	591.4 (646.31)	461.5 (422.00)	550.8 (340.6)
Min, Max	81.6, 2515.5	80.0, 2952.0	76.1, 2711.2	93.7, 1558.0
South Africa, n(%)			25	21
Mean (SD)			236.7 (220.22)	424.1 (658.8)
Min, Max			76.5, 960.0	77.0, 2494.0
Australia/New Zealand, n(%)			2	4
Mean (SD)			1491.0 (199.40)	(1080.0 (1777.72)
Min, Max			1350.0, 1632.0	121.0, 3744.0
Major Cutaneous Abscess, n(%)	100	98	68	68
Mean (SD)	266.7 (578.85)	208.0 (177.25)	267.3 (358.55)	218.1 (145.53)
Min, Max	48.8, 5572.8	27.0, 1293.8	78.8, 2385.0	77.0, 864.0
North America, n(%)	100	98	41	39
Mean (SD)	266.7 (578.85)	208.0 (177.25)	222.7 (180.61)	225.8 (122.33)
Min, Max	48.8, 5572.8	27.0, 1293.8	78.8, 1037.0	78.0, 506.0
Latin America, n(%)			0	1
Mean (SD)				210.0 (.)
Min, Max				210.0, 210.0
Europe, n(%)			13	14
Mean (SD)			523.4 (705.97)	280.7 (220.45)
Min, Max			84.3, 2385.0	86.3, 864.0
South Africa, n(%)			14	12
Mean (SD)			160.1 (133.85)	122.2 (44.78)
Min, Max			79.3, 504.0	77.0, 184.8
Australia/New Zealand, n(%)			0	2
Mean (SD)				208.0 (169.71)
Min, Max				88.0, 328.0
Wound infection	97	98	98	98
Mean (SD)	205.6 (145.36)	237.9 (267.6)	372.6 (310.60)	351.6 (330.28)
Min, Max	28.0, 924.0	72.0, 2397.0	75.0, 1566.0	76.0, 1640.0
North America, n(%)	89	87	51	55
Mean (SD)	205.3 (148.86)	240.0 (277.10)	222.7 (180.61)	225.8 (122.33)

Min, Max	28.0, 924.0	72.0, 2397.0	78.8, 1037.0	78.0, 506.0
Latin America, n(%)	0	2	0	1
Mean (SD)		178.1 (121.4)		506.0 (.)
Min, Max		92.3, 264.0		506.0, 506.0
Europe, n(%)	8	9	36	30
Mean (SD)	208.7 (105.84)	230.5 (200.42)	515.6 (346.59)	481.1 (317.7)
Min, Max	88.0, 420.0	110.0, 748.0	78.0, 1566.0	76, 1177.8
South Africa, n(%)			9	13
Mean (SD)			215.1 (315.32)	169.2 (92.12)
Min, Max			80.0, 1054.0	78.8, 391.0
Australia/New Zealand, n(%)			1	0
Mean (SD)			101.5 (.)	
Min, Max			101.5, 101.5	

Table 6-3: Local Sign or Symptom of Infection

Local Sign or Symptom of Infection	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Erythema				
Absent, n(%)	0	0	0	0
Mild, n(%)	21 (6.3)	22 (6.6)	30 (9.0)	17 (5.1)
Moderate, n(%)	180 (54.2)	178 (53.1)	158 (47.6)	172 (51.5)
Severe, n(%)	131 (39.5)	135 (40.3)	144 (43.4)	145 (43.4)
Swelling				
Absent, n(%)	7 (2.1)	5 (1.5)	7 (2.1)	3 (0.9)
Mild, n(%)	45 (13.6)	41 (12.2)	35 (10.5)	33 (9.9)
Moderate, n(%)	148 (44.6)	154 (46.6)	147 (44.3)	173 (51.8)
Severe, n(%)	132 (39.8)	135 (40.3)	143 (43.1)	125 (37.4)
Localized Warmth				
Absent, n(%)	0	1 (0.3)	3 (0.9)	0
Mild, n(%)	23 (6.9)	22 (6.6)	18 (5.4)	32 (9.6)
Moderate, n(%)	183 (55.1)	188 (56.1)	163 (49.1)	160 (47.9)
Severe, n(%)	126 (38.0)	124 (37.0)	148 (44.6)	142 (42.5)
Tenderness or Palpation				
Absent, n(%)	3 (0.9)	4 (1.2)	0	2 (0.6)
Mild, n(%)	23 (6.9)	18 (5.4)	23 (6.9)	22 (6.6)
Moderate, n(%)	165 (49.7)	160 (47.8)	155 (46.7)	162 (48.5)
Severe, n(%)	141 (42.5)	153 (45.7)	154 (46.4)	148 (44.3)
Pain (present), n(%)	315 (94.9)	318 (94.9)	296 (89.2)	298 (89.2)
Fluctuance (present), n(%)	124 (37.3)	116 (34.6)	99 (29.8)	102 (30.5)
Induration (present), n(%)	296 (89.2)	291 (86.9)	290 (87.3)	297 (88.9)
Drainage and/or Discharge				
Absent, n(%)	134 (40.5)	124 (37.0)	120 (36.1)	129 (38.6)
Serious, n(%)	8 (2.4)	11 (3.3)	15 (4.5)	13 (3.9)
Seropurulent, n(%)	84 (25.4)	98 (29.3)	63 (19.0)	65 (19.5)
Purulent, n(%)	105 (31.7)	102 (30.4)	134 (40.4)	127 (38.0)

