CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205436Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Memo

Date	(electronic stamp)
From	Katherine Laessig, MD
Subject	Deputy Division Director Summary Memo
NDAs #	205-435 and 205-436
Applicant Name	Cubist Pharmaceuticals, Inc.
Date of Submission	September 21, 2013
PDUFA Goal Date	June 21, 2014
Established (USAN) Name	Tedizolid phosphate, tradename Sivextro®
Dosage Forms / Strength	Tedizolid phosphate 200 mg tablet and 200 mg lyophilized powder for reconstitution and injection in single use vial
Approved Indications	Treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of designated Gram-positive bacteria
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package including:	**Names of discipline reviewers**
Medical Officer Review	Sheral Patel, Shrimant Mishra
Statistical Review	Margaret Gamalo-Siebers
Pharmacology Toxicology Review	Owen McMaster
Product Quality Reviews	Rajiv Agarwal, Robert Mello, Xuhong Li, Vinayak Pawar, Minerva Hughes
Microbiology Review	Avery Goodwin
Clinical Pharmacology and Pharmacometrics Reviews	Zhixia (Grace) Yan, Yongheng Zhang, Fang Li, Jeffry Florian
CDTL Review	Shrimant Mishra
Labeling Reviews	Carrie Newcomer, Christine Corser, Sharon Williams

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

1.0 Background

Cubist has submitted NDAs 205-435 and 205-436 in support of two formulations of their new molecular entity, tedizolid phosphate (hereafter referred to as tedizolid). The first formulation is 200 mg tablets, with a proposed dose and regimen of 200 mg orally once a day for six days. The second formulation is 200 mg lyophilized powder for reconstitution and injections, also with a proposed dose and regimen of 200 mg iv daily for six days.

Tedizolid phosphate is the second member in the class of antibacterial drugs known as oxazolidinones. Tedizolid phosphate is a prodrug that is rapidly converted in vivo by phosphatases to the active entity, tedizolid. Tedizolid acts by binding to the 50S subunit of the bacterial ribosome, resulting in inhibition of protein synthesis. Tedizolid has demonstrated activity in vitro and in vivo against Gram-positive organisms, including *Staphylococci* and *Streptococci*.

The regulatory history of tedizolid for the treatment of ABSSSI is somewhat complicated. This is due to the evolution in our understanding and recommendation of the appropriate primary endpoint to demonstrate noninferiority of a study drug to an approved comparator for this indication. At the time that the Phase 3 study, TR701-112 (henceforth referred to as Study 112), was designed, we were recommending a primary endpoint of cessation of spread of primary skin lesion compared to baseline, with temperature $\leq$ 37.6ºC (oral) and the next measurement within 24 hours is also $\leq$ 37.6ºC (oral), at the 48-72 h timepoint. This recommendation was based on our review of the literature to define the treatment effect of antibacterial drugs compared to placebo and was consistent with our draft guidance at the time. However, based on comments to the docket for the draft guidance, and work done by the Foundation of the National Institutes of Health, a new primary endpoint of reduction of the primary skin lesion by $\geq$ 20% at the 48-72 h timepoint was recommended for the second Phase 3 trial, TR701-113 (hereafter referred to as Study 113). The new endpoint is what is currently recommended in the final guidance for development of products for ABSSSI. The $\geq$ 20% reduction endpoint was included as a sensitivity analysis in Study 112.

Under the provisions of the Generating Antibiotic Incentives Now Act of the Food and Drug Administration Safety and Innovation Act of 2012, tedizolid tablets and powder for injection were granted Qualified Infectious Disease Product designation and therefore this application was granted a priority review. QIDP designation qualifies tedizolid for an additional five years of marketing exclusivity.

This memo will summarize important findings and conclusions by review discipline. For further details, please refer to discipline specific reviews and the CDTL memo by Shrimant Mishra, MD, MPH.

2.0 Product Quality

These NDAs have been reviewed by multiple product quality reviewers. Dr. Rajiv Agarwal conducted the review of the drug substance and drug products, Dr. Minerva Hughes conducted the review of the biopharmaceutics of the tablet, Dr. Robert Mello conducted the review of the product quality microbiology of the lyophilized powder for intravenous injection, and Dr. Bryan Riley has reviewed the product quality microbiology for the tablets. They have concluded that the information provided by the applicant is

sufficient to assure the identity, strength, purity, and quality of the drug, and that the proposed dissolution method and acceptance criterion are acceptable. The Office of Compliance has made a final recommendation of acceptable for the manufacturing establishments filed in this NDA. Major conclusions from their reviews are discussed below.

