Merck Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	Comparative Assessment of Tedizolid Tissue Penetration and Pharmacokinetic Profile Between Diabetic Patients With Wound Infections and Healthy Volunteers via *In Vivo* Microdialysis
Request Date:	26-AUG-2015
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	***2.1.1 Primary Objectives:*** To describe the pharmacokinetic profile of oral tedizolid in the plasma and subcutaneous tissue of diabetic patients with ongoing wound infections of the lower extremities, i.e., below the knee, (study group) and compare it to the profile in healthy volunteers (control group) using *in vivo* microdialysis. ***2.1.2 Secondary Objectives:*** To describe the safety and tolerability of oral tedizolid in diabetic patients with diabetic foot infections and in healthy volunteers
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	The annual incidence of foot ulcers among diabetics has been estimated at between 6% to 11.5%, and 10 to 15% of those with diabetes will have at least one foot ulcer during their lifetime.[1] The majority (upwards of 60%) of these diabetic ulcers become infected.[2] Treatment of these complicated diabetic wound infections primarily involve surgical intervention, topical antiseptics, and systemic antibiotic therapy.[3] However, despite advances in these areas, outcomes from such infections remain poor and often lead to limb amputation in 15% to 20% of participants within 5 years.[4] Gram-positive organisms, particularly *Staphylococcus aureus*, are the main pathogens found in diabetic wound infections.[3] As antibiotic resistance rates have risen, methicillin-resistant *S. aureus* (MRSA) has also become more frequent in acute bacterial skin and skin structure infections (ABSSSI).[5] Additionally, diabetic wound infections caused by MRSA are associated with worse outcomes compared with other pathogens.[5,6] As a result, antibiotics targeting MRSA are often prescribed for the treatment of diabetic wound infections either as monotherapy, or in combination with other antibiotics to cover Gram-negative and anaerobic bacteria that also may be present. Tedizolid (Sivextro®, Cubist Pharmaceuticals Inc., Lexington, MA), the active moiety of the prodrug tedizolid phosphate, is an oxazolidinone antibiotic approved by the FDA for the treatment of ABSSSI caused by *S. aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Enterococcus faecalis*.[7] A 6-day course of tedizolid was well-tolerated and non-inferior to 10-day course of linezolid in Phase II and Phase III clinical trials of ABSSSI.[8,9,10] The pharmacokinetic profile of tedizolid has been described in numerous patient populations.[11] However, the penetration into tissue during an active infection has yet to be elucidated. The most accurate method to calculate overall penetration is to evaluate the entire drug exposure, or AUC, in the tissue of interest and compare this with the overall AUC in blood. In the setting of clinical infection, our group has successfully applied a technique called *in vivo* microdialysis to assess the interstitial (i.e., extracellular) concentration profile of antimicrobials in comparison to their systemic exposures.[12,13,14,15] This approach involves placing a probe with a semi-permeable membrane at the tip into tissue and constantly perfusing the probe with a physiologic solution via a pump; this approach allows for the continuous collection of extracellular fluid from the tissue and enables assessment of drug concentration over a specified time period (i.e., the entire dosing interval). Using this methodology, the penetration of a single 600 mg oral dose of tedizolid into muscle and subcutaneous adipose tissue of the thigh was assessed in 12 healthy volunteers.[16] Tedizolid demonstrated an $AUC_{tissue}/AUC_{plasma}$ ratio of 1.1 and 1.2 for adipose tissue and muscle, respectively, indicating excellent tissue penetration for the oral route of the drug administration into healthy volunteers. Although these data are promising, the

tissue penetration into actively infected tissue may vary from that of healthy volunteers. Furthermore, the dose tested was three-fold greater than the currently approved dosage of tedizolid. Because ABSSSI are very common in the diabetic patient and tedizolid may be a suitable oral therapeutic option, a study examining the tissue penetration of oral tedizolid in this population with ongoing infection is required to provide a more complete understanding of the pharmacokinetic profile of this novel compound. Hence a more comprehensive assessment of the interstitial fluid concentrations at the site of infection will serve as the pharmacologic basis for the clinical utility of tedizolid in the infected diabetic patient.