Table 6-4: Regional/Systemic Sign of Infection

Regional/Systemic Sign of Infection	Study TR701-112		Study TR701-113	
	Tedizolid phosphate N = 332	Linezolid N = 335	Tedizolid phosphate N = 332	Linezolid N = 334
Lymphadenopathy, n(%)	289 (87.0)	289 (86.3)	235 (70.8)	235 (70.4)
Lymph node tenderness, n(%)	283 (85.2)	286 (85.4)	230 (69.3)	229 (68.6)
Lymph node increase in volume or palpable, n(%)	287 (86.4)	281 (83.9)	231 (69.6)	229 (68.6)
WBC ≥ 10,000/mm3 or < 4000/mm3, n(%)	140 (42.2)	133 (39.7)	176	151
Immature neutrophils > 10%, n(%)	12 (4.1)	8 (2.6)	53	40
Temperature, n(%)	56 (16.9)	63 (18.8)	103 (31.0)	97 (29.0)

Table 6-5: Early Clinical Response at 48-72 Hour Visit by Infection Surface area at Baseline - ITT/ITT* populations

Baseline Infection Surface Area (SA)	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
<75, N1	10	11	2	0
Responder, n (n/N1%)	10 (100.0)	9 (81.8)	2 (100.0)	0
75≤ SA < 150, N1	101	104	113	100
Responder, n (n/N1%)	81 (80.2)	84 (80.8)	98 (86.7)	85 (85.0)
150 ≤ SA < 300, N1	128	128	73	97
Responder, n (n/N1%)	105 (82.0)	97 (75.8)	62 (84.9)	78 (80.4)
300 ≤ SA < 600, N1	44	45	97	73
Responder, n (n/N1%)	30 (68.2)	36 (80.0)	83 (85.6)	62 (84.9)
600 ≤ SA < 1000, N1	19	24	20	43
Responder, n (n/N1%)	15 (79.0)	19 (79.2)	18 (90.0)	40 (93.0)
1000 ≤ SA, N1	21	14	27	21
Responder, n (n/N1%)	15 (71.4)	13 (92.9)	23 (85.2)	16 (76.2)

Table 6-6: Investigator's Assessment of Clinical Response at EOT- ITT/ITT* populations

Response	Study TR 701-112 *		Study TR 701-113	
	Tedizolid phosphate N = 323	Linezolid N = 326	Tedizolid phosphate N = 332	Linezolid N = 334
Clinical response at EOT in the ITT/ITT* population				
Clinical success	277 (85.8)	281 (86.2)	317 (95.5)	325 (97.3)
Difference (CI)	0.4 (-5.0, 5.8)		1.8 (-1.1, 4.9)	
Clinical failure/Indeterminate or Improving	46 (14.2)	45 (13.8)	15 (4.5)	9 (2.7)
Clinical response at EOT in the CE-EOT/CE-EOT* population				
Clinical success	273 (95.7)	277 (94.5)	289 (95.1)	290 (97.0)
Difference (CI)	-1.3 (-5.0, 2.4)		1.9 (-1.3, 5.3)	
Clinical failure/Indeterminate or Improving	12 (4.2)	16 (5.5)	15 (4.9)	9 (3.0)

*Excludes patients from Sites 120, 121, and 122.

Table 6-7: Concordance between Clinical Response at EOT and Investigator's Assessment of Clinical Response at EOT – ITT/ITT* population

Early Clinical Response at 48-72 Hours	Programmatic Determination of Sustained Clinical response at EOT	STUDY TR 701-112 (ITT*) Tedizolid phosphate N=323 n (%)	STUDY TR 701-112 (ITT*) Linezolid N=326 n (%)	Study TR 701-113 (ITT) Tedizolid phosphate N=332 n (%)	Study TR 701-113 (ITT) Linezolid N=334 n (%)
Clinical success	Clinical success	268 (95.3)	276 (96.8)	289 (100.0)	294 (100.0)
	Clinical failure[1]	13 (4.6)	9 (3.2)	0	0
Clinical failure	Clinical success	9 (21.4)	5 (12.2)	28 (65.1)	31 (77.5)
	Clinical failure[1]	33 (78.6)	36 (87.8)	15 (34.9)	9 (22.5)