The drug substance, tedizolid phosphate, is manufactured (b) (4) Process development studies concluded that the tedizolid phosphate drug substance manufacturing process is well-controlled and robust.

The applicant amended the application with 12 more months of stability data. There was no observed change in (b) (4) bacterial endotoxins, or microbial limits for any of the test conditions. No trends were noted in (b) (4) impurity levels for the primary batches or the supportive batch for up to 48 months when held at 25°C/60% RH and 6 months at 40°C/75% RH. The stability data support a retest period (b) (4) when the drug substance is stored (b) (4) as defined by USP (b) (4) Dr. Mello accepts the endotoxin limits and the microbial limits specifications.

The drug product, tedizolid phosphate for injection 200 mg, is a sterile, lyophilized powder. It is isolated as the free phosphoric acid and is formulated as the disodium salt (b) (4) Each vial contains (b) (4) tedizolid phosphate. Following reconstitution with 4 mL of sterile water for injection, a final volume (b) (4) is obtained. This volume facilitates withdrawal of 4 mL of the 50 mg/mL of tedizolid phosphate solution. The acceptance criteria for each of the critical manufacturing process steps are in place to ensure the purity, quality, and strength of the lyophilized drug product can be maintained during the manufacturing process.

In use reconstitution stability studies were performed at the 12, 18 and 24 month timepoints for several batches. Stability data were also submitted for tedizolid phosphate for injection stored under the accelerated conditions of 40°C/75% RH for six months. The results indicate that there are no significant changes for any of the tests for reconstituted solutions after 24 hours storage at room temperature. The provided stability data support expiry of 36 months when stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature).

The drug product, 200 mg oral tablets, are available as immediate release, film-coated, yellow, oval tablets debossed with "TZD" on the obverse and "200" on the reverse side. Tedizolid phosphate tablets will be packaged in HDPE 40 cc bottles with white (b) (4) child resistant closure (b) (4) ((b) (4) tablets for commercial and (b) (4) tablets for physician's sample) or as blister packs ((b) (4) push/peel) with (b) (4) aluminum foil backing (six tablets). All excipients used in the manufacture of the tablets are listed in the FDA's Inactive Ingredient Guide at or below the levels outlined for oral formulations. Adequate in process tests and critical parameters and their acceptance criteria are in place to ensure the purity, quality, and strength of the tablet drug product can be maintained during the manufacturing process. The dissolution method and the proposed acceptance criteria (at release and during stability testing) are deemed acceptable to the Biopharmaceutics reviewer, Dr. Minerva Hughes. Dr. Bryan Riley accepts the microbial limits specification for the drug product. The stability data provided for packaging tablets in an HDPE bottle container/closure and (b) (4) foil blisters. A 36 month expiry is granted, when stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C (USP Controlled Room Temperature).

3.0 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. James Wild, recommends approval. He notes that the nonclinical toxicology data for tedizolid phosphate and tedizolid suggest relative safety for clinical administration of the clinical therapeutic dose of 200 mg tedizolid phosphate for up to 14 days. Major findings from his review include the following:

- Tedizolid phosphate was immunotoxic in animal studies at high doses. It also showed the potential to produce toxicities associated with mitochondrial protein synthesis inhibition and monoamine oxidase (MAO) inhibition, as well as effects consistent with transient neural impairment, but at exposures much higher than those expected to occur at the clinical therapeutic dose.
- In a rat fertility study, oral tedizolid had no adverse effects on the fertility or reproductive performance in male or female rats at plasma AUC exposures 4- and 5-fold greater than that in humans at the therapeutic dose. In embryofetal studies, tedizolid phosphate was shown to produce fetal developmental toxicities in mice, rats, and rabbits. Fetal developmental effects occurring in mice in the absence of maternal toxicity included reduced fetal weights and an increased incidence of costal cartilage anomalies. In rats, decreased fetal weights and increased skeletal variations including reduced ossification of the sternabrae, vertebrae, and skull

were observed at doses associated with maternal toxicity (reduced maternal body weights and mortality). In rabbits, reduced fetal weights but no malformations or variations were observed at doses associated with reduced maternal body weights and abortions. The no observed maternal effect levels (NOAELs) for fetal toxicity in mice (5 mg/kg/d) and maternal and fetal toxicity in rats (2.5 mg/kg/d) and rabbits (1 mg/kg/d) were associated with tedizolid plasma AUC values approximately equivalent to (mice and rats) or 0.04 fold (rabbit) the AUC value associated with the oral human therapeutic dose. The proposed pregnancy category is C.