2.3 Study Design

2.3.1 Sites

The study will be conducted at Hartford Hospital, Hartford, CT. For participants enrolled in the study group (i.e., infected diabetic patients), all study interventions will occur while admitted as a Hartford Hospital inpatient. For participants enrolled in the control group (i.e., healthy adult volunteers), study interventions will occur in a study physician's office (baseline screening), at a local clinical laboratory (baseline laboratory screening), and in the Clinical Research Center (CRC) at Hartford Hospital.

2.3.2 Inclusion Criteria

2.3.2.1 Study Group

Participants with a documented medical history of Type 1 or Type 2 diabetes (for which they are receiving insulin or oral anti-hyperglycemic agents), and a suspected complicated skin and skin structure infection will be included. The suspected infection will be an ongoing and infection will be defined as mild or moderate by the Infectious Diseases Society of America,[17] or as Grade 2 or 3 by the International Consensus on the Diabetic Foot (Table 1).[18] Other anti-infective agents besides the study drug, except linezolid, will be permitted for the purposes of treatment.

Table 1. Clinical Classification of Infections

Clinical manifestations of infection	Infection severity[a]	PEDIS grade[b]
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of ≥2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a participant who is systemically well and metabolically stable but which has ≥1 of the following characteristics: cellulitis extending >2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a participant with systemic toxicity or metabolic instability (e.g., fever,	Severe	4

	chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)

[a] Infectious Diseases Society of America; [b] International Consensus on the Diabetic Foot; PEDIS, perfusion, extent/size, depth/tissue loss, infection, and sensation

2.3.2.2 Control Group

Male or female healthy adult (≥ 18 years of age) volunteers who will be identified via hospital and local advertisements (newspaper, postings, and internet) in the Greater Hartford, Connecticut region would be eligible to be enrolled.

2.3.3 Exclusion Criteria

Participants in the study or control group will be excluded if any of the following criteria are met:

1. Less than 18 years of age
2. History of hypersensitivity to tedizolid or linezolid
3. History of hypersensitivity to lidocaine or lidocaine derivatives
4. Pregnant or breastfeeding
5. Presence of anemia, thrombocytopenia, or leukopenia as defined by hematocrit, platelet, or white blood cell count < 75% of the lower limit of normal[7]
6. Concomitant receipt of linezolid
7. Any other reason felt by the investigator to potentially affect the outcomes of the study

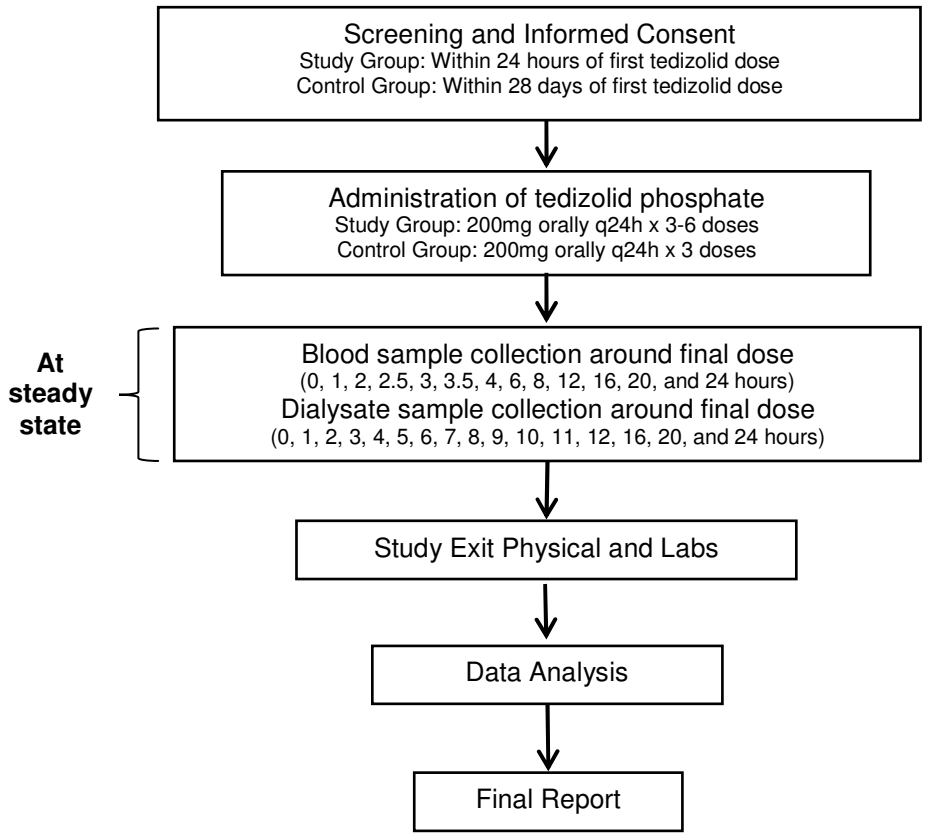
2.3.3.1 Additional Exclusion Criteria for Study Group