[1] Clinical failure/Indeterminate or Improving

Table 6-8: Percent Change from Baseline in Infection Measurements

	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate n (n/N1%)	**Linezolid n (n/N1%)**	**Tedizolid phosphate n (n/N1%)**	**Linezolid n (n/N1%)**
Day 2, N1	311	319	322	318
Any increase	34 (10.9)	33 (10.3)	16 (5.0)	24 (7.5)
0-<5% decrease	87 (28.0)	90 (28.2)	54 (16.8)	36 (11.3)
5-<10% decrease	31 (10.0)	31 (9.7)	24 (7.5)	30 (9.4)
10-<15% decrease	24 (7.7)	26 (8.2)	46 (14.3)	29 (9.1)
15-<20% decrease	20 (6.4)	24 (7.5)	38 (11.8)	33 (10.4)
20-<30% decrease	35 (11.3)	41 (12.9)	42 (13.0)	47 (14.8)
30-<40% decrease	25 (8.0)	17 (5.3)	26 (8.1)	35 (11.0)
40-<50% decrease	14 (4.5)	20 (6.3)	29 (9.0)	24 (7.5)
≥50% decrease	41 (13.2)	37 (11.6)	47 (14.6)	60 (18.9)
48-72 Hour, N1	298	298	324	317
Any increase	17 (5.7)	21 (7.0)	12 (3.7)	13 (4.1)
0-<5% decrease	10 (3.4)	7 (2.3)	9 (2.8)	4 (1.3)
5-<10% decrease	1 (0.3)	3 (1.0)	5 (1.5)	5 (1.6)
10-<15% decrease	10 (3.4)	10 (3.4)	8 (2.5)	9 (2.8)
15-<20% decrease	7 (2.3)	11 (3.7)	6 (1.9)	10 (3.2)
20-<30% decrease	18 (6.0)	17 (5.7)	39 (12.0)	37 (11.7)
30-<40% decrease	41 (13.8)	22 (7.4)	45 (13.9)	38 (12.0)
40-<50% decrease	35 (11.7)	41 (13.8)	32 (9.9)	36 (11.4)
≥50% decrease	159 (53.4)	166 (55.7)	168 (51.9)	165 (52.1)
Day 7-9, N1	292	290	307	307
Any increase	4 (1.4)	3 (1.0)	6 (2.0)	1 (0.3)
5-<10% decrease	0	1 (0.3)	0	0
10-<15% decrease	0	1 (0.3)	0	0
15-<20% decrease	2 (0.7)	0	0	0
20-<30% decrease	2 (0.7)	3 (1.0)	7 (2.3)	3 (1.0)
30-<40% decrease	3 (1.0)	1 (0.3)	5 (1.6)	6 (2.0)
40-<50% decrease	12 (4.1)	8 (2.8)	11 (3.6)	13 (4.2)
≥50% decrease	269 (92.1)	273 (94.1)	276 (89.9)	280 (91.2)
Day 11-13, N1	288	287	299	296
Any increase	1 (0.3)	1 (0.3)	2 (0.7)	0
5-<10% decrease	1 (0.3)	0	0	0
20-<30% decrease	1 (0.3)	1 (0.3)	3 (1.0)	2 (0.7)
30-<40% decrease	1 (0.3)	3 (1.0)	6 (2.0)	1 (0.3)
40-<50% decrease	3 (1.0)	1 (0.3)	0	5 (1.7)
≥50% decrease	281 (97.6)	281 (97.9)	287 (96.0)	286 (96.6)
Day ≥ 14, N1	293	287	298	300
40-<50% decrease	0	1 (0.3)		
≥50% decrease	293 (100)	286 (99.7)	292 (98.0)	295 (98.3)

Table 6-9: Investigator assessment of Clinical Response at PTE Visit by Presence/Absence of Fever at Baseline - ITT/ITT* populations

Presence/Absence of Fever at Baseline	Study TR 701-112 (ITT*) Tedizolid phosphate N = 323	Study TR 701-112 (ITT*) Linezolid N = 326	Study TR 701-113 (ITT) Tedizolid phosphate N = 332	Study TR 701-113 (ITT) Linezolid N = 334
Fever, N1	52	59	103	97
Clinical success, n (n/N1%)	45 (86.5)	51 (86.4)	100 (97.1)	91 (93.8)
No Fever, N1	271	267	229	237
Clinical success, n (n/N1%)	232 (85.6)	228 (85.4)	192 (83.8)	202 (85.2)

Table 6-10: Percentage of Patients Who Achieved a Greater than 50% Decrease from Baseline Surface Area at the 48-72 Hour Visit by Type of Infection – ITT/ITT* population

	Study TR 701-112 Tedizolid phosphate N = 323 n (%)	Study TR 701-112 Linezolid N = 326 n (%)	Study TR 701-113 Tedizolid phosphate N = 332 n (%)	Study TR 701-113 Linezolid N = 334 n (%)
Cellulitis/erysipelas	131	135	166	168
≥50% decrease from baseline	53 (40.4)	62 (45.9)	68 (41.0)	70 (41.7)
Infected Wound	96	96	98	98
≥50% decrease from baseline	43 (44.8)	46 (47.9)	58 (59.2)	43 (43.9)
Major Cutaneous Abscess	96	95	68	68
≥50% decrease from baseline	63 (65.6)	58 (61.1)	41 (60.3)	50 (73.5)

Table 6-11: Percentage of Patients Who Achieved a Greater than 50% Decrease from Baseline Surface Area at the 48-72 Hour Visit by Use of I&D –ITT/ITT* population

	Study TR 701-112 Tedizolid phosphate N = 323 n (%)	Study TR 701-112 Linezolid N = 326 n (%)	Study TR 701-113 Tedizolid phosphate N = 332 n (%)	Study TR 701-113 Linezolid N = 334 n (%)
I&D	148	153	175	177
≥50% decrease from baseline	89 (60.1)	85 (55.6)	95 (54.2)	87 (49.2)
No I&D	175	173	157	157
≥50% decrease from baseline	70 (40.0)	81 (46.8)	72 (45.9)	76 (48.4)

