INSTRUCTIONS:

- *Prepare a document with the following sections. Note that, depending on the nature of what you are doing, certain sections below may not be applicable. Indicate this as appropriate.*
- *For any items described in the sponsor's protocol or other documents submitted with the application, you may reference the title and page numbers of these documents (include the Protocol Version date/number and Section number and/or heading). If you reference page numbers, attach those pages to this protocol. Limit attached pages to those referenced in this protocol.*
- *When you write a protocol, keep an electronic copy in iRIS. You will need to modify this copy when making changes.*
- *Omit starred (*) items if this is the activation of a protocol at a new site or sites that will be overseen by a principal investigator who will take separate and full responsibility for that site or those sites. Complete by describing information specific to the site(s). Do not repeat information in the approved protocol that applies to all site(s).*

1) Protocol Title

Include the full protocol title as listed on the application form.

Tolerability, Safety, and Efficacy of Tedizolid as Oral Treatment for Bone and Joint Infections

2) HSC Review History

If you have submitted this protocol for review by an external HSC, provide the previous study identification number and provide details of the review including the HSC name, date of review, and HSC contact information.

No previous review.

3) Investigator

Include the principal investigator's name as listed on the Application for Human Research.

Loren G. Miller, MD MPH

4) Objectives*

Describe the purpose, specific aims, or objectives.

State the hypotheses to be tested.

The objective of our study is to quantify the tolerability and safety of tedizolid for bone and joint infections, both hardware and non-hardware associated. The study will focus on tolerability (e.g., gastrointestinal), hematologic toxicities, and neurologic toxicities.

Tedizolid is a FDA approved antibiotic with an indication for skin and soft tissue infection. It's spectrum of activity is nearly all gram positive cocci, i.e., the primary causes of osteomyelitis. Unlike the other commercially available medication in its class, linezolid, tedizolid does not appear to be associated with hematologic and neurologic toxicities in short term and animal studies. However, longer term studies with tedizolid have not been performed.

This study is a pilot study. We realize that efficacy is of primary concern for treatment of bone and joint infection, but the purpose of this study is more exploratory and will focus primary on the tolerability/toxicity issues outlined above.

Additional outcomes will be measured, but these are not primary outcomes. We will measure efficacy of tedizolid, but comparative efficacy (e.g., compared to non-tedizolid based regimens) will not be measured based on small sample size and funding limitations. Of great importance to highlight is that clinical trials, even non-comparative ones, are extremely rare for bone and joint infection. Randomized clinical trials comparing one antibiotic to another for bone and joint infection are almost never performed in the current era.

Hypotheses:
1. Tedizolid is well tolerated for prolonged (≥ 4 weeks) courses of antibiotic therapy for patients with bone and joint infection
2. Tedizolid is safe for prolonged (≥ 4 weeks) courses of antibiotic therapy for patients with bone and joint infection
3. Tedizolid is effective for the treatment of bone and joint infection

5) Background*

Describe the relevant prior experience and gaps in current knowledge.

Describe any relevant preliminary data.

Provide the scientific or scholarly background for, rationale for, and significance of the Human Research based on the existing literature and how will it add to existing knowledge.

Bone and joint infection is a common infection seen in both general practice and in Infectious Disease specialty practices. Recent data suggest the incidence of bone and joint infection is increasing dramatically. More specifically, population-based U.S. data from Olmstead County showed that the incidence of bone and joint infection has doubled from rates 30 years prior. The reasons for this dramatic increase are unclear but believed to stem from the increased prevalence of co-morbidities, such as diabetes, in the general population. Bone and joint infection treatment is particularly problematic because it requires prolonged therapy for weeks or months, which incurs risk of treatment-related adverse side effects.

Treatment for bone and joint infection is not standardized, which allows a wide range of antibiotic therapy to potentially be given. Treatments include medications from many different antibiotic classes, which may be administered through intravenous (IV) therapy or oral therapy. Oral therapy is increasingly popular, as recent data suggest that oral therapy for bone and joint infection achieves similar cure rates to traditional intravenous therapies while avoiding risks associated with IV catheters such as thrombosis, clogged catheters, and catheter-associated infections. Oral therapies also avoid cost associated with IV therapy given at home or at infusion centers.

S. aureus is the most common cause of bone and joint infection. Methicillin resistant *S. aureus* (MRSA) are increasingly common and currently over half of all *S. aureus* are MRSA in most U.S. and non-U.S. medical centers. Treatment of *S. aureus*, MRSA, and other Gram-positive bone and joint infection with oral therapy has been difficult, as many of these organisms are not susceptible to oral antibiotics, with the exception of linezolid. However, linezolid is used to treat bone and joint infection with great trepidation, as prolonged linezolid therapy is associated with hematologic toxicity and neurologic toxicity such as peripheral and optic neuropathy. Most concerningly, these neurologic toxicities may be irreversible. Thus many patients receive IV therapy to treat bone and joint infection, which carries risk of nephrotoxicity (vancomycin), requires regular monitoring of renal functions and serum levels (vancomycin), and/or has high associated drug costs (daptomycin, ceftaroline).

Trauma-associated bone and joint infection is also a common problem. Victims of major trauma often suffer bone fractures, which require temporary or permanent use of orthopedic devices such as external-fixation pins, plates, and screws. Approximately 5% of these internal fixation devices become infected. Medical and surgical treatment of these infections incur significant costs. Coagulase negative *Staphylococci* are a common cause of these infections, and oral treatment options are similarly limited to linezolid, which again, is highly problematic to use as a prolonged therapy that is required for these infections.

Tedizolid is a new FDA-approved oxazolidinone antibiotic, available both intravenously and orally. Tedizolid has a favorable adverse event profile and low thrombocytopenia rates compared to linezolid, due to its potency against Gram-positive bacteria that allows it to be given as a significantly lower daily drug dose compared to linezolid, its lower systemic free drug exposure compared to linezolid, and its lower duration of treatment compared to linezolid. Further, the lower incidence of thrombocytopenia rates with tedizolid compared to linezolid may be due to its differential potential to inhibit mitochondrial protein synthesis, as shown in pre-clinical studies (Flanagan S, et al. Antimicrob Agents Chemother 2014 58:6462-70). At FDA-approved doses, tedizolid has hematologic side effects similar to that of placebo. Additionally, unlike linezolid, interactions with SSRIs appear unlikely. Drug-mitochondrial binding, which is believed to be the mechanism to which mid- and long-term toxicities of linezolid such as neuropathy are acquired, is not seen with tedizolid, suggesting that the side effects associated with long-term therapy of linezolid may not be found with tedizolid.

Given the large and increasing burden of disease of bone and joint infection and the increasing acceptability of oral antibiotics for its management, tedizolid holds promise as a well-tolerated oral therapy that can be used for patients with bone and joint infection when intravenous options are not pursued and other oral options are problematic. Harbor-UCLA Medical Center is a large tertiary care medical center and 1 of only 4 Level One trauma centers in the County of Los Angeles, the most populous County in the United States. The Infectious Disease consult service sees a high incidence of non-trauma and post-traumatic device-associated bone and joint infection. Use of prolonged antibiotics is common in this setting. We believe tedizolid addresses the unmet need for an oral antibiotic that is well-tolerated and efficacious for use as a prolonged therapy for bone and joint infection.