1. Participants likely to require multiple surgical interventions during the study period, which therefore could affect placement of the microdialysis catheter

2.3.3.2 Additional Criteria for Control Group

1. Positive urine drug screen (cocaine, THC, opiates, benzodiazepines, and amphetamines).
2. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for men (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of screening.
3. Use of tobacco- or nicotine-containing products in excess of the equivalence of 5 cigarettes per day.
4. Use of prescription or nonprescription drugs, vitamins, or dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication, with the exception of acetaminophen at doses of ≤ 1 g/day. Herbal supplements, hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing IUDs, postcoital contraceptive methods), and hormone replacement therapy must be discontinued at least 14 days prior to the first dose of study medication. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study medication.

2.4 Study Flowchart	



2.5 Study Procedures

2.5.1 Screening Procedure

2.5.1.1 Study Group

Electronic medical records of admitted diabetic patients who are being followed by podiatrists for infections of the lower limbs will be pre-screened to identify patients eligible for study enrollment through evaluating each patient's profile for the meeting of inclusion and exclusion criteria. Pre-screening will involve accessing patient's medical record to determine eligibility. If eligible, written informed consent will be obtained (see 2.5.2) followed by complete screening, which will include a physical exam, medical, surgical, and medication history and collection of blood and urine for laboratory assessment (see 2.5.5.1). Screening will occur within 24 hours of the first dose of tedizolid.

2.5.1.2 Control Group

Adult healthy volunteers will be identified via hospital and local advertisements (newspaper, postings, and internet) and will be initially pre-screened via phone interview. If eligible, all volunteers will be screened by a study physician within 28 days of the scheduled study period to confirm that inclusion and exclusion criteria are met after providing written informed consent (see 2.5.2). This will include a physical exam, medical, surgical, and medication history and collection of blood and urine for laboratory assessment (see 2.5.5.1).

2.5.2 Informed Consent

Prior to study enrollment, patients and healthy volunteers identified as eligible for the study will be approached for consenting, where they will be provided with written informed consent that will document their election and agreement to participate in the study. The consenting process will be conducted by the principal investigator, co-investigators, or trained research staff members. A copy of the signed consent will be provided to the participant and placed in the medical record (study group only).

2.5.3 Study Drug

All participants will receive tedizolid phosphate 200 mg orally every 24 hours. The study group will receive 3-6 doses, to allow flexibility in sample collection among other medical/surgical interventions required during his/her hospitalization. The control group will receive 3 doses to achieve steady-state before sample collection. All participants in the study group will also receive standard intravenous or oral antibiotic therapy to treat their diabetic foot infections.

2.5.4 Summary of Interventions

- Screening physical exam and baseline blood and urine laboratory assessment
- Administration of oral tedizolid phosphate to achieve steady-state
- Insertion of microdialysis probe by study physician (see 2.5.5.3)
- Collection of blood samples
- Collection of dialysate samples
- End of study physical exam and blood and urine laboratory assessment

2.5.5 Procedures

2.5.5.1 Baseline Participant Evaluations

At screening, eligibility will be verified using inclusion/exclusion criteria. A general physical examination, including pedal pulses (study group only), a medical/surgical/medication history and vital signs (temperature, blood pressure, heart rate, respiratory rate) will be conducted by the study physician. Clinical laboratory tests, including serum electrolyte panel, serum creatinine, liver function panel, complete blood count with differential, glycosylated hemoglobin (HbA1c)(study group only), albumin, and microscopic urinalysis will be performed unless drawn within the last three days and the participant is clinically stable. Urine pregnancy tests will be required for women of childbearing potential. Concomitant medications will be recorded. A blood sample for screening of common drugs of abuse (cocaine, tetrahydrocannabinol (THC), opiates, benzodiazepines, and amphetamines) will be collected (control group only).