Table 6-12: Presence of Local Signs and Symptoms of the Primary ABSSSI Site by Post-Baseline Study Visit

Local Sign or Symptom of Infection	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 323 n(%)	Linezolid N = 326 n(%)	Tedizolid phosphate N = 332 n(%)	Linezolid N = 334 n(%)
Erythema (present)				
Day 2	312 (96.6)	316 (96.9)	328 (98.8)	321(96.1)
48-72 Hour Visit	293 (90.7)	291 (89.3)	309 (93.1)	298 (89.2)
Day 7	221 (68.4)	228 (69.9)	**256 (77.1)**	**231 (69.2)**
Day 11 (End of Therapy)	135 (41.8)	140 (42.9)	130 (39.2)	112 (33.5)
Day ≥ 14 (Post Therapy Evaluation)	37 (11.5)	36 (11.0)	45 (13.6)	47 (14.1)
Swelling (present)				
Day 2	299 (92.6)	311(95.4)	315 (94.9)	316(94.6)
48-72 Hour Visit	265 (82.0)	268 (82.2)	289 (87.0)	278 (83.2)
Day 7	160 (49.5)	163 (50.0)	**190 (57.2)**	**205 (61.4)**
Day 11 (End of Therapy)	63 (19.5)	68 (20.9)	**81 (24.4)**	**66 (19.8)**
Day ≥ 14 (Post Therapy Evaluation)	16 (5.0)	13 (4.0)	19 (5.7)	21 (6.3)
Localized Warmth (present)				
Day 2	318 (98.5)	313 (96.9)	313 (94.9)	312 (93.4)
48-72 Hour Visit	250 (77.4)	250 (76.7)	**273 (82.2)**	**252 (75.4)**
Day 7	**106 (32.8)**	**91 (27.9)**	144 (43.4)	145 (43.4)
Day 11 (End of Therapy)	30 (9.3)	38 (11.7)	35 (10.5)	37 (11.1)
Day ≥ 14 (Post Therapy Evaluation)	4 (1.2)	3 (0.9)	7 (2.1)	8 (2.4)
Tenderness or Palpation				
Day 2	304 (94.1)	309 (94.8)	317 (95.5)	309 (92.5)
48-72 Hour Visit	274 (84.8)	266 (81.6)	**278 (83.7)**	**260 (77.8)**
Day 7	159 (49.2)	157 (48.2)	**155 (46.7)**	**143 (42.8)**
Day 11 (End of Therapy)	57 (17.6)	66 (20.2)	63 (19.0)	53 (15.9)
Day ≥ 14 (Post Therapy Evaluation)	12 (3.7)	12 (3.7)	17 (5.1)	15 (4.5)
Pain (present)				
Day 2	285 (88.2)	286 (87.7)	250 (75.3)	224 (67.1)
48-72 Hour Visit	229 (70.9)	234 (71.8)	**182 (54.8)**	**147 (44.0)**
Day 7	108 (33.4)	110 (33.7)	**64 (19.3)**	**50 (15.0)**
Day 11 (End of Therapy)	30 (9.3)	35 (10.7)	26 (7.8)	19 (5.7)
Day ≥ 14 (Post Therapy Evaluation)	4 (1.2)	5 (1.5)	4 (1.2)	1 (0.3)
Fluctuance (present)				
Day 2	49 (15.2)	51 (15.6)	48 (14.5)	39 (11.7)
48-72 Hour Visit	29 (9.0)	23 (7.1)	32 (9.6)	24 (7.2)
Day 7	7 (2.2)	8 (2.5)	7 (2.1)	11 (3.3)
Day 11 (End of Therapy)	2 (0.6)	3 (0.9)	9 (2.7)	6 (1.8)
Day ≥ 14 (Post Therapy Evaluation)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

Induration (present)				
Day 2	271 (83.9)	264 (81.0)	263 (79.2)	265 (79.3)
48-72 Hour Visit	**251 (77.7)**	**225 (69.0)**	236 (71.1)	228 (68.3)
Day 7	177 (54.8)	167 (51.2)	166 (50.0)	177 (53.0)
Day 11 (End of Therapy)	101 (31.3)	101 (31.0)	**99 (29.8)**	**86 (25.7)**
Day $\geq$ 14 (Post Therapy Evaluation)	39 (12.1)	32 (9.8)	43 (13.0)	48 (14.4)
Drainage and/or Discharge				
Day 2	186 (57.6)	200 (61.3)	197 (59.3)	199 (59.6)
48-72 Hour Visit	126 (39.0)	138 (42.3)	**174 (52.4)**	**155 (46.4)**
Day 7	72 (22.3)	78 (23.9)	127 (38.3)	121 (36.2)
Day 11 (End of Therapy)	30 (9.3)	29 (8.9)	48 (14.5)	31 (9.3)
Day $\geq$ 14 (Post Therapy Evaluation)	9 (2.8)	12 (3.7)	16 (4.8)	12 (3.6)

Table 6-13: Regional or Systemic Signs of Infection of the Primary ABSSSI Site by Post-Baseline Study Visit