6) Setting of the Human Research

Describe the sites at which your research team will conduct the research. If applicable, describe:

- *Identify the site(s) where your research team will identify and recruit potential subjects.*

Potential subjects will be identified and recruited in the emergency department, outpatient clinics including the infectious disease clinic, and inpatient units at Harbor-UCLA Medical Center.

- *Identify the site(s) where your research procedures will be performed.*

Research procedures will be performed in the Emergency Department, Outpatient Clinics including the Infectious Disease Clinic, and Inpatient units at Harbor-UCLA Medical Center, as well as in buildings RB-2 and RB-3 on the Harbor-UCLA Campus. Specifically, the CTRC outpatient clinic in RB-3 will be used for the screening and enrollment visits as well as follow-up visits. Lab work will be performed in Room 235 of RB-3.

- *Composition and involvement of any community advisory board.*

Not applicable.

- *For research outside of the organization and its affiliates:*
  - *Site-specific regulations or customs affecting the research for research outside the organization.*
  - *Local scientific and ethical review structure outside the organization.*

Not applicable.

7) Resources Available to Conduct the Human Research

Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

We believe the study is very feasible to enroll. Based on previous rates of presentation of patients with bone and joint infection (approx. 4-7 new cases per week), we believe there will be more than an adequate number of eligible subjects for this study.

Describe the time that you will devote to conducting and completing the trial within the agreed trial period.

Dr. Miller will be contributing a 10%, or 1.2 month time commitment to the trial. A dedicated study coordinator will also help with the trial. A back up study coordinator will be available when the main study coordinator is unavailable.

Describe the number and qualifications of your staff, their experience in conducting research, their knowledge of the local study sites, culture, and society.

Study staff will include Dr. Loren Miller, Dr. Michael Bolaris, Dr. Pooja Modi, Bryn Launer, and Margarita Flores.

Dr. Miller has conducted numerous studies on bone and joint infection. He has extensive research experience in the area of MRSA infection and colonization. Over the last 6 years, Dr. Miller's group has enrolled over 3,500 subjects into epidemiologic studies and clinical trials focused on infectious diseases.

Dr. Michael Bolaris is an Infectious Disease physician at Harbor-UCLA and currently runs the antimicrobial stewardship program. He has experience in pharmaceutical and investigator-initiated trials as well as microbiological research.

Pooja Modi, MD has worked as a clinical research associate for the past two months and has experience enrolling patients into clinical trials during this time. She has completed 4 externships and observerships in Internal Medicine and thus has extensive experience in the inpatient setting from which we will recruit patients.

Bryn Launer has 3 years of experience recruiting participants into psychological research studies, and an additional year of experience recruiting patients at Harbor-UCLA. She is familiar with the hospital's online medical charting system, which will be used to identify potential patients.

Margarita Flores has over 8 years of experience recruiting patients into research studies. She is familiar with the staff at the emergency department as well as an extremely accomplished recruiter.

Describe your facilities.

Study recruitment and procedures related to the initial study visit will be carried out at Harbor-UCLA Medical Center in the Emergency Department, Inpatient units or Outpatient Clinics. Follow-up visits at week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, and week 13 after the first visit, will occur at the CTRC Outpatient Clinic in RB-3. All laboratory procedures will occur in the Miller lab in room 235 in RB-3. Study coordinators will be based out of the office in room 228 in RB-2.

Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

There are medical and psychological resources available through Harbor-UCLA Medical Center and appropriate referrals will be made should a subject experience an anticipated or unanticipated consequence of the research.

Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

The study team will be kept informed about the protocol with regular study team meetings during which we will discuss issues surrounding the study including any new findings, any changes to the protocol, subject withdrawals and assess recruitment efforts with regards to achieving study goals.

8) Prior Approvals

Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

This study has been approved for funding by Merck Pharmaceuticals. The grant was a peer-reviewed by personnel chosen by Merck.

9) Study Design

a) Recruitment Methods

Describe when, where, and how potential subjects will be recruited.

Dr. Loren Miller, the primary investigator, and his team will inform select hospital staff (e.g., Orthopedic Surgery, Infectious Diseases, Trauma Surgery/Limb Salvage Service) of the study and seek their assistance in identifying and notifying the study staff of possible subjects who have presented to the Emergency Department, Inpatient Units, or Outpatient Clinic with bone and joint infection.

The Investigator and study staff will also use the Harbor-UCLA Medical Center's Electronic Medical Records to screen for potential subjects. Additionally, the Investigator and study staff will review clinical cultures from the Harbor-UCLA Microbiological Laboratory to identify wound cultures growing *gram positive organism* and review the Electronic Medical Record to identify those cultures that were taken from bone and joint infections.

After identifying a potential patient, the Investigator or study staff will approach the subject's primary treatment team and ask for their permission to introduce the study and the study staff to the patient. Study staff will then present information about the study (See Recruitment Script V1.0) to see if they are interested. Permission will be sought from the subject by their primary treatment team before anyone outside the patient's primary treating team approaches them about the study.

Describe the source of subjects.

Subjects presenting to the Emergency Department, inpatient Units ,Outpatient Clinics or referred by a communityphysician with bone and joint infection will be recruited.

Describe the methods that will be used to identify potential subjects.

Either the Investigator, Dr. Loren Miller, who is an attending physician of Internal Medicine and Infectious Diseases, or other study staff or staff members of Harbor-UCLA Medical Center will identify potential subjects based on a clinical culture, chart review or diagnosis of bone and joint infection. The providers will first ask the subject for permission before any non-treatment team members of the study staff can approach the subject.

Describe materials that will be used to recruit subjects. Include copies of these documents with the application. For advertisements, submit the final copy of printed advertisements. When advertisements are taped for broadcast, provide the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the HSC reviews the final audio/video tape.

No materials will be used to directly recruit patients. Flyers will be given to select Inpatient and Outpatient Clinic staff. Flyers will also be given to physicians outside Harbor UCLA Medical Center. Once the physician identifies a potential patient and receives verbal consent from the patient, the physician will call the study staff. At that point the study staff will screen the patient via phone and a waiver of written consent will be utilized for screening purposes only.

Describe the amount and timing of any payments to subjects.

The subjects will be paid in cash for their follow up visits. They will be paid $30 for the visit on week 1, $35 for the visit on week 2, $40 for the visit on week 3, $40 for the visit on week 4, $45 for the visit on week 5, $45 for the visit on week 6, and $50 each visit for visits on weeks 7, 8, 9, 10, 11, 12 and 13.

The total amount of compensation will range between $240 and $585 based on the number of follow up visits the subject completes. All subjects will complete visits on Weeks 1,2,3,4,5, and 12. Subjects still taking the study drug at week 6 will be required to return for a Week 6 follow up visit. Subjects still taking the study drug at week 7 will be required to return for a week 7 follow up visit, and so on- while patients are receiving the study drug they will return for weekly follow up visits until they have completed the course, or until they have reached 12 weeks. Once subjects complete the course of the study drug, they will return for one additional weekly follow up visit (e.g. if a patient completes the study drug at 7 weeks, they will return for visits on weeks 1-8 and week 12). If subjects take the study drug for 12 weeks, they will return for a final follow up visit on week 13.

b) Inclusion and Exclusion Criteria*

Describe how you will screen for eligibility.