Study group participants will be screened within 24 hours of first dose of tedizolid. Control group participants will be screened within 28 days of first dose of tedizolid.

2.5.5.2 Clinical Research Center (CRC) – (Control group only)

Once enrolled and confirmed eligible at baseline screening, control group participants will be admitted to the CRC at Hartford Hospital on the evening of Study Day -1. A second screening of selected control group participants, which will include a brief physical exam, vital signs, medical history, and repeat of all labs tested in 2.5.5.1 except for drugs of abuse screening, will take place. This is to confirm study eligibility is maintained. Study drug will be administered on Study Days 1, 2, and 3. A microdialysis catheter (see 2.5.5.3) will be inserted on Study Day 3, followed by blood and dialysate collection (see 2.5.5.5 and 2.5.5.6). A final end of study physical exam and collection of blood and urine for laboratory assessment will be conducted on Study Day 4 before discharge. On Study Days 1 and 2 (only), participants are permitted to leave the CRC for work/school or at discretion of the Principal Investigator after oral dosing and a 4 hour monitoring period. Participants must return to the CRC for dinner time (7pm) on the same day. During the remainder of the study (Day 3 and Day 4), participants will not be permitted to leave the CRC. Lunch and Dinner will be provided for participants while they are in the CRC. Participants must refrain from consuming caffeinated and alcoholic beverages during the study (Day -1 to Day 4)..

2.5.5.2 Microdialysis Procedure

A microdialysis probe (63 MD catheter; MDialysis Inc., N. Chelmsford, MA) with a membrane length of 30 mm and molecular cut-off of 20 kDa will be inserted into subcutaneous tissue near the margin of the wound (study group) or healthy thigh tissue (control group) via a guidance cannula, following a local injection of lidocaine 0.5% solution to minimize pain.[12] Specifically, for the study population a puncture hole will be made 10 cm away from the margin of the wound, in order to place the semi-permeable probe at the tip of the catheter within 5 cm of the wound (i.e., peri-ulcer area).[19] The microdialysis probe will be inserted just prior to the final planned tedizolid dose in all participants. The guidance cannula will then be removed, leaving the microdialysis probe implanted subcutaneously.

The microdialysis system will be connected and constantly perfused with lactated Ringer's solution (perfusate) at a flow rate of 2 µL/min with a microinfusion pump (CMA 107 microdialysis pump, CMA Microdialysis AB, Solna, Sweden). After a 30-minute baseline sampling period, sampling of the interstitial fluid will begin before the start of the final dose of oral tedizolid for baseline values. At the beginning of the final dose, sampling will occur as noted in section 2.5.5.6. Once dialysate sampling is complete, the probe will be calibrated by the retrodialysis technique over a 1-hour interval to assess recovery of the antibiotic through the dialysis membrane. A calibration standard concentration of tedizolid 100 µg/mL will be added to the perfusate and its rate of disappearance through the membrane will determine the recovery rate by obtaining a dialysate sample. Recovery of tedizolid via retrodialysis will be calculated as follows: % Recovery = 100 – ($Concentration_{dialysate}$ / $Concentration_{perfusate}$ × 100).

2.5.5.4 Study Drug Administration

Tedizolid 200 mg will be administered by the oral route every 24 hours for 3-6 doses (study group only) or for 3 days (control group only). The doses will be administered by the nursing staff on the morning of the study days with a glass of water. Each dose will be preceded by an 8-hour fast and followed by a 4-hour fast. A record log of the date and time of administration will be maintained.

2.5.5.5 Plasma Sample Collection

Blood samples to assess tedizolid concentrations will be collected over a 24-hour period after the final dose. Blood samples of 10 mL each will be collected through a Jelco® catheter at pre-determined time points. Blood sample times will be at 0 (just before administration of the final dose), 1, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 20, and 24 hours. Blood samples will be collected in a 10-mL BD Vacutainer® containing sodium heparin (green top). All blood samples will be immediately centrifuged (2,000 × *g* for 10 min) to collect the separated plasma, which will be stored in amber-colored polypropylene tubes to protect from light at -80 °C until concentration determination.