	Study TR 701-112		Study TR 701-113	
	Tedizolid phosphate N = 323 n(%)	**Linezolid N = 326 n(%)**	**Tedizolid phosphate N = 332 n(%)**	**Linezolid N = 334 n(%)**
Lymph node tenderness				
Day 2	255 (78.9)	258 (79.1)	175 (52.7)	160 (47.9)
48-72 Hour Visit			**90 (27.1)**	**73 (21.9)**
Day 7	130 (37.5)	125 (38.3)	15 (4.5)	17 (5.1)
Day 11 (End of Therapy)	32 (11.8)	38 (11.7)	11 (3.3)	11 (3.3)
Day ≥ 14 (Post Therapy Evaluation)	2 (0.6)	3 (0.9)	2 (0.6)	4 (1.2)
Lymph node increase in volume or palpable				
Day 2	245 (75.9)	239 (73.3)	169 (50.9)	166 (49.7)
48-72 Hour Visit			105 (31.6)	98 (29.3)
Day 7	121 (37.5)	124 (38.0)	31 (9.3)	32 (9.6)
Day 11 (End of Therapy)	38 (11.8)	43 (13.2)	20 (6.0)	11 (3.3)
Day ≥ 14 (Post Therapy Evaluation)	9 (2.8)	6 (1.8)	3 (0.9)	4 (1.2)
WBC ≥ 10,000/mm3 or < 4000/mm3				
Day 2	0	2 (0.6)		
48-72 Hour Visit	18 (5.6)	11 (13.4)	54 (16.3)	50 (15.0)
Day 7	42 (13.0)	39 (12.0)	51 (15.4)	37 (11.1)
Day 11 (End of Therapy)	36 (11.1)	39 (12.0)	64 (19.3)	49 (14.7)
Day ≥ 14 (Post Therapy Evaluation)	45 (13.9)	45 (13.8)	59 (17.8)	35 (10.5)

Part of the figures here are lifted from Sponsor's Table 14.2.24.1 on pp 1057-1063 of CSR for Study TR 701-112 and Table 14.2.22.1 on pp 648-654 of CR for Study TR 701-113. Data on WBC, immature neutrophils and temperature in Study TR 701-112 could not be found in the adss (ADAM) and ss (SDTM) datasets. Data on immature neutrophils and temperature in Study TR 701-113 is not available in adss (ADAM) dataset.

Table 6-14: Study TR 701-112 Pain Score using VAS by Study Visit

	Tedizolid phosphate		Linezolid	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline, n	316	NA	320	NA
Mean (SD)	60.8 (26.4)	NA	60.2 (26.9)	NA
Day 2, n	310	297	319	305
Mean (SD)	46.5 (27.2)	-14.0 (21.4)	46.5 (26.2)	-12.9 (22.1)
Day 3, n	68	62	58	57
Mean (SD)	32.9 (29.6)	-22.3 (25.0)	34.2 (26.9)	-21.3 (28.0)
Day 4-6, n	238	231	257	244
Mean (SD)	27.6 (23.8)	-34.3 (26.6)	28.6 (24.1)	-31.1 (28.0)
Day 7-9, n	288	275	288	274
Mean (SD)	14.2 (20.6)	-45.8 (29.3)	12.5 (18.2)	-46.0 (28.3)
Day 10-13, n	285	272	284	270
Mean (SD)	5.9 (12.4)	-53.0 (27.4)	4.8 (11.9)	-53.8 (27.5)

Table 6-15: Study TR 701-113 Pain Score using VAS by Study Visit

	Tedizolid phosphate		Linezolid	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline, n	330	NA	332	NA
Mean (SD)	62.7 (28.1)	NA	62.8 (26.8)	NA
Day 2, n	324	324	322	319
Mean (SD)	45.5 (27.7)	-15.6 (21.4)	41.4 (26.5)	-20.1 (22.6)
Day 3	163	163	154	152
Mean (SD)	26.4 (24.1)	-36.1 (28.2)	26.9 (25.8)	-37.4 (29.3)
Day 4-6, n	162	162	168	167
Mean (SD)	29.3 (27.5)	-29.5 (28.9)	23.2 (21.9)	-34.8 (28.2)
Day 7-9, n	305	305	306	303
Mean (SD)	12.3 (20.2)	-49.4 (30.7)	12.3 (18.7)	-49.3 (30.7)
Day 10-13, n	299	299	296	293
Mean (SD)	6.6 (14.8)	-54.5 (29.8)	6.4 (14.2)	-55.2 (29.9)