Describe the criteria that define who will be included or excluded in your final study sample.

For this investigation, we will use strict inclusion and exclusion criteria.

Inclusion criteria will include:
a) Treatment of bone and joint infection in which therapy for Gram-positive organisms is suspected or documented, as determined by the treating physician and treatment of at least 4 weeks is planned. Bone and joint infection and trauma-associated bone and joint infection will

defined clinically using radiologic (e.g., MRI) and/or surgical (e.g., intra-operative findings) definitions. All subjects must have confirmation (diagnosis mentioned in chart) by the patient's primary physician and consultants that the patients has or likely has bone and joint infection and requires prolonged antibiotic therapy.
b) Aged between 18 years and 85 years.
c) Plans to treat bone and joint infection in outpatient setting.
d) No limited planned course of antibiotics. Co-administration of other antibiotics that target other causative or potentially causative organisms (e.g., fluoroquinolones) is acceptable.
e) Able to come to the research clinic for study follow-up visits for the study period.

Exclusion criteria for subjects will include:
a) Planned prolonged hospitalization (> 1 week).
b) Pregnancy (all female subjects of childbearing age will be given a pregnancy test prior to enrollment) or breast feeding. If a women is of childbearing potential, she must consistently use two acceptable methods of contraception (IUD, injectable contraceptive, birth control patch, OCP, barrier method, abstinence) from baseline through the course of antibiotics (4-12 weeks). If a male patient's sexual partner is of childbearing potential, the male patient must acknowledge that they will consistently use an acceptable method of contraception as defined above from baseline through the course of antibiotics (4-12 weeks).
c) Comorbidities that, in the opinion of the investigator, are uncontrolled (e.g., diabetes, hypertension, psychiatric disease).
d) Peripheral or optic neuropathy.
e) Underlying hematologic cytopenias (e.g., baseline thrombocytopenia, or severe anemia, or leukopenia) as determined by the following limits from a baseline CBC/CMP obtained within the past 14 days. Note that if a CBC has not been performed within the past 14 days, a CBC will be performed on the day of enrollment prior to any study drug being administered to ensure the patient does not meet exclusion criteria. Cytopenias are defined as:

- Hemoglobin (Hgb) $\leq$ 8.0g/dL
- WBC $\leq$ 4,000 k/cumm
- Platelets $\leq$ 150,000 k/cumm

f) Severe hepatic dysfunction as defined by liver function tests (ALT, ALP, AST, total bilirubin) $\geq$ 3.0 times the upper limit of normal. as determined by the following limits from a baseline CMP obtained within the past 7 days. If a CMP has not been performed within the past 7 days, baseline levels may be used from a CMP performed within the past 2 months as long as another CMP is performed on the day of enrollment and the subject's levels are within the following limits.
g) Hypersensitivity to tedizolid or other oxazolidinone-class antibiotics or similar compounds.
h) Ongoing antibiotic-associated colitis.
i) A diet high in tyramine-containing foods such as pickled or fermented meats and cheeses, wine, or avocados per investigator discretion.
j) Concurrent use of sodium picosulfate (brand names: Sodipic Picofast, Laxoberal, Laxoberon, Purg-Odan, Picolax, Guttalax, Namilax, Pico-Salax and Prepopik).
k) Concurrent use of any monoamine oxidase inhibitors (MAOIs) or use of MAOIs within two weeks of starting the study medication.
l) Previous participation in the study.
m) Use of tedizolid for any condition in the past 3 months.

n) Any other medical, psychological, or social condition that, in the opinion of the Investigator, would prevent the patient from fully participating in the study or would represent a concern for study compliance or constitute a safety concern to the patient.

c) Local Number of Subjects

Indicate the total number of subjects to be accrued locally.

We will enroll subjects until we obtain 50 subjects who are analyzable and have completed all follow-ups through 12 weeks. The attrition rate for this study is unclear but we estimate a possible attrition rate of 10%, which would require enrollment of approximately 55 subjects.

If applicable, distinguish between the number of subjects who are expected to be enrolled and screen, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

We anticipate enrolling approximately 55 patients as we anticipate an approximate 10% attrition rate in order to have study outcomes for 50 subjects in total. However, the attrition rate for a study of this length is unclear and we may need to enroll a different number of subjects to achieve our analyzable population of 50 subjects.

d) Study-Wide Number of Subjects*

If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

This is the only enrollment site.

e) Study Timelines*

Describe:

- *The duration of an individual subject's participation in the study.*

Approximately 12 weeks of in person follow up visits, with a final phone call three months after completion of antibiotic treatment. Thus, the total duration of an individual subject will range from 16 weeks to 24 weeks.

- *The duration anticipated to enroll all study subjects.*

Approximately 16 months.

- *The estimated date for the investigators to complete this study (complete primary analyses)*

Approximately 2 years.

f) Study Endpoints*

Describe the primary and secondary study endpoints. Describe any primary or secondary safety endpoints.

The primary study endpoint is the tolerability of prolonged (≥ 4 weeks) courses of tedizolid antibiotic therapy for patients with bone and joint infection. CBC and a CMP (comprehensive chemistry panel including liver function tests) will be performed at the following intervals after initiation of tedizolid. We will administer standardized surveys about drug side effects and tolerability at all follow-up visits (weeks 1, 2, 3, 4, 5, 6 (optional), 7 (optional), 8 (optional), 9 (optional), 10 (optional), 11 (optional), 12). Adverse events will be measured using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 18.1 (or the most current version).

The secondary study endpoint is the safety of prolonged (≥ 4 weeks) courses of tedizolid antibiotic therapy for patients with bone and joint infection. CBC and a CMP (comprehensive chemistry panel including liver function tests) will be performed at the following intervals after initiation of tedizolid. We will administer standardized surveys about drug side effects at all follow visits (weeks 1, 2, 3, 4, 5, 6 (optional), 7 (optional), 8 (optional), 9 (optional), 10 (optional), 11 (optional), 12). Adverse events will be measured using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 18.1 (or the most current version).

The tertiary study endpoint is efficacy, which will be defined using criteria as determined by the subject's primary provider. Specifically, cure will be defined as no need for further antibiotics beyond the originally planned duration (i.e., 6 weeks for non-device associated bone and joint infection or until hardware removal for subjects with implants). Unplanned surgical procedures prompted by inadequate infection control will be categorized as treatment failure. We will also measure long-term efficacy by performing a phone survey 3 months after completion of antibiotics. Recurrence of signs or symptoms of bone and joint infection will be considered a long-term treatment failure. Confirmation of subjects self-report with medical record review will be performed on an as needed basis when categorization of self-reported outcomes is not clear.

g) Procedures Involved in the Human Research*

Describe and explain the study design.

The design of this study is a prospective, open-label, non-comparative clinical trial of tedizolid for the treatment of bone and joint infection. We will follow patients for between 16 and 24 weeks, depending on the length of their antibiotic treatment, for the purpose of determining tolerability, safety, and efficacy of prolonged use (≥ 4 weeks) of tedizolid in the treatment of bone and joint infection. Participants will be enrolled regardless of race, ethnicity, or gender (as long as they are within 18-85 years of age).