2.5.5.6 Dialysate Sample Collection

Interstitial fluid concentrations of the soft tissue in the lower extremity will be assessed by *in vivo* microdialysis. Participants will refrain from excessive movement during the sampling process. After catheter insertion, the probe will be perfused with lactated Ringer's solution for 30 minutes prior to sampling. A baseline dialysate sample (120 µL) will be taken over an hour after placement of the microdialysis catheters just before the administration of the final dose. Further dialysate samples of approximately 120 µL each will be collected at 0 (just before administration of tedizolid dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, and 24 hours. After all sampling is complete, recovery of the antibiotic through the dialysis filter will be assessed by the retrodialysis technique over a 1-hour interval. All dialysate samples will be collected in 200 µL microvials (CMA Microdialysis AB, Solna, Sweden), which will be additionally stored within amber-colored polypropylene tubes at -80 °C to protect against light and evaporation until concentration determination.

	2.5.5.7Protein Binding Analysis and Determination Protein binding studies will be conducted using Centrifree® Ultrafiltration devices (Millipore Corporation, Billerica, MA).. An additional blood sample of 20 mL will be collected at the estimated peak concentration (3 hours after the dose was administered) into two 10-mL BD Vacutainer® tubes containing sodium heparin (green top). Samples will be immediately centrifuged to collect the separated plasma. Approximately 0.9 mL of plasma will be transferred into six separate ultrafiltration devices, three devices per filter type, and centrifuged for 45 minutes at 25 °C at 2,000 × *g* to generate an ultrafiltrate volume of approximately 250 µL. In addition, an aliquot of plasma will be retained for total drug concentration determinations and will be kept frozen at -80°C. In addition, non-specific binding to the ultrafiltration membrane will be determined at a single tedizolid concentration similar to the peak observed in patients. For these studies, an aqueous standard of tedizolid will be prepared in accordance to manufacturer's recommendation and ultrafiltration will be performed as outlined above for both ultrafiltration devices.. Individual protein binding percentages will be applied to each participant's data at each time point to determine free plasma concentrations. The percentage of protein binding will be calculated using the following formula: % Protein Binding = 100 – ($Concentration_{ultrafiltrate}$ / $Concentration_{plasma}$ × 100). *2.5.5.8 Study Exit Evaluation* After completion of all sampling and removal of microdialysis catheters, an end of study exit evaluation will occur. This will include a full physical examination, including vital signs. Blood and urine will be collected to repeat all labs tested in 2.5.5.1, except for the pregnancy test and drugs of abuse screening. All abnormal determinations will be followed until resolution unless follow-up is determined to be unnecessary by the study physician. For the control group, participants will be discharged from the study after a 4 hour monitoring period from removal of microdialysis catheters. *2.5.5.9 Determination of Tedizolid Concentrations* Tedizolid concentrations in plasma, dialysate fluid, and aqueous standards will be assessed using validated high performance liquid chromatography (HPLC) assays at the Center for Anti-Infective Research and Development of Hartford Hospital.
2.6 Study Duration	IRB Submissions and Approval — 2 months Enrollment and Sampling of 10 Patients — 6-12 months Enrollment and Sampling of 6 Healthy Volunteers — 4 months Tedizolid HPLC — 1 month Pharmacokinetic Analysis — 1 month Final Report — 2 months
2.7 Statistical Analysis and Sample Size Justification	***2.7.1 Data Validation and Analysis*** The Principal Investigator will be responsible for the review, validation, and analysis of these data as collected and recorded by the study staff. ***2.7.2 Primary Endpoint:*** The primary endpoints of the study are to assess the penetration of tedizolid into infected skin tissue and compare it to the penetration into healthy skin tissue, as well as to assess the pharmacokinetics of tedizolid in plasma of both study populations.