Table 6-16: Clinical Response at EOT by Subgroup - ITT/ITT* population

	Study TR 701-112 (MITT*)		Study TR 701-113 (MITT)	
	Tedizolid phosphate N = 323 n(%)	Linezolid N = 326 n(%)	Tedizolid phosphate N = 332 n(%)	Linezolid N = 334 n(%)
Age				
< 65years	294	302	43	33
Responder	254 (86.4)	263 (87.1)	39 (90.7)	28 (84.8)
≥ 65 years	29	24	289	301
Responder	27 (93.1)	22 (91.7)	250 (86.5)	266 (88.4)
Sex				
Male	198	195	225	214
Responder	169 (85.4)	169 (86.7)	199 (88.4)	189 (88.3)
Female	125	131	107	120
Responder	112 (89.6)	116 (88.5)	90 (84.1)	105 (87.5)
Race				
White	274	268	285	282
Responder	240 (87.6)	239 (89.2)	250 (87.7)	252 (89.4)
Black or African American	36	36	38	37
Responder	30 (83.3)	29 (80.6)	**32 (84.2)**	**29 (78.4)**
Asian or Pacific Islander	2	9	6	8
Responder	**2 (100.0)**	**7 (77.8)**	**5 (83.3)**	**8 (100.0)**
Other	11	13	3	7
Responder	**9 (81.8)**	**10 (76.9)**	2 (66.7)	5 (71.4)
Region				
North America	261	259	156	158
Responder	223 (85.4)	222 (85.7)	124 (79.5)	131 (82.9)
Europe	53	55	112	111
Responder	50 (94.3)	53 (96.4)	108 (96.4)	107 (96.4)
Rest of the World	9	12	64	65
Responder	**8 (88.9)**	**10 (83.3)**	57 (89.1)	56 (86.2)

Table 6-17: Investigator Assessment of Clinical Response at PTE by Subgroup - ITT/ITT* population

	Study TR 701-112 (MITT*)		Study TR 701-113 (MITT)	
	Tedizolid phosphate N = 323 n(%)	Linezolid N = 326 n(%)	Tedizolid phosphate N = 332 n(%)	Linezolid N = 334 n(%)
Age				
< 65years	294	302	289	301
Responder	249 (84.7)	258 (85.4)	252 (87.2)	263 (87.4)
≥ 65 years	29	24	43	33
Responder	28 (96.6)	21 (87.5)	40 (93.0)	30 (90.9)
Sex				
Male	198	195	225	214
Responder	167 (84.3)	165 (84.6)	203 (90.2)	187 (87.4)
Female	125	131	107	120
Responder	110 (88.0)	114 (87.0)	89 (83.2)	106 (88.3)
Race				
White	274	268	285	282
Responder	237 (86.5)	233 (86.9)	251 (88.1)	253 (89.7)
Black or African American	36	36	38	37
Responder	29 (80.6)	30 (83.3)	34 (89.5)	28 (75.7)
Asian or Pacific Islander	2	7	4	7
Responder	2 (100.0)	5 (71.4)	3 (75.0)	7 (100.0)
Other	11	15	5	8
Responder	9 (81.8)	11 (73.3)	4 (80.0)	5 (62.5)
Region				
North America	261	259	156	158
Responder	219 (83.9)	219 (84.6)	127 (81.4)	129 (81.7)
Europe	53	55	112	111
Responder	51 (92.2)	51 (92.7)	108 (96.4)	105 (94.6)
Rest of the World	9	12	64	65
Responder	7 (77.8)	9 (75.0)	57 (89.1)	59 (90.8)

Table 6-18: Clinical Response at EOT by Harder to Treat Subgroups - ITT/ITT* population

	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323 n(%)	**Linezolid N = 326 n(%)**	**Tedizolid phosphate N = 332 n(%)**	**Linezolid N = 334 n(%)**
BMI				
< 35 kg/m2	**287**	**288**	**280**	**288**
Responder	**249 (86.8)**	**249 (86.5)**	**247 (88.2)**	**254 (88.2)**
≥ 35 kg/m2	**36**	**38**	**52**	**46**
Responder	**32 (88.9)**	**36 (94.7)**	**42 (80.8)**	**40 (87.0)**
Diabetes Mellitus				
Diabetic	21	25	32	41
Responder	**17 (81.0)**	**23 (92.0)**	**25 (78.1)**	**38 (92.7)**
Not diabetic	302	301	300	293
Responder	264 (87.4)	262 (87.0)	264 (88.0)	256 (87.4)
IV Drug Use				
Current or recent IV drug User	117	132	66	74
Responder	105 (89.7)	114 (86.4)	**50 (75.8)**	**62 (83.8)**
Not a current or recent IV drug user	206	194	266	260
Responder	176 (85.4)	171 (88.1)	239 (89.8)	232 (89.2)
Renal Impairment				
Normal (CrCl >=90 mL/min)	264	277	263	266
Responder	231 (87.5)	241 (87.0)	230 (87.5)	235 (88.3)
Mild (CrCl 60-89 mL/min)	48	34	51	44
Responder	**40 (83.3)**	**31 (91.2)**	47 (92.2)	39 (88.6)
Moderate (CrCl 30-59 mL/min)	11	13	12	13
Responder	**10 (90.9)**	**11 (84.6)**	**7 (58.3)**	**12 (92.3)**
Severe (CrCl <30 mL/min)	0	2	3	1
Responder		2 (100.0)	2 (66.7)	1 (100.0)
SIRS Flag = Y	151	156	206	200
Responder	123 (81.5)	132 (84.6)	182 (88.3)	182 (91.0)
SIRS Flag = N	172	170	126	134
Responder	158 (91.9)	153 (90.0)	107 (84.9)	112 (83.6)

Table 6-19: Investigator's Assessment of Clinical Response at PTE by Harder to Treat Subgroups - ITT/ITT* population