Subjects will be given tedizolid orally 200 mg once daily for duration of therapy of between 4 and 12 weeks. The exact duration of tedizolid therapy will be decided by the subject's treating physician. In other words, the primary/consulting physician who is managing the treatment of the patient's bone and joint infection will be the one who decides the length of the tedizolid treatment.

Safety and tolerability of tedizolid through this study will be guaranteed for 12 weeks. Provision of tedizolid therapy beyond 12 weeks is not guaranteed by the clinical trial as excessively prolonged therapy is associated with increased monitoring cost (e.g., subject payments, laboratory tests, clinic utilization costs). If patients require greater than 12 weeks of therapy for Gram-positive pathogens, study

staff will contact the subject's primary provider to arrange alternative oral or IV therapy. Medications will be provided by the Investigational Drug Service (IDS) on the LA BioMed/Harbor-UCLA campus, which supplies all research related medications to study subjects at our center.

Subjects will be enrolled as outpatients or as inpatients when discharge is expected in the near future (≤ 1 week). Dr. Loren Miller, the primary investigator, and his team will advise the hospital staff of the study and seek their assistance in identifying and notifying the study staff of possible subjects who have presented to the Emergency Department, Inpatient Floors, or Outpatient Clinic with bone and joint infection. The Investigator or study staff will approach the subject's primary treatment team and ask for their permission to introduce the study and the study staff to the patient. Study staff will then present information about the study (See Recruitment Script V1.0) to see if they are interested. Permission will be sought from the subject by their primary treatment team before anyone outside the patient's primary treating team approaches them about the study.

Once an interested patient is identified, study staff will explain the details of the study to the subject. If the patient is interested in participating, study staff will complete the informed consent process in a private setting in the patient's preferred language (English or Spanish).

Once informed consent is obtained, we will collect data on all subjects' demographics, co-morbidities, surgical history, pertinent microbiology results, and all concomitant medications using standardized forms. For exclusion criteria e) and f) regarding cytopenias and liver function, CBC/CMPs from the past 14 days will be evaluated through a medical chart review. Note that if a CBC has not been performed within the past 14 days, a CBC will be performed on the day of enrollment prior to any study drug being administered to ensure the patient does not meet exclusion criteria (see exclusion criteria e) and f)).

Upon confirmation of eligibility, the study coordinators will call the pharmacy, which will be the LA BioMed Investigational Drug Service (IDS). The research pharmacists at the LABioMed Investigational Drug Service (IDS) will dispense the medication to the subject. Subjects will be given detailed verbal instructions on the use of the medication in either English or Spanish as preferred by the subject. The subject will be given a medication diary and asked to record the time of day when they take each pill as well as any side effects or comments. The subject will be given a small card to keep on their person with information about the study and study staff and emergency contact information. The study staff will answer any questions that the subject has at this time and will encourage the subject to contact the study staff with any future questions.

The subject will present to the Clinical and Translational Research Unit (CTRU), the clinical site of the UCLA Clinical and Translational Science Institute (CTSI) on the Harbor-UCLA campus for follow up visits. These follow up visits will occur at week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12 and week 13. All subjects will return for follow up visitson weeks 1 – 5 and 12, and subjects still taking the study drug after week 5 will continue to return for weekly follow up visits until they complete the course or until they reach 12 weeks. Once subjects complete the course of the study drug, they will return for one additional weekly follow up visit (e.g. if a patient completes the study drug at 7 weeks, they will return for visits on weeks 1-8 and week 12). If subjects take the study drug for 12 weeks, they will return for a final follow up visit on week 13.

At each follow up visit, CBC and CMP (comprehensive chemistry panel including liver function tests) will be collected via a blood draw. This blood sample will be sent to Quest Diagnostics by the

CTSI/CTRU, an outside laboratory that is contracted with the CTSI/CTRU to process blood samples. Additionally, standardized surveys (See Data Collection Fields V 1.0, Neuropathy Scale V 1.0, attached) will be administered about drug side effects and tolerability, and adverse events will be measured using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 18.1 (or the most current version). At these follow up visits, we will also record data points relevant to defining the efficacy of the treatment, such as the duration of the antibiotic treatment, any unplanned surgical procedures prompted by inadequate infection control, recurrence of signs or symptoms of bone and joint infection, and any other relevant comments or observations from the subject. The subject will also be asked to bring their study drug medication bottle and medication diary in order to assess compliance. If a subject suspects pregnancy during a follow up visit, they will be given a pregnancy test and the study team will track their reported menstrual cycle. If the subject does become pregnant, they will be discontinued from the study drug. Study staff will follow and collect data on the course of the pregnancy and the health of the child for at least 6-8 weeks after delivery.

Patients with evidence of myelosuppression will continue to have weekly CBCs performed until resolution of the myelosuppression.

Subjects who are concurrently taking serotenergic agents while receiving the study drug will be monitored for signs and symptoms of serotonin syndrome at each scheduled follow-up visit. Symptoms of serotonin syndrome include agitation or restlessness, confusion, rapid heartbeat and high blood pressure, dilated (big) pupils, loss of muscle coordination or twitching muscles, muscle rigidity (stiffness), heavy sweating, diarrhea, headache, shivering and goose bumps.

The subjects will be paid in cash for their follow up visits. They will be paid $30 for the visit on week 1, $35 for the visit on week 2, $40 for the visit on week 3, $40 for the visit on week 4, $45 for the visit on week 5, $45 for the visit on week 6, and $50 each visit for visits on weeks 7, 8, 9, 10, 11, 12 and 13.

The total amount of compensation will range between $240 and $585 based on the number of follow up visits the subject completes. All subjects will complete visits on Weeks 1,2,3,4,5, and 12. Subjects still taking the study drug at week 6 will be required to return for a Week 6 follow up visit. Subjects still taking the study drug at week 7 will be required to return for a week 7 follow up visit, and so on- while patients are receiving the study drug they will return for weekly follow up visits until they have completed the course, or until they have reached 12 weeks. Once subjects complete the course of the study drug, they will return for one additional weekly follow up visit (e.g. if a patient completes the study drug at 7 weeks, they will return for visits on weeks 1-8 and week 12). If subjects take the study drug for 12 weeks, they will return for a final follow up visit on week 13.

A phone survey 3 months after the subject's completion of antibiotics will be performed. They will be asked about their overall well-being, recurrence of signs or symptoms of bone and joint infection and any self-reported medical conditions or adverse events (medical record review will be performed on an as needed basis when categorization of self-reported outcomes is not clear).

Provide a description of all procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks. Include procedures

being performed already for diagnostic or treatment purposes and differentiate between these and the procedures performed solely for the research.

All procedures will be performed either in the Emergency Department, Inpatient Wards and Critical Care Units (ICU, MICU, SICU, CCU, PCU) or Outpatient Clinics during study Visit 1 (enrollment). Subsequent study visits (week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12 and week 13) will take place in the CTRC Outpatient Clinic in building RB-3. Laboratory procedures are performed in RB-3, room 235.

Describe procedures taken to lessen the probability or magnitude of risks.

We have provided access to study staff 24/7 so that if study subjects or parents have concern of side effects from the treatment, they can call a coordinator.