	2.7.2.1 Primary Endpoint Definition: Percentage of tissue penetration of tedizolid will be defined based on the AUC in plasma and tissue and will be calculated as: AUC_{tissue} / *free*AUC_{plasma} × 100. Plasma pharmacokinetic parameters that will be estimated including: $AUC_{0\text{-}24\ (plasma)}$, elimination rate constant (K_e), half-life ($t_{½}$), total plasma clearance (CL_T), and Volume of distribution (V_d). ***2.7.3 Statistical Analysis*** Non-compartmental pharmacokinetic analyses for tedizolid will be conducted using Phoenix (version 6.3, Pharsight Corporation, Mountain View, CA). Pharmacokinetic parameters for plasma will be determined using each individual's plasma concentration-time profile. The maximum concentration (C_{max}) for each participant will be estimated by visual inspection of the concentration-time profiles. The log-linear trapezoidal method will be used to determine $AUC_{0\text{-}24\ (plasma)}$ for each participant. The elimination rate constant (K_e) will be estimated by the slope of the terminal portion of the concentration-time profile; half-life ($t_{½}$) will be calculated by $0.693/K_e$. Total plasma clearance (CL_T) will be calculated by Dose/$AUC_{0\text{-}24\ (plasma)}$. Volume of distribution (V_d) will be calculated by CL_T/K_e. All microdialysis concentrations will be corrected for recovery before pharmacokinetic analysis as follows: $Concentration_{tissue}$ = 100 × ($Concentration_{sample}$ / % *in vivo* recovery). The $AUC_{0\text{-}24\ (tissue)}$ will be assessed by the log-linear trapezoidal rule. Percentage of penetration into tissue will be calculated as follows: AUC_{tissue} / *free*AUC_{plasma} × 100. A Student's *t*-test will be used to compare the penetration ratio and pharmacokinetics of tedizolid between study and control groups. ***2.7.4 Sample Size Determination*** Ten patients with diabetic foot infection (Study Group) and six healthy volunteers (Control Group) are to be enrolled in the study. This is primarily a descriptive, controlled study to observe the exposure and penetration ratio of tedizolid into the interstitial fluid of infected tissue of diabetic patients and compare it to that of healthy volunteers. In similar study designs, 10 study patients were sufficient to describe the central tendency of these penetration estimates and some confidence of dispersion. Given reduced variability in healthy participants, 6 volunteers will be utilized.
2.8 Specific Drug Supply Requirements	Tedizolid phosphate 200 mg tablets will be provided by Merck, Inc. as an open label supply.
2.9 Adverse Experience Reporting	Participants will be monitored for any sign or symptom of adverse events throughout the course of the study. Unanticipated, life-threatening or fatal adverse events will be reported to the IRB, the manufacturer, and the Food and Drug Administration according to federal guidelines. All adverse events requiring medical attention will be treated by the study physician and will be recorded by the investigator. ***2.9.1 Definitions*** For the purpose of this study, an adverse event will be defined as any pathologic or unintended change in the structure (signs), function (symptoms), or chemistry (laboratory values) of the body associated with the use of the study drug, whether or

	not considered drug related, and will be categorized as one of the following: • MILD – present, but easily tolerated • MODERATE – discomfort that interferes with usual activities • SEVERE – incapacitating, inability to work or do usual activities A serious adverse event will be defined as any of the above which results in death or is immediately life-threatening, requires in-participant hospitalization, or is an important medical event that may jeopardize the participant or require medical intervention to prevent one of the previously mentioned outcomes. ***2.9.2 Relationship to Study Medication*** Relationship of the adverse event to the study medication (i.e., causality) will be evaluated according to the investigator's opinion, as one of the following: • Concurrent condition – unrelated to study drug • REMOTE adverse drug event – little or no temporal relationship to study drug • POSSIBLE adverse drug event – temporal relationship to study drug • PROBABLE adverse drug event – commonly associated with study drug • DEFINTE adverse drug event – reappeared on re-challenge of study drug ***2.9.3 Expectedness of Adverse Event*** As AEs are expected with the study medication, patients will be closely monitored throughout the study for any AE occurrence and will be managed accordingly by the study physician. All AEs will be recorded by the investigator as described in Section 2.9.4 below. ***2.9.4 Recording and Reporting an Adverse Event*** All adverse events requiring medical attention will be recorded by the investigator as such: categorization by severity (mild, moderate, or severe), established time frame (start and stop time), complete description of event, all interventions (medical and pharmacological), and causality. ***2.9.5 Recording and Reporting a Serious Adverse Event (SAE)*** All SAEs will be reported to the Institutional Review Board, sponsor, and the Food and Drug Administration according to Federal guidelines. A serious adverse event will be defined as any adverse event that results in death, is immediately life-threatening, requires or prolongs hospitalization, or is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the previously mentioned outcomes.
2.10 References	1. Margolis D, Malay DS, Hoffstad OJ, et al. Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008. Data Points #2 (prepared by the University of Pennsylvania DEcIDE Center, under Contract No. HHSA29020050041I). Rockville, MD: Agency for Healthcare Research and Quality. January 2011. AHRQ Publication No. 10(11)-EHC009-1-EF 2. Lipsky BA. New developments in diagnosing and treating diabetic foot infections. *Diabetes Metab Res Rev* 2008; 24 Suppl 1:S66-71. 3. Lipsky BA. Medical treatment of diabetic foot infections. *Clin Infect Dis* 2004; 39:S104-114. 4. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in participants with diabetes. *Diabetes Care* 1999; 22:382-387. 5. Tentolouris N, Petrikkos G, Vallianou N, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* in infected and uninfected diabetic foot ulcers. *Clin Microbiol Infect* 2006; 12:186-189. 6. Vardakas KZ, Horianopoulou M, Falagas ME. Factors associated with treatment failure in participants with diabetic foot infections: an analysis of