	Study TR 701-112 (ITT*)		Study TR 701-113 (ITT)	
	Tedizolid phosphate N = 323 n(%)	**Linezolid N = 326 n(%)**	**Tedizolid phosphate N = 332 n(%)**	**Linezolid N = 334 n(%)**
BMI				
< 35 kg/m2	287	288	280	288
Responder	246 (85.7)	244 (84.7)	250 (89.3)	253 (87.8)
≥ 35 kg/m2	36	38	52	46
Responder	**31 (86.1)**	**35 (92.1)**	**42 (80.8)**	**40 (87.0)**
Diabetes Mellitus				
Diabetic	21	25	32	41
Responder	18 (85.7)	22 (88.0)	26 (81.3)	40 (97.6)
Not diabetic	302	301	300	293
Responder	259 (85.8)	257 (85.4)	266 (88.7)	253 (86.3)
IV Drug Use				
Current or recent IV drug User	117	132	66	74
Responder	99 (84.6)	110 (83.3)	53 (80.3)	63 (85.1)
Not a current or recent IV drug user	206	194	266	260
Responder	178 (86.4)	169 (87.1)	239 (89.8)	230 (88.5)
Renal Impairment				
Normal (CrCl >=90 mL/min)	264	277	263	266
Responder	226 (85.6)	237 (85.6)	233 (88.6)	233 (87.6)
Mild (CrCl 60-89 mL/min)	48	34	51	44
Responder	40 (83.3)	30 (88.2)	45 (88.2)	39 (88.6)
Moderate (CrCl 30-59 mL/min)	11	13	12	13
Responder	11 (100.0)	11 (84.6)	8 (66.7)	13 (100.0)
Severe (CrCl <30 mL/min)	0	2	3	1
Responder		1 (50.0)	3 (100.0)	1 (100.0)
SIRS				
SIRS Flag = Y	151	156	206	200
Responder	124 (82.1)	131 (84.0)	181 (87.9)	178 (89.0)
SIRS Flag = N	172	170	126	134
Responder	153 (89.0)	148 (87.1)	111 (88.1)	115 (85.8)

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/s/

MARGARET A GAMALO
05/08/2014

THAMBAN I VALAPPIL
05/08/2014

DIONNE L PRICE
05/08/2014
Concur with overall conclusion

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:	**Applicant:**	**Stamp Date:**
205435 & 205436	Trius Therapeutics	21 October, 2013
Sivextro (tedezolid phosphate) 200 mg Oral and IV	**NDA/BLA Type:**	**Goal Date**
	NDA, Priority Review (PDUFA V)	21 June, 2013

On **initial** overview of the NDA/BLA application for refuse to file (RTF):

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			See remark #7

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?

The Statistical Section of the NDA is fileable for both oral and IV formulations of TR-701 FA for the treatment of ABSSSI.

A total of 19 TR-701/FA clinical studies have been completed: 15 Phase 1 studies, 2 Phase 2 studies (TR701-104 and TR701-126) in patients with complicated skin or skin structure infections (cSSSI) or cellulitis or abscess, and 2 Phase 3 studies in patients with ABSSSI. The two Phase 3 studies conducted to support TR-701 FA for the treatment of ABSSSI are shown in Table 1.

Table 1: List of Efficacy Studies Included in Statistical Analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population	Endpoint
TR 701-112	phase 3, randomized, double-blind, non-inferiority	TR 701 FA QD × 6 days + placebo QD × 4 days Linezolid BID × 10 days	18-25 days after the EOT Visit (Day 11)	TR 701 FA: N=332 Linezolid: N=335	ABSSSI patients	Cessation of lesion spread and afebrile at 48 to 72 Hours
TR 701-113	phase 3, randomized, double-blind, non-inferiority	TR 701 FA QD × 6 days + placebo QD × 4 days Linezolid BID × 10 days	18-25 days after the EOT Visit (Day 11)	TR 701 FA: N=332 Linezolid: N=334	ABSSSI patients	≥20% reduction in lesion size at 48 to 72 Hours

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			SPA Agreement: June 2010 for TR701-112 and August 2011 for TR701-113
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			Final SAP submitted December 1, 2011 for TR701-112 and November 08, 2012 for TR701-113
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			See Remark #8

Remarks:

1. Efficacy Results. Table 2 shows the efficacy results of the two efficacy studies.

Table 2: Efficacy Results

Study	Treatment Arm	≥20% Reduction from Baseline at ECE	Difference (%) 95% Conf. Int.	Afebrile and Cessation at ECE	Clinical Response at EOT	Investigator's Assessment of Clinical Response at PTE
TR701-112	TR-701 FA	78.0 (259/332)	1.9	79.5 (264/332)	69.3 (230/332)	85.5 (284/332)
	Linezolid	76.1 (255/335)	(-4.5, 8.3)	79.4 (266/335)	71.9 (241/335)	86.0 (288/335)
TR701-113	TR-701 FA	85.2 (283/332)	2.6	85.8 (285/332)	87.0 (289/332)	88.0 (292/332)
	Linezolid	82.6 (276/334)	(-3.0, 8.2)	81.4 (272/334)	88.0 (294/334)	87.7 (293/334)

Early clinical evaluation (ECE) is at 48-72 hours after initiation of therapy. EOT Visit is at Day 11 and the PTE Visit happened 7 to 14 days after the EOT Visit. The LFU Visit happened 18 to 25 days after EOT.