Identify which procedures are being done as part of the Human Research and which are being conducted anyway for other reasons.

All blood tests, study medications and data collection are being done as part of human research.

Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Tedizolid is a new FDA-approved oxazolidinone antibiotic, available both intravenously and orally. Tedizolid has a favorable adverse event profile and low thrombocytopenia rates compared to linezolid, due to its potency against Gram-positive bacteria that allows it to be given as a significantly lower daily drug dose compared to linezolid, its lower systemic free drug exposure compared to linezolid, and its lower duration of treatment compared to linezolid. Further, the lower incidence of thrombocytopenia rates with tedizolid compared to linezolid may be due to its differential potential to inhibit mitochondrial protein synthesis, as shown in pre-clinical studies (Flanagan S, et al. Antimicrob Agents Chemother 2014 58:6462-70). At FDA-approved doses, tedizolid has hematologic side effects similar to that of placebo. Additionally, unlike linezolid, interactions with SSRIs appear unlikely. Drug-mitochondrial binding, which is believed to be the mechanism to which mid- and long-term toxicities of linezolid such as neuropathy are acquired, is not seen with tedizolid, suggesting that the side effects associated with long-term therapy of linezolid may not be found with tedizolid. Tedizolid will be used in this research to treat bone and joint infection in patients who need prolonged antibiotic treatment for 4-12 weeks.

Because the use of tedizolid as prolonged antibiotic therapy (4-12 weeks) has not been approved by the FDA, it is unknown whether this dosage level will significantly increase the risks associated with the use of the drug product. Therefore, we have obtained an IND from the FDA. We were notified that this IND, no. 133495 may proceed on 1/12/17.

Please note that while we are seeking an IND, this study does not meet the following IND criteria:
- Tedizolid is lawfully marked in the United States under the brand name Sivextro
- This research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for tedizolid (Sivextro). This is a pilot study only.

-This research is not intended to support a significant change in the advertising for tedizolid (Sivextro).
- This research is conducted in compliance with the marketing limitations described in 21 CFR §312.7.

Describe the source records that will be used to collect data about subjects. Attach all surveys, scripts, and data collection forms.

All data will be captured using the REDCap data collection system which is an online, secure database. A list of the data fields to be collected is attached (See Data Collection Fields, V1.0). Surveys administered to patients on enrollment and follow up visits are attached (See Data Collection Fields, V1.0, Neuropathy Survey V1.0). A script for enrollment is also attached (See Recruitment Script, V1.0). We will collect lab (chemistry and hematology) and microbiological (culture) reports extracted from the patient's EMR, including values, upper and lower limits of normal, and date and time of collection. We will collect a medication diary that each patient will complete that captures the timing of their daily dosage and any side effects (See Medication Diary V1.0, attached).

Describe what data will be collected including long-term follow-up.

Data will be collected for the initial visit and all the follow up visits. All data for follow up visits will be captured using the REDcap data collection system. A complete list of the data fields to be collected is attached (See Data Collection Fields, V1,0).

h) Data and Specimen Banking*

If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.

All banked/stored data will be kept in REDcap, a secure online database. Paper copies of PHI (contact info and ICFs) will be stored separately from the paper copies of other study data. The links between PHI and study data will be kept in password-protected computers and in locked cabinet files in room 228 of RB-2 on a locked floor of a secure building (RB-2). Access to study computers and files will be limited to study personnel approved by the IRB. Human research records including signed and dated consent forms and other PHI-containing documents will be stored for at least three years after the study has been completed. Only study personnel approved by the IRB will have access to the locked file cabinets.

List the data to be stored or associated with each specimen.

The specimens we collect will be blood draws for the CBC and CMP tests, which are tests run on blood to determine the cellular and chemical makeup of the blood. The data associated with each specimen will be limited to the subjects' ID number and visit number.

All specimens will be coded meaning these items will be labeled the subjects Study ID number and will include dates (case report forms) rather than his/her name and/or date of birth. We will maintain a separate password-protected key list/log (electronic file) linking each subject to their

Study ID and a hardcopy will be maintained separate from individual subject files in a separate locked filing cabinet. Access to study computers and files will be limited to study personnel.

Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

If other investigators request use of the data, written request must be performed and use of the data will be approved only by the Principal Investigator. Researchers must seek approval from their IRB and provide a copy of the approval to LABioMed study staff and HSC before any data is shared.

i) Data Management *

Describe the data analysis plan, including any statistical procedures.

The study is descriptive and thus no formal statistical analysis plan has been performed. The number of subjects chosen (n=50) is based on a sample size believed to have sufficient power to reassure clinicians that tedizolid is safe, tolerable, and efficacious for the treatment of native bone and hardware-associated bone and joint infection.

Of note, confidence intervals for safety and efficacy will be calculated. Confidence intervals for outcomes of low incidence (e.g., thrombocytopenia) will be approximately +/-3 - 7%. E.g., assuming n=50 subjects, a low incidence outcome with a probability of 2.5% will have 95% confidence intervals of <0.1%-6.8%. Outcomes with probabilities farther from 0% or 100% will have wider confidence intervals. For example, we anticipate cure rate will be 80%, in which assuming n=50, 95% confidence intervals will be 69%-91%.

Provide a power analysis.

Confidence intervals for safety and efficacy will be calculated. Confidence intervals for outcomes of low incidence (e.g., thrombocytopenia) will be approximately +/-3 - 7%. E.g., assuming n=50 subjects, a low incidence outcome with a probability of 2.5% will have 95% confidence intervals of <0.1%-6.8%. Outcomes with probabilities farther from 0% or 100% will have wider confidence intervals. For example, we anticipate cure rate will be 80%, in which assuming n=50, 95% confidence intervals will be 69%-91%.

Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

All source documents and specimens will be coded meaning these items will be labeled the subjects Study ID number and will include dates (case report forms) rather than his/her name and/or date of birth. We will maintain a separate password-protected key list/log (electronic file) linking each subject to their Study ID and a hardcopy will be maintained separate from individual subject files in a separate locked filing cabinet. Access to study computers and files will be limited to study personnel. Human research records including Informed Consent Forms

will be stored in locked file cabinets for at least three years after the completion of the study. Only study personnel approved by the IRB will have access to the locked file cabinets.

Describe any procedures that will be used for quality control of collected data.

All collected data will be reviewed by a second study coordinator and the study Principal Investigator for internal consistency and validity.

Describe how data and specimens will be handled study-wide:

- *What information will be included in that data or associated with the specimens?*

  All data and specimens will be labeled with the the subject ID number. Data (including Subject ID number and dates related to study procedures, etc.) will be entered into a secure online computer database, REDCap.

- *Where and how data or specimens will be stored?*

  Data will be stored on an online, secure database in password-protected computers in a locked office. Source documents including consent forms will be stored in locked file cabinets in a locked office of a secure building (room 228, RB-2). Specimens will be stored in a locked laboratory in a secure building (room 235, RB-3).

- *How long the data or specimens will be stored?*

  De-identified data will be banked for 25 years after the completion of the study. Source documents and other forms and/or data containing PHI or linking data with PHI will be stored for at least 3 years after the completion of the study.