- Tedizolid phosphate was negative for genotoxicity in all in vitro assays (Ames, Chinese hamster lung cell chromosomal aberration) and in all in vivo tests (mouse bone marrow micronucleus, rat liver unscheduled DNA synthesis). Tedizolid was positive in an in vitro Chinese hamster lung cell chromosomal aberration assay, but negative for genotoxicity in other in vitro assays (Ames, mouse lymphoma mutagenicity) and in vivo in a mouse bone marrow micronucleus assay. The weight of evidence suggests that tedizolid phosphate and tedizolid have limited potential to be genotoxic in humans.
- In safety pharmacology studies (neural, cardiovascular, respiratory, renal, and GI), limited tedizolid phosphate related effects occurred only at high doses. Hexobarbital induced sleep time was significantly increased with an oral dose of 100 mg/kg tedizolid phosphate. Spontaneous locomotor activity in mice was significantly reduced with oral administration of 30 and 100 mg/kg tedizolid phosphate. A high oral dose of 100 mg/kg tedizolid phosphate significantly increased urinary sodium and chloride concentrations and mean gastric volume was significantly reduced by 39% and mean total gastric acidity was reduced 48% (not statistically significant) while gastric pH remained unchanged. Tedizolid phosphate produced no significant effects in cardiovascular (hERG, isolated rat heart, and ECG in dog) and respiratory safety pharmacology studies.
- Serotonin syndrome and MAO inhibition have been reported for the other member of the oxazidolinone class, linezolid. In vitro studies with tedizolid phosphate and tedizolid indicated that tedizolid was a weak inhibitor of MAO-A and MAO-B with IC_{50} values comparable to linezolid. However, in a mouse head twitch experiment and a tyramine challenge experiment in rats, linezolid doses comparable to the human therapeutic dose produced positive results (increased head twitch or increased mean arterial blood pressure), but tedizolid phosphate doses associated with plasma tedizolid C_{max} and AUC values greatly exceeding the human exposures with recommended dosing did not.
- The nonclinical toxicity of tedizolid phosphate was investigated in rats and dogs in two-week, one-month, and/or three-month studies by both the IV and PO

routes. The major toxicities were hematopoietic (more pronounced in the rat and including decreased RBC, WBC, platelets and bone marrow hypocellularity), gastrointestinal, and injection site reactions (dog only). The systemic toxicities were dose and duration dependent, reversible, and occurred at tedizolid plasma exposures between four and ten times higher than the human exposure. At longer durations and higher exposures in the rate, toxicities to the liver (increased liver enzymes and hepatocellular centrilobular degeneration and atrophy), renal tubular degeneration, and reproductive organ degeneration and atrophy in both males and females were observed.

- The potential for peripheral and optic neuropathy was evaluated in a nine-month neurotoxicity study for oral tedizolid phosphate administered daily to pigmented rats. The results of this study indicated that tedizolid phosphate doses corresponding to seven to eight times the clinical plasma exposure did not change functional observational battery reactions or locomotor activity or produce peripheral nerve or ocular histopathology in rats. Clinical signs consistent with transitory neurotoxicity in the one-month IV rat toxicology study occurred only at C_{max} and AUC exposures in excess of 17 times that expected with clinical administration of the recommended dose.

4.0 Clinical Pharmacology

The clinical pharmacology team finds that the information provided by the applicant in support of these two NDAs is acceptable and supports the proposed dose and duration for the treatment of ABSSSI. Fourteen in vitro studies with human biomaterials were submitted, evaluating plasma protein binding, biotransformation of prodrug in plasma, metabolism in hepatic microsomes, and inhibition/induction of cytochrome P450 (CYP) enzymes and membrane transporters. Sixteen Phase 1 studies evaluating the PK of tedizolid phosphate and tedizolid were submitted. Studies included single and multiple dose PK (oral and IV), metabolism and elimination via mass balance and metabolite profiling, effect of food, hepatic impairment (moderate and severe), renal impairment (severe and ESRD in intermittent hemodialysis), age, effect on the pressor response of tyramine and pseudoephedrine, and impact on QT prolongation. Two supportive Phase 2 trials and two Phase 3 trials evaluating safety and efficacy were submitted. The major findings from the clinical pharmacology review are discussed below.