There is apparent loss of response from the ECE Visit to the EOT Visit. This is primarily due to patients determined to be "indeterminate." Please see comment #8 for the details.

The information about clinical studies provided in the label uses both the >20% Reduction in Lesion Area from Baseline and the Investigator Assessed Clinical Response at Post-therapy Evaluation in ITT population. The reviewer thinks that the Clinical Response at EOT should be reported as well.

2. Frequency distribution of lesion. As requested during the Pre-NDA meeting held on 13 May, 2013, the Sponsor provided tables for the frequency distribution of the surface area of the lesion at baseline and at different visits during the trial. They also provided the frequency distribution of patients achieving different lesion area with cut-offs by infection type. Digital photos of primary lesions are also available.

3. Early clinical response by subgroup. There are some observed differences in the responders at the 48-72 hour visit by NSAIDs/oral steroids through 48-72 hour visit use and by Baseline lesion area with cut-offs at >300-600 cm2 and >1000 cm2 in Study TR701-112 as shown in the table below. Study TR701-113 also shows a slight difference in the NSAIDs/oral steroids through 48-72 hour visit use. Although these are probably spurious differences, investigations and sensitivity analysis that adjusts for these factors can be done.

Table 3: Early Clinical Response by Subgroup (TR701-112)

Subgroup	TR-701 FA (N = 332) n (%)	Linezolid (N = 335) n (%)	Difference (%)
NSAIDs/oral steroids through 48-72 hour visit	**18**	**18**	
Responders	11 (61.1)	14 (77.8)	-16.7
Baseline lesion area			
>300-600 cm^2	**44**	**45**	
Responders	30 (68.2)	36 (80.0)	-11.8
>600-1000 cm^2	**19**	**24**	
Responders	15 (78.9)	19 (79.2)	-0.3
>1000 cm^2	**21**	**14**	
Responders	15 (71.4)	13 (92.9)	-21.5

Based on Sponsor's Table

4. Listings for patients receiving confounding surgical procedure. During the Pre-NDA meeting, the Agency also requested if the Sponsor can identify patients with ABSSSI that were excluded from the CE-PTE EOT and CE-PTE population because of their receipt of confounding surgical procedure. These were provided in Listing 16.2.3.2: Reasons for Exclusion from Analysis Sets for TR701-112. A similar listing is also provided for TR701-113. Furthermore, tables for the type and timing of surgery performed for both TR-701 FA and linezolid treatment groups were also provided. See Comment #8 for the CRF request.

5. Regional differences. Some differences were noted between groups in early clinical response by geographic region in TR701-112. Early clinical response was seen in a higher percentage of patients treated with TR-701 FA in Europe (84.9% TR-701 FA vs 74.5% linezolid), while early response was seen in a higher percentage of patients treated with linezolid in Latin America (75.0% linezolid vs 66.7% TR-701 FA). There was little difference between groups in early clinical response in North America (78.9% TR-701 and 80.6% linezolid).

Some differences were also noted between groups in early clinical response in the other regions (Latin America, South Africa, and Australia/New Zealand), however, this may be due to fewer patients being enrolled in these regions.

Investigation of regional differences in responses needs to be performed, nevertheless.

6. CRF. CRFs were provided for a number of patients in the submission. The reviewer requests for a listing identifying whether the CRF is for a

- patient in the ITT analysis found to have an indeterminate response due to missing data
- patient excluded from the CE-EOT and CE PTE analysis sets for the following reasons: Missing data, did have response assessment, did not receive minimum dose amount and met unspecified disqualifying exclusion criteria.

In addition, please provide CRFs of the following randomly selected patients. Please provide an identifier for this set as well. See listing provided.

7. Datasets. Data were both provided in CDISC SDTM and ADaM format with accompanying SAS codes for the creation of ADaM datasets for the primary efficacy and key secondary analyses for the individual studies and for any integrated analyses across studies. The codes were written in ASCII format.

8. Indeterminate at EOT. Patients were defined as an indeterminate responder if any data needed to determine whether a patient was a clinical success or failure at the EOT Visit was missing (programmatic determination of response), or if the Investigator could not determine whether the patient was a clinical success or failure (response of indeterminate). By definition, patients with an indeterminate response were included in the denominator for analyses in the ITT and MITT analysis sets, and thus were considered failures. We have requested for the CRFs of these patients at the Pre-NDA meeting. They were probably part of the CRFs submitted although this needs to be verified.

Table 4: Requested Random CRF

TR-112		TR-113	
103-277	101-263	103-019	289-493
105-391	103-657	103-035	289-640
240-666	129-336	105-165	291-447
101-429	130-371	143-116	292-503
130-249	135-395	143-159	292-570
103-193	101-481	146-419	292-629
129-128	126-090	160-243	296-366
175-293	103-012	160-516	297-291
105-196	128-224	162-344	298-172
103-231	120-591	165-478	298-299
105-421	102-082	286-565	358-500
255-572	104-117	289-235	441-358
130-538	242-617	289-265	449-602
105-324	130-089	289-269	450-266
105-265	105-510	289-304	450-448
105-291		289-371	450-461
		289-474	

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/s/

MARGARET A GAMALO
12/02/2013

THAMBAN I VALAPPIL
12/02/2013