- *Who will have access to the data or specimens?*

  The study investigators and the study personnel involved in the conduct of this research and analysis of the data.

- *Who is responsible for receipt or transmission of the data or specimens?*

  The study coordinators/staff as indicated in the study site Delegation of Authority Log is responsible for receipt or transmission of the data. The CTRU/CTSI is responsible for transmitting all collected blood samples from the follow up visits to Quest Diagnostics.

  How data and specimens will be transported?
  Any data if necessary to be shared amongst the investigators will be done through the use of the CTSI's REDCap system, an online secure database. The specimens will be transported per Quest Diagnostics' and the CTRU/CTSI's standards for transporting blood samples, as the CTRU/CTSI sends all blood samples collected at follow up visits to Quest Diagnostics for processing.

j) Confidentiality

Describe the local procedures for maintenance of confidentiality.

- *Where and how data or specimens will be stored locally?*

  All source documents/data will be maintained in Room 228 of Building RB-2 in a locked file cabinet in a locked office. Data will be stored digitally via the REDCap system, an online secure database. Specimens will be stored in a locked laboratory in a secure building (room 235, RB-3).

- *How long will the data or specimens will be stored locally?*

  All PHI or other identifying information, including the subject log linking the subject name and study ID will be stored for at least 3 years after the completion of the study. De-identified data and specimens will be stored for 25 years after the completion of the study.

  Who will have access to the data or specimens locally?
  Only persons listed on the Delegation of Authority Log will have access to the data locally.

  Who is responsible for receipt or transmission of the data or specimens locally?

  The Principal Investigator and main study coordinator(s) are responsible for receipt or transmission of the data. The CTRC/CSTI is responsible for transmission of the specimens to Quest Diagnostics. The specimens will be transported per Quest Diagnostics' and the CTRU/CTSI's standards for transporting blood samples, as the CTRU/CTSI sends all blood samples collected at follow up visits to Quest Diagnostics for processing.

  How data and specimens will be transported locally?

  Data will be recorded on paper, using a Case Report Form Binder (See Data Collection Fields, V1.0). Source documents will be stored in a locked office on a locked floor of a secure building in Room 228 of Building RB-2.

k) Provisions to Monitor the Data to Ensure the Safety of subjects*

This is required when Human Research involves more than minimal risk to subjects.

Describe the plans to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

We will review safety/tolerability summary data monthly. On a quarterly basis, we will provide the reports to the Data and Safety Monitor for the study, Dr. Scott Filler.

The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Describe:

- *The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.*

  Study staff will review all recorded data at regular monthly intervals with the primary investigator, Dr. Loren Miller. If Dr. Loren Miller is not available, the co-investigator, Dr. Michael Bolaris, will review the monthly data.

  The Data Safety Monitor (Dr. Filler) will review safety data including labs, vital signs, results of peripheral neuropathy scales, and all reported adverse events, side effects, complications, or other patient feedback. This review will occur on a quarterly basis, with the first review happening after either three months or after 10 patients have been enrolled, whichever comes first.

- *What data are reviewed, including safety data, untoward events, and efficacy data.*

  All reported adverse events, side effects, or complications will be reviewed.

  How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

  Safety information will be recorded by patients in the medication diary, which will be given to study staff and reviewed (See attached Medication Diary, V1.0). Additionally, study staff will inquire with patients at each visit (week 1, week 2, week 3, week 4, week 5, week 6 (optional), week 7(optional), week 8 (optional), week 9 (optional), week 10 (optional), week 11 (optional), week 12, and week 13 (optional) and the phone call at 3 months after end of antibiotic treatment) about safety information and any experienced side effects or adverse events. This data will be recorded on the Data Collection Form by study staff (See Data Collection Fields, V1.0) and entered into REDCap, an online secure database.

  The frequency of data collection, including when safety data collection starts.

  Data collection, which also includes safety data collection (all reported adverse events, side effects, or complications) will begin at the initial visit/time of screening and enrollment and continue at each follow up visit (week 1, week 2, week 3, week 4, week 5, week 6 (optional), week 7(optional), week 8 (optional), week 9 (optional), week 10 (optional), week 11 (optional), week 12, week 13 (optional) and the phone call at 3 months after end of antibiotic treatment).

  Who will review the data.

The study staff and study investigators will review the data.

Study staff will review all recorded data at regular monthly intervals with the primary investigator, Dr. Loren Miller. If Dr. Loren Miller is not available, the co-investigator, Dr. Michael Bolaris, will review the monthly data.

The Data Safety Monitor (Dr. Filler) will review safety data including labs, vital signs, results of peripheral neuropathy scales, and all reported adverse events, side effects, complications, or other patient feedback. This review will occur on a quarterly basis, with the first review happening after either three months or after 10 patients have been enrolled, whichever comes first.

The frequency or periodicity of review of cumulative data.

Cumulative safety data will be reviewed by the study staff and study investigators as it becomes available.

The statistical tests for analyzing the safety data to determine whether harm is occurring.

We will perform reviews once per quarter of the cumulative side effects. A summary of these safety data including labs, vital signs, results of peripheral neuropathy scales, and all reported adverse events, side effects, complications, or other patient feedback will be shared with the study's Data Safety Monitor, Dr. Scott Filler. If there is a statistically significant side effects, the Principal Investigator and/or the Data and Safety Monitor for the study, will consider reporting this to the IRB if the side effects are felt to put subjects at harm. Any serious adverse events that pose a risk to the subject or others and are deemed unexpected and possibly or probably related to the study will be reported to the IRB within 24 hours of the study staff being aware of this event, in accordance with HRP-214.

- *Any conditions that trigger an immediate suspension of the research.*

  If, in the belief of the Principal Investigator or the Data and Safety Monitor, there are events that put subjects at undue risk, due to either cumulative or individual events outlined above, the study will be immediately suspended.

l) Withdrawal of Subjects*

Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Subjects will be withdrawn from the study without their consent if the principal investigator determines this is necessary to protect the safety of the subject.
Additionally, subjects may be withdrawn in the following circumstances development of significant cytopenias and liver function abnormalities, symptoms of neuropathy, gastrointestinal intolerance, or, in the opinion of the investigator, any new severe signs or symptoms that may be related to the study drug.

If a subject becomes pregnant during the study, they will be discontinued from the study drug. Study staff will follow and collect data on the course of the pregnancy and the health of the child for at least 6-8 weeks after delivery.

Describe any procedures for orderly termination.
Termination of the study will occur based on the primary investigators judgment. Subjects will be provided referrals for their medical conditions, if needed.

Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Subjects who withdraw from the study will be asked to notify the study team. No further visits will be required. Additionally, if a subject withdraws from the study, a member of the study team will contact their primary treatment physician and/or infectious disease consultant to ensure that the patient is given antibiotic therapy immediately upon discontinuation of study drug.

10) Risks to Subjects*

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the HSC's consideration, describe the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

According to the package insert for tedizolid (Sivextro), adverse reactions were evaluated for 1050 patients treated with tedizolid (200 mg oral/intravenous once daily for 6 days) in two Phase 2 and two Phase 3 ABSSSI (acute bacterial skin and soft structure infection) clinical trials. The median age of patients treated with tedizolid (200 mg oral/intravenous once daily for 6 days) in the Phase 2 and Phase 3 ABSSSI trials was 42 years, ranging between 17 and 86 years old. Patients treated with tedizolid (200 mg oral/intravenous once daily for 6 days) were predominantly male (65%) and white (82%).