Tedizolid phosphate is a prodrug that is rapidly and extensively converted by phosphatases to tedizolid, the microbiologically active moiety, following oral and IV administration. Following multiple once daily oral or IV administration, steady-state concentrations are achieved within approximately three days with moderate drug

accumulation of approximately 30%. Steady state PK parameters following oral administration of 200 mg are as follows: $AUC_{0-\infty}$ of 25.6 mcg•h/mL, C_{max} of 2.2 mcg/mL, C_{min} of 0.44 mcg/mL, T_{max} of 3.5 h, and CL of 8.4 L/h. Following IV administration of 200 mg, steady state parameters were AUC_{0-24} 29.2 mcg•h/mL, C_{max} of 3.0 mcg/mL, C_{min} of 0.36 mcg/mL, T_{max} of 1.2 h, and CL of 5.9 L/h. Peak plasma tedizolid concentrations are achieved at approximately 3 hours following oral administration under fasting conditions or at the end of the one hour IV infusion. The absolute bioavailability is approximately 91% and no dose adjustment is necessary when changing from IV to oral administration. Tedizolid phosphate may be administered with or without food. Protein binding of tedizolid to human plasma proteins is approximately 70 to 90%. The mean steady state volume of distribution of tedizolid in healthy adults following a single IV dose of 200 mg ranged from 67 to 80 L (approximately twice total body water).

Tedizolid penetrates into the interstitial space fluid of adipose and skeletal muscle tissue with exposure similar to free drug exposure in plasma. Other than tedizolid, there are no other significant circulating metabolites in plasma. Following single oral administration of ^{14}C labeled tedizolid phosphate, 82% of the radioactive dose was recovered in feces and 18% in urine, primarily as a non-circulating and microbiologically inactive sulfate conjugate. Most of the elimination occurred within 96 hours. Less than 3% of the tedizolid phosphate administered dose is excreted as tedizolid.

Clinical studies demonstrated that no dose adjustment is needed for adolescent or elderly patients, males or females, patients with severe renal impairment, patients on hemodialysis, and patients with moderate to severe hepatic impairment. The population PK analysis identified ideal body weight and total bilirubin as significant covariates for tedizolid exposure. However, the impact of these two covariates as well as all other evaluated covariates (age, gender, race, ethnicity, renal or liver function) did not result in any clinically relevant changes (>20%) in tedizolid exposure.

In vitro, neither tedizolid phosphate nor tedizolid was shown to be a substrate/inhibitor/inducer of major CYP enzymes. Nor was either shown to be a substrate or inhibitor of major membrane transporters except for BCRP. Tedizolid inhibited BRCP with an IC_{50} of 51.1 μM; however, this is unlikely to be of clinical significance as the $C_{max, ss}$ of tedizolid ranged from 6-8 μM after oral and IV administration of 200 mg tedizolid phosphate once daily for six days.

Tedizolid is a weak and reversible inhibitor of MAO in vitro. Drug interaction studies with 200 mg once daily oral tedizolid phosphate showed no meaningful changes in blood pressure or heart rate with pseudoephedrine, and no clinically relevant increase in

tyramine sensitivity. Therefore, no restrictions are necessary on concomitant use of drugs with adrenergic or serotonergic activity or food containing tyramine. However, palpitations were reported in 21/29 [72.4%] subjects exposed to SIVEXTRO compared to 13/28 [46.4%] exposed to placebo in the tyramine challenge study.

The unbound $AUC_{0\text{-}24h}$ to MIC ratio (AUC/MIC) was the PK/PD parameter best associated with in vivo efficacy for tedizolid based on studies in the neutropenic mouse thigh infection model. In an MRSA infection produced in neutropenic mice, bacterial stasis was achieved at an *f*AUC/MIC ratio of approximately 50, corresponding to a total AUC/MIC ratio of approximately 250 for protein binding of 80%. In a study conducted in non-neutropenic animals, tedizolid activity against MRSA was enhanced by the presence of granulocytes by a factor of 25 (range from 16-35) compared to neutropenic animals. Based on this finding, a target unbound AUC/MIC ratio (adjusted for the previously obtained AUC/MIC ratio from neutropenic mice by a factor of 16) of 3 was identified, corresponding to a total AUC/MIC ratio of 15 (using an 80% protein binding factor). Because this finding of decreased activity of tedizolid in neutropenic mice has implications for neutropenia in humans, and neutropenia was an exclusion criterion in the Phase 3 clinical trials, information in Warnings and Precautions will be incorporated in the package insert for healthcare providers that efficacy and safety of tedizolid for ABSSSI in neutropenic patients has not been studied and to consider alternate therapy in neutropenic patients.