	data from randomized controlled trials. *Diabetes Res Clin Pract* 2008; electronically published ahead of print. 7. Sivextro® (tedizolid) Prescribing Information, Cubist Pharmaceuticals Inc. Lexington, MA. 2014. 8. Prokocimer P, Bien P, Surber J et al. Phase 2, randomized, double-blind, doseranging study evaluating the safety, tolerability, population pharmacokinetics, and efficacy of oral torezolid phosphate in participants with complicated skin and skin structure infections. *Antimicrob Agents Chemother*. 2011; 55:583-92. 9. Prokocimer P, De Anda C, Fang E et al. Tedizolid phosphate vs. linezolid for the treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. *JAMA*. 2013; 309:559-69. 10. Moran GJ, Fang E, Corey GR, Das AF, De anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2014;14(8):696-705. 11. Flanagan S, Passarell J, Lu Q, Fiedler-kelly J, Ludwig E, Prokocimer P. Tedizolid population pharmacokinetics, exposure response, and target attainment. *Antimicrob Agents Chemother*. 2014;58(11):6462-70. 12. Müller M, Haag O, Burgdorff T, et al. Characterization of peripheral-compartment kinetics of antibiotics by *in vivo* microdialysis. *Antimicrob Agents Chemother* 1996; 40:2703-2709. 13. Bhalodi AA, Housman ST, Shepard A, Nugent J, Nicolau DP. Tissue pharmacokinetics of cefazolin in patients with lower limb infections. *Antimicrob Agents Chemother*. 2013;57(11):5679-83. 14. Wiskirchen DE, Shepard A, Kuti JL, Nicolau DP. Determination of tissue penetration and pharmacokinetics of linezolid in patients with diabetic foot infections using *in vivo* microdialysis. *Antimicrob Agents Chemother*. 2011;55(9):4170-5. 15. Bulik CC, Wiskirchen DE, Shepard A, Sutherland CA, Kuti JL, Nicolau DP. Tissue penetration and pharmacokinetics of tigecycline in diabetic patients with chronic wound infections described by using *in vivo* microdialysis. *Antimicrob Agents Chemother*. 2010;54(12):5209-13. 16. Sahre M, Sabarinath S, Grant M, et al. Skin and soft tissue concentrations of tedizolid (formerly torezolid), a novel oxazolidinone, following a single oral dose in healthy volunteers. *Int J Antimicrob Agents*. 2012;40(1):51-4. 17. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):e132-73. 18. Lipsky BA, Berendt AR, Embil J, De Lalla F. Diagnosing and treating diabetic foot infections. *Diabetes Metab Res Rev* 2004; 20:S56-S64. 19. Walker M, Hadgraft J, Lane ME. Investigation of the permeability characteristics of peri-ulcer and whole ischaemic skin tissue. *Int J Pharm* 2008; 357(1-2):1-5.
2.11 Publication Plan	The results of this study would be presented at an international congress such as the Interscience Conference on Antimicrobial Agents and Chemotherapy. A final publication would be submitted to a peer-reviewed journal such as Antimicrobial Agents and Chemotherapy, Journal of Antimicrobial Chemotherapy, or International Journal of Antimicrobial Agents. One abstract and one manuscript are anticipated to be presented at the conference and published.