Serious adverse reactions occurred in 12/662 (1.8%) of patients treated with tedizolid (200 mg oral/intravenous once daily for 6 days). Tedizolid (200 mg oral/intravenous once daily for 6 days) was discontinued due to an adverse reaction in 3/662 (0.5%) of patients.

The most common adverse reactions in patients treated with tedizolid (200 mg oral/intravenous once daily for 6 days) were nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%). The median time of onset of adverse reactions was 5 days for both tedizolid(200 mg oral/intravenous once daily for 6 days) with 12% occurring on the second day of treatment.

The following selected adverse reactions were reported in tedizolid-treated patients at a rate of less than 2% in the pooled Phase 3 ABSSSI clinical trials:
Blood and Lymphatic System Disorders: anemia
Cardiovascular: palpitations, tachycardia
Eye Disorders: asthenopia, vision blurred, visual impairment, vitreous floaters
General Disorders and Administration Site Conditions: infusion-related reactions

Immune System Disorders: drug hypersensitivity
Infections and Infestations: Clostridium difficile colitis, oral candidiasis, vulvovaginal mycotic infection
Investigations: hepatic transaminases increased, white blood cell count decreased
Nervous System Disorders: hypoesthesia, paresthesia, VIIth nerve paralysis
Psychiatric Disorders: insomnia
Skin and Subcutaneous Tissue Disorders: pruritus, urticaria, dermatitis
Vascular Disorders: flushing, hypertension

Additionally, hematology laboratory abnormalities that were determined to be potentially clinically significant in the pooled Phase 3 ABSSSI clinical trials are provided in Table 1.

Table 1: Potentially Clinically Significant Lowest Laboratory Values*† in the Pooled Phase 3 ABSSSI Clinical Trials

Laboratory Assay	Tedizolid (200 mg oral/intravenous once daily for 6 days) (N=618) ‡
Hemoglobin (<10.1 g/dL [M]) (<9 g/dL [F])	3.1%
Platelet count (<112 × 10^3/mm^3)	2.3%
Absolute neutrophil count (<0.8 × 10^3/mm^3)	0.5%

M = male; F = female
* <75% (<50% for absolute neutrophil count) of lower limit of normal (LLN) for values normal at baseline
† Represents lowest abnormal post-baseline value through the last dose of active drug
‡ Number of patients with non-missing laboratory values

Phase 1 studies conducted in healthy adults exposed to tedizolid (200 mg oral/intravenous once daily) for 21 days showed a possible dose and duration effect on hematologic parameters beyond 6 days of treatment.

Peripheral and optic neuropathy have been described in patients treated with another member of the oxazolidinone class for longer than 28 days. In Phase 3 ABSSSI trials, reported adverse reactions for peripheral neuropathy and optic nerve disorders were similar between both treatment arms (peripheral neuropathy 1.2% vs. 0.6% for tedizolid phosphate and linezolid, respectively; optic nerve disorders. 3% vs. 0.2%, respectively). No data are available for patients exposed to tedizolid for longer than 6 days.

If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Use of prolonged tedizolid treatment (4-12 weeks) has not yet been studied or approved by the FDA, which may pose currently unforeseeable risks. However, tedizolid has a favorable adverse event profile and low thrombocytopenia rates compared to linezolid which is approved by the FDA for prolonged antibiotic therapy. Additionally, at FDA-approved doses, tedizolid has

hematologic side effects similar to that of placebo. Additionally, unlike linezolid, interactions with SSRIs appear unlikely. Drug-mitochondrial binding, which is believed to be the mechanism to which mid- and long-term toxicities of linezolid such as neuropathy are acquired, is not seen with tedizolid, suggesting that the side effects associated with long-term therapy of linezolid may not be found with tedizolid. Tedizolid will be used in this research to treat bone and joint infection in patients who need prolonged antibiotic treatment for 4-12 weeks.

Despite these promising initial results, there still may be currently unforeseeable risks. For this reason, Drs. Miller and Bolaris will closely monitor subject data in monthly reviews, and a Data Safety Monitor (Dr. Filler) will review all safety data (including labs, vital signs, results of peripheral neuropathy scales, and all reported adverse events, side effects, complications, or other patient feedback) every three months or after 10 patients have been enrolled, whichever comes first.

If there is a statistically significant side effects, the Principal Investigator and/or the Data and Safety Monitor for the study, will consider reporting this to the IRB if the side effects are felt to put subjects at harm. Any serious adverse events that pose a risk to the subject or others and are deemed unexpected and possibly or probably related to the study will be reported to the IRB within 24 hours of the study staff being aware of this event, in accordance with HRP-214. Additionally, if in the belief of the Principal Investigator or the Data and Safety Monitor, there are events that put subjects at undue risk, due to either cumulative or individual events outlined above, the study will be immediately suspended.

If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Per the Merck Package Insert, there are no adequate and well-controlled studies of tedizolid in pregnant women. In embryo-fetal 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 at the high dose of 25 mg/kg/day (4-fold the estimated human exposure level based on AUCs). In rats, decreased fetal weights and increased skeletal variations including reduced ossification of the sternebrae, vertebrae, and skull were observed at the high dose of 15 mg/kg/day (6-fold the estimated human exposure based on AUCs) and were associated with maternal toxicity (reduced maternal body weights). In rabbits, reduced fetal weights but no malformations or variations were observed at doses associated with maternal toxicity. The no observed adverse effect levels (NOAELs) for fetal toxicity in mice (5 mg/kg/day), maternal and fetal toxicity in rats (2.5 mg/kg/day), and rabbits (1 mg/kg/day) were associated with tedizolid plasma area under the curve (AUC) values approximately equivalent to (mice and rats) or 0.04-fold (rabbit) the tedizolid AUC value associated with the oral human therapeutic dose. In a pre-postnatal study, there were no adverse maternal or offspring effects when female rats were treated during pregnancy and lactation with tedizolid phosphate at the highest tested dose of 3.75 mg/kg/day, with plasma tedizolid exposure (AUC) approximately equivalent to the human plasma AUC exposure at the clinical dose of 200 mg/day.

For this study, if a women is of childbearing potential, she must consistently use an acceptable method of contraception (IUD, injectable contraceptive, birth control patch, OCP, barrier method, abstinence) from baseline through the course of antibiotics (4-12 weeks). If a male patient's sexual partner is of childbearing potential, the male patient must acknowledge that they

will consistently use an acceptable method of contraception as defined above from baseline through the course of antibiotics (4-12 weeks).

If applicable, describe risks to others who are not subjects.

Tedizolid is excreted in the breast milk of rats. It is not known whether tedizolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tedizolid is administered to a nursing woman. In this study, nursing mothers will be excluded.

11) Potential Benefits to Subjects*

Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the HSC's consideration, the probability, magnitude, and duration of the potential benefits.