A flat exposure-response relationship was identified between tedizolid exposure (AUC_{SS}, AUC_{SS}MIC) and clinical response using combined data from the two Phase 3 studies. This observed exposure response relationship may be due, in part, to the clinical response rates (79.5%) observed with tedizolid treatment and the limited range of exposures resulting from the fixed 200 mg daily dose used in the Phase 3 studies. No efficacy differences were noted in the Phase 2 study with tedizolid doses of 200 mg, 300 mg, or 400 mg. Thus, it is likely that the exposures achieved with the dose administered in the Phase 3 trials are on the plateau of the exposure-response curve.

5.0 Clinical Microbiology

The clinical microbiology reviewer states that based on the clinical microbiology data submitted by the applicant, these NDAs may be approved. Major conclusions from Dr. Goodwin's review of the microbiology data are as follows:

- Data from surveillance and other investigator studies support the claim that tedizolid demonstrates in vitro activity against selected Gram-positive bacteria associated with ABSSSI. Specifically, tedizolid has demonstrated activity against

staphylococcal isolates from the US and Europe. These include isolates with the Panton-Valentine leukocidin (pvl) gene, vancomycin-intermediate and resistant *S. aureus* (VISA/VRSA) isolates; methicillin-susceptible coagulase-negative staphylococci; and methicillin-resistant staphylococci. The MIC values ranged from as low as 0.12 mcg/mL to 1.0 mcg/mL. Additionally, tedizolid appears to have limited activity against a number of linezolid-resistant *S. aureus* isolates. Against a subset of these isolates, MIC_{90} values of 8 mcg/mL were reported for linezolid resistant *S. aureus* isolates with MICs ranging from 0.25-16 mcg/mL. Tedizolid is active against *Streptococcus pneumoniae* with an MIC_{90} of 0.25, other beta-hemolytic streptococci (*S. pyogenes, S. agalactiae*) with an MIC_{90} of 0.5 mcg/mL, and viridans group streptococci with an MIC_{90} of 0.25 mcg/mL. Tedizolid also has in vitro activity against *Enterococcus faecalis* with MICs ranging from 0.5 to 1 mcg/mL and against *Enterococcus faecium* with MIC_{90} values from 0.25 to 1 mcg/mL.

- Tedizolid inhibits bacterial translation and protein synthesis, including mitochondrial protein synthesis. Resistance is mediated through mechanisms that include mutations in genes encoding the 23S rRNA, the ribosomal proteins L3 and L4, and/or the acquisition of the *cfr* methyltransferase gene. In vitro studies have demonstrated the selection of tedizolid resistance in certain staphylococcal and entercoccal isolates during serial passages, and these mutants were cross-resistant to linezolid. However, under laboratory conditions, tedizolid demonstrated activity against cfr+ isolates of *S. aureus*.
- In vitro studies evaluating the fractional inhibitory concentration indices of tedizolid in combination with a wide array of antimicrobial agents showed no apparent antagonism or synergy against both Gram-positive and Gram-negative bacteria. Tedizolid penetrates human macrophages and exhibits enhanced cellular accumulation that is both pH and temperature dependent. Tedizolid exhibits an intracellular to extracellular ratioof 10 to 14. Dose dependent activity was demonstrated against the intracellular pathogens, *Listeria monocytogenes and Legionella pneumophila.*
- The applicant has provided data from a number of animal models including staphylococcal systemic infections in mice, enterococcal systemic infections in mice, streptococcal systemic infections in mice, MRSA skin and soft tissue infections in mice, mouse thigh infection model with MRSA and MSSA, rat skin and soft tissue infection, lung infection and epithelial lining fluid exposure in mice, a neutropenic mouse pneumonia model, a *S. aureus* endocarditis model in rabbits, and a mouse *Streptococcus pneumoniae* model. Effectiveness of tedizolid was demonstrated in all animal models that were evaluated.

- The applicant has proposed and the clinical microbiology and clinical pharmacology reviewers agree on the proposed susceptibility interpretive criteria as shown in Table 1 below.

Table 1 Susceptibility Test Interpretive Criteria for SIVEXTRO

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2	≥19	16-18	≤15
Streptococcus pyogenes	≤0.5	-	-	≥18	-	-
Streptococcus agalactiae	≤0.5	-	-	≥18	-	-
Streptococcus anginosus Group*	≤0.25	-	-	≥17	-	-
Enterococcus faecalis	≤0.5	-	-	≥19	-	-

S=susceptible, I=intermediate, R=resistant

*Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

6.0 Summary of Clinical Efficacy

The biometrics reviewer and the CDTL (who also did the primary medical officer review of efficacy) conclude that the applicant has demonstrated substantial evidence of the efficacy of tedizolid for the treatment of ABSSSI as the results of the two Phase 3 trials demonstrate that tedizolid is noninferior to the comparator, linezolid. Therefore, they recommend approval. I concur with their assessment.

These NDAs contain the results of two Phase 3 trials, Studies 112 and 113. Both were randomized, double-blind, double-dummy, multicenter, noninferiority trials comparing either oral (Study 112) or intravenous with a switch to oral (Study 113) tedizolid 200 mg daily for a treatment duration of six days to oral (Study 112) or intravenous with a switch to oral (Study 113) linezolid 600 mg every 12 hours for 10 days. Both studies enrolled subjects with ABSSSI, including cellulitis/erysipelas, major cutaneous abscess, and wound infections. Subjects were randomized 1:1 to study treatment and stratified by the presence/absence of fever (Study 112 only), geographic region, and specific type of

ABSSSI infection. Six hundred sixty-seven adults from 82 sites globally were enrolled in Study 112 while 666 subjects from 130 sites globally were enrolled in Study 113.

The primary objective for both studies was to determine the noninferiority of tedizolid compared to linezolid for the primary endpoint of early clinical response. As noted earlier, the definition of early clinical response was slightly different for the two trials. In study 112, subjects who had, by the 48-72 hour visit, cessation of spread of the primary lesion compared to baseline (no increase in surface area as calculated by measuring length times width) and temperature $\leq$ 37.6 ºC orally and the next measurement within 24 hours of the 48 to 72 hour visit was also $\leq$ 37.6 ºC orally were considered responders. For trial 113, a subject was defined as a responder at the 48-72 hour visit if they had $\geq$ 20% reduction in the area of erythema, edema, and/or induration (length times width) compared to baseline. For each trial, the primary endpoint from the other Phase 3 trial was assessed as an important sensitivity analysis.

For both trials, the two arms were balanced with respect to baseline demographics, fever, type of infection, anatomical site of infection, prior medications (including antibacterial drugs) and/or procedures such as incision and drainage (I&D), and baseline symptoms of the primary ABSSSI infection.

There were several secondary outcomes of interest including the clinical response at end-of-therapy (EOT) that was performed 11-13 days after the first receipt of study drug in the intent-to-treat (ITT) population, the investigator's assessment of clinical success at the post-therapy evaluation (PTE) visit that was 7-14 days after the EOT visit, and outcome by baseline pathogen isolated. Clinical response as assessed by the investigator was defined as resolution or near resolution of all signs and symptoms observed at baseline, absence or near resolution of systemic signs of infection if present at baseline, and no new signs, symptoms, or complications attributable to ABSSSI that would require further antibacterial therapy for the primary lesion.

Note that the applicant identified issues at three sites in Study 112 such 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 who were excluded from all analysis populations.

The results for early clinical response and the investigator's assessment of clinical success at PTE are depicted for both trials in Tables 2 and 3, respectively.

Error! Reference source not found. The lower bound of the 95% confidence interval (CI) for the difference in early clinical response rates for tedizolid compared to linezolid in Trial 112 is -6.2 and in Trial 113 is
-3.5, which is greater than the prespecified noninferiority margin of -10%, indicating that tedizolid is noninferior to linezolid for the treatment of ABSSSI. In addition, the lower bounds of the 95% CIs of the secondary analyses using the primary endpoint from the other Phase 3 trial are also greater than -10%, demonstrating that the conclusion would be the same whether the cessation of lesion spread plus afebrile status definition or the ≥ 20% reduction in lesion size definition is used.

Table 3: Investigator Assessed Clinical Response at Post-therapy Evaluation in ITT and CE Patient Population from Two Phase 3 ABSSSI Trials

	SIVEXTRO (200 mg) n/N (%)	Linezolid (1200 mg) n/N (%)	Treatment Difference (2 sided 95% CI)
Trial 112			
ITT	277/323 (85.8)	279/326 (85.6)	0.2 (-5.3, 5.6)
CE	257/270 (95.2)	260/273 (95.2)	-0.0 (-3.9, 3.7)
Trial 113			
ITT	292/332 (88.0)	293/334 (87.7)	0.3 (-4.8, 5.3)
CE	268/290 (92.4)	269/280 (96.1)	-3.7 (-7.7, 0.2)

The results at EOT are in good alignment with the early clinical response rates and the success rates at PTE (data not shown).