Given the large and increasing burden of disease of bone and joint infection and the increasing acceptability of oral antibiotics for its management, tedizolid holds promise as a well-tolerated oral therapy that can be used for patients with bone and joint infection when intravenous options are not pursued and other oral options are problematic. Tedizolid has been shown to have less hematologic and neurologic side effects in animals compared to similar drugs in its class, specifically linezolid. However, these advantages have not been evaluated in humans and may not occur.

Indicate if there is no direct benefit. Do not include benefits to society or others.

Not Applicable

12) Provisions to Protect the Privacy Interests of Subjects

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Every effort will be taken to make subjects feel at ease with the research, and all interactions with subjects will take place in a private setting.

Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

In an effort to make subjects feel at ease with the research, all interactions with subjects will take place in a private setting. The study procedures (obtaining health information, collection of blood samples, etc.) will be performed in a private setting, such as an exam room.

Indicate how the research team is permitted to access any sources of information about the subjects.

Only study team members and the study investigator will have access to the subjects' information with permission from the subject (See Protected Health Information Form, V1.0).

13) Compensation for Research-Related Injury

If the research involves more than minimal risk to subjects, describe the available compensation in the event of research related injury.

Financial compensation for any injury from this research is not available.

Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Not Applicable

14) Economic Burden to Subjects

Describe any costs that subjects may be responsible for because of participation in the research.

There are no additional costs to subjects participating in this study.

The study drug will be provided at no cost. Subjects will be responsible for costs related to their hospitalization or visit to the Emergency Department, etc. and any other costs associated with the management of their condition that is not part of this research.

15) Consent Process

Indicate whether you will you be obtaining consent, and if so describe:

Where will the consent process take place

The consent process will take place in a private setting of the emergency department, inpatient wards, or outpatient clinics at Harbor-UCLA Medical Center.

Any waiting period available between informing the prospective subject and obtaining the consent.

Subjects will be given ample time to make their decision regarding their participation. We will encourage subjects to discuss the research study with their family members and treating physician before making a decision.

Any process to ensure ongoing consent.
With each contact with the subject, the subject will be reminded that participation is voluntary and of the procedures required at the contact/visit.

- *Whether you will be following "SOP: Informed Consent Process for Research (HRP-090)."*

We will follow "SOP: Informed Consent Process for Research (HRP-090)

Non-English Speaking Subjects

- *Indicate what language(s) other than English are understood by prospective subjects or representatives.*

  We seek to enroll Spanish speaking individuals as well.

- *If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language.*

  The consent document and PHI authorization, once approved, will be translated into Spanish. Informed consent for Spanish-speaking subjects will be obtained via one of the study physicians or study coordinators fluent in Spanish. All consent procedures for Spanish-speaking individuals will take place in a private setting in the inpatient floors, emergency department, or outpatient setting at Harbor-UCLA Medical Center.

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

Not Applicable

- *Review the "CHECKLIST: Criteria for Waiver or Alteration of the Consent Process" to ensure you have provided sufficient information for the HSC to make these determinations.*
- *If the Human Research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Criteria for Waiver of the Consent Process for Planned Emergency Research" to ensure you have provided sufficient information for the HSC to make these determinations.*

Subjects who are not yet adults (infants, children, teenagers)

- *Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the Human Research under the applicable law of the jurisdiction in which the Human Research will be conducted. (E.g., individuals under the age of 18 years.)*

  Not Applicable

  - *For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*
  - *For research conducted outside of the state, submit a statement from legal counsel describing which persons have not attained the legal age for consent to treatments or*

procedures involved in <u>this</u> Human Research, under the applicable law of the jurisdiction in which <u>this</u> Human Research will be conducted. To obtain this statement, have legal counsel review the definition of "children" in 45 CFR 46.402(a) or 21 CFR 50(0). The HSC can provide you a copy of these regulations. Also provide legal counsel with a copy of the protocol or other document describing the procedures involved in the Human Research.

- *Describe whether parental permission will be obtained from:*

  Not Applicable

  - *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
  - *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*
- *Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.*
- *Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.*
- *When assent of children is obtained describe whether and how it will be documented.*

Cognitively Impaired Adults

- *Describe the process to determine whether an individual is capable of consent.*

Study population is limited to competent adults.

Adults Unable to Consent

Study population is limited to competent adults.

- *List the individuals from whom permission will be obtained in order of priority. (E.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.)*
  - *For research conducted in the state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative."*
  - *For research conducted outside of the state, submit a statement from legal counsel describing which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in <u>this</u> Human Research. To obtain this statement, have legal counsel review the definition of "legally authorized representative" in 45 CFR 46.102(c) or 21 CFR 50(l). The HSC can provide you a copy of these regulations. Also, provide legal counsel with a copy of the protocol or other document describing the procedures involved in the Human Research.*
- *Describe the process for assent of the subjects. Indicate whether:*

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent.*

16) Process to Document Consent in Writing

Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be documented in writing.

We will be following SOP: Written Documentation of Consent (HRP-091).

If the consent of the subject will not be documented in writing (consent will be obtained but the subject or representative will not sign a consent document) review "CHECKLIST: Criteria for Waiver of Written Documentation of Consent" to ensure that you have provided sufficient information.

Not Applicable

17) Vulnerable Populations

If the Human Research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

Individuals or populations that might be vulnerable include, but are not limited to those who:

- *Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).*
- *Lack comprehension of the research and its risks (e.g., educationally disadvantaged, dementia, schizophrenia, or depression).*
- *Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status).*

Indicate specifically whether you will include or exclude each of the following special populations:

- Adults unable to consent-EXCLUDED
- Individuals who are not yet adults (infants, children, teenagers)-EXCLUDED
- Pregnant women-EXCLUDED
- Prisoners-EXCLUDED

(You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

If the Human Research involves cognitively impaired adults, review the "CHECKLIST: Criteria for Research Involving Cognitively Impaired Adults" to ensure that you have provided sufficient information.

If the Human Research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Criteria for Research Involving Children" to ensure that you have provided sufficient information.

If the Human Research involves pregnant women, review the "CHECKLIST: Criteria for Research Involving Pregnant Women" to ensure that you have provided sufficient information.

If the Human Research involves neonates of uncertain viability or non-viable neonates, review the "CHECKLIST: Criteria for Research Involving Neonates" to ensure that you have provided sufficient information.

18) Drugs or Devices

If the Human Research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Tedizolid 200 mg oral tablets will be stored at and dispensed by the LA BioMed Investigational Drug Service (IDS) by trained pharmacists to the study team member who will then provide to the subjects. The IDS will maintain a drug dispensation log and provide to the investigator at the end of the study.

Because this study is using tedizolid for longer than the FDA approved duration, we have received an IND (133495) which was approved to proceed on 1/12/17. The study drug will be prescribed/administered as prolonged antibiotic therapy for a duration of time based on the judgment of the primary/consulting physician who is treating the subject's bone and joint infection.

19) Multi-Site Human Research*

Not Applicable – not a multi-site study.

If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's HSC of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's HSC of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

20) Community-Based Participatory Research

Describe involvement of the community in the design and conduct of the research.

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Not Applicable

21) Sharing of Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Any clinically significant (as determined by Dr. Loren Miller or Dr. Michael Bolaris) lab, culture, or survey results (See Data Collection Fields, V1.0 for a complete list) or other incidental findings will be shared with the subject and their primary care providers if clinically indicated.