Table 4 shows the results of the outcomes by baseline pathogen in the microbiologic intent-to-treat population (MITT). The outcomes across pathogens listed are fairly

consistent, though beyond *S. aureus* sample sizes are too small to draw definitive conclusions, and therefore these bacterial species will be included as part of the indication.

Table 4. Clinical Outcome at PTE By Baseline Pathogen (MITT Population)

	Clinical Response at PTE	
Pathogen	**SIVEXTRO (200 mg) n/N (%)**	**Linezolid (1200 mg) n/N (%)**
Staphylococcus aureus	299/337 (88.7)	314/354 (88.7)
Methicillin-resistant *S. aureus*	127/150 (84.6)	129/156 (82.7)
Methicillin-susceptible *S. aureus*	172/187 (92.0)	185/198 (93.4)
Streptococcus pyogenes	30/33 (90.9)	19/20 (95.0)
Streptococcus anginosus Group	23/32 (71.9)	24/28 (85.7)
Streptococcus agalactiae	8/9 (88.9)	7/9 (77.8)
Enterococcus faecalis	7/10 (70.0)	5/5 (100.0)

Notes: Pooled analysis; n=number of patients in the specific category; N=Number of patients with the specific pathogen isolated from the ABSSSI.
*** Baseline bacteremia in the tedizolid arm with relevant pathogens included two subjects with MRSA, four subjects with MSSA, two subjects with *S. pyogenes*, one subject with *S. constellatus,* and one subject with *S. agalactiae.*

7.0 Summary of Clinical Safety

The medical officer conducting the primary safety review and CDTL conclude that adequate evidence of safety has been provided to support the use of tedizolid for the treatment of adults with ABSSSI. I concur with their assessment.

The data supporting the safety of tedizolid comes from multiple Phase 1 studies, two Phase 2 trials, and two Phase 3 trials. In the Phase 1 studies, there were 437 subjects enrolled, who received formulations of oral or intravenous tedizolid as a single oral dose of 50 to 1200 mg, multiple oral administrations of 200 to 400 mg per day for up to 21 days, single IV infusions from 50 to 400 mg, and multiple IV infusions of 200 or 300 mg per day for up to seven days.

In the Phase 2 and 3 trials, there were 1048 subjects who received tedizolid phosphate at doses $\geq$ 200 mg for treatment of complicated skin and skin structure infections or ABSSSI. The most common treatment emergent adverse events, occurring at $\geq$ 2% incidence, were diarrhea, nausea, vomiting, abscess, cellulitis, dizziness, and headache. In the Phase 3 trials, treatment emergent adverse events occurring at $\geq$ 2% incidence in

the gastrointestinal disorders system or organ class (SOC) were numerically lower in the tedizolid arm compared to the linezolid arm (16 vs. 23%, respectively).

There were three deaths reported during the development of tedizolid. An 86 year old man enrolled in Study 112 in Peru died of septic shock. An 84 year old man enrolled in Study 113 in South Africa died of myocardial infarction. Both of these subjects received tedizolid. There was one death in a subject receiving linezolid in an HIV+ 33 year old woman enrolled in Study 113 in South Africa who died of tuberculous meningitis. None of the deaths appeared to be study drug-related. In the Phase 2 and 3 trials, nonfatal serious adverse events occurred in 1.8% of subjects receiving tedizolid. Infections and infestations was the most commonly reported SOC. There were two patients each with pneumonia, septic shock, and staphylococcal infection. Three patients had abscesses.

Adverse events of interest because of their known relationship with the other member of the oxazolidinone class, linezolid, were also evaluated. These included peripheral and ophthalmic neuropathy, myelosuppression, MAO-related drug interactions, serotonergic syndrome, lactic acidosis, hypoglycemia, and convulsions. In addition, the potential for tedizolid to cause QT prolongation, hepato- and nephrotoxicity was also assessed.

A thorough QT study showed that a single therapeutic or supratherapeutic dose of tedizolid did not prolong the QT interval in healthy volunteers. No patients met Hy's Law criteria who received tedizolid and potentially clinically significant changes in transaminases, bilirubin, and alkaline phosphatase were infrequent. Potentially clinically significant changes in blood urea nitrogen and creatinine were also infrequent.

Standardized MeDRA queries (SMQ) for optic nerve disorders in the Phase 2 and 3 trials found two patients who received tedizolid experienced this type of adverse event compared to one patient who received linezolid. The dictionary derived term for the AEs were for tedizolid: one subject with visual acuity reduced and one with visual impairment while the one linezolid treated subject experienced reduced visual acuity. SMQ analysis of peripheral nerve disorders of the Phase 3 studies found eight subjects who received tedizolid reporting such an AE, compared to four linezolid subjects. Using the dictionary derived terms, of the eight tedizolid subjects, there were four events of hypoaesthesia, one event of peripheral neuropathy, and three events of paraesthesias. Among the four linezolid subjects, one reported hypoaesthesia, three reported paraesthesia, and one reported sensory loss (one subject had more than one event).

The applicant conducted a dedicated Phase 1, open label ophthalmology and neurology safety study of 200 mg tedizolid po for 10 days and no clinically meaningful findings were noted. Results of a Phase 1 study suggest that with increased dose and duration of tedizolid therapy, there was a trend of decreases in platelets, white blood cell counts, and

red blood cell counts. In the Phase 2 and 3 trials, there were no subjects who experienced lactic acidosis, convulsions, or hypoglycemia. Monitoring for these events will be done as part of routine post-marketing pharmacovigilance. Information about hematologic, optic and peripheral nerve safety findings will be discussed in the Adverse Reactions sections of the package inserts.

9.0 Advisory Committee Meeting

The NDAs for tedizolid tablets and powder for injection were presented at a meeting of the Anti-infective Drugs Advisory Committee (AIDAC) on March 31, 2014. One question was posed to the committee:

1. Has the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of ABSSSI caused by susceptible isolates of the designated microorganisms?

   a. If yes, please provide any recommendations concerning labeling.

   b. If no, what additional studies/analyses are needed?

All committee members voted "yes". Some of the comments included the lack of a diverse patient population in the pivotal trials, the inadequacy of the adolescent data and the need to conduct pediatric trials, concern regarding the results of animal data regarding neutropenia, and concern that new safety issues may arise if longer durations of therapy are used.

10.0 Pediatrics

The applicant's proposed pediatric plan was present to the Pediatric Research Committee and the following PREA requirements were found acceptable:

> 1. Conduct a randomized Single-Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO (tedizolid phosphate) and Intravenous to Oral Comparator for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged 12 to <18 Years
>
> 2. Conduct a randomized, Single-Blind, Multicenter Safety and Efficacy Study of Intravenous to Oral SIVEXTRO (tedizolid phosphate) and Intravenous to Oral Comparator for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients Aged >3 Months to < 12 years.

3. Conduct an open-Label, Multicenter Study of 10-14 days IV SIVEXTRO (tedizolid phosphate) for hospital-acquired late onset sepsis in full term and preterm neonates and infants aged 5 days to ≤ 3 months.

4. Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and IV SIVEXTRO (tedizolid phosphate) in Patients 2 years to < 12 years of age.

5. Conduct a Phase 1 Single-Dose Safety and Pharmacokinetic Study of Oral and IV SIVEXTRO (tedizolid phosphate) in Inpatients Under 2 Years Old.

11.0 Other Regulatory Issues

Four sites and the applicant were selected for inspection by the Office of Scientific Investigations. Three were domestic, and one was in St. Petersburg, Russia. The latter was not inspected due to instability in U.S.-Russian international relations.

The classification for Cubist/Trius was NAI, and VAI for the three investigational sites. The data collected from these three sites appear generally reliable in support of the proposed indication. OSI concluded that, based on the inspectional findings from the three clinical sites and the applicant, that the Phase 3 trials were conducted adequately.

The carton and container labeling have been reviewed by ONDQA and DMEPA and recommendations incorporated. The proprietary name Sivextro has been found acceptable by DMEPA.

12.0 Benefit/Risk Assessment and Recommendation

I concur with the findings and the recommendations of the review team that sufficient evidence of safety and efficacy has been submitted to support the approval of tedizolid tablets and powder for injection for the treatment of adults with ABSSSI, caused by susceptible isolates of the designated bacteria. In addition, the benefit/risk assessment for tedizolid is favorable as it has been shown to be safe for its use as labeled in the package insert based on a safety database of over 1300 patients, and has demonstrated noninferiority to linezolid, a drug commonly used and approved for the treatment of skin infections.

As noted above, the Applicant has proposed pediatric studies to be completed to address requirements of PREA. In addition, they have agreed to a postmarketing requirement to evaluate for the development of resistance to tedizolid, as follows:

6. Conduct US surveillance studies for five years from the date of marketing SIVEXTRO to determine if resistance to tedizolid has developed in those organisms specific to the indication in the label for ABSSSI.

Katherine A. Laessig, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE A LAESSIG
06/13